Protocol Title:

An evaluation of the efficacy beyond progression of vemurafenib combined with cobimetinib associated with local treatment compared to second-line treatment in patients with BRAF^{V600} mutation-positive metastatic melanoma in focal progression with first-line combined vemurafenib and cobimetinib.

Version 2.0, date: November 15, 2017

Abbreviated title: BeyPro2

EudraCT Number: 2017-003038-98

Protocol Code: BeyPro2

Sponsor: IMI – Intergruppo Melanoma Italiano

Study Coordinator: Dr. Paola Queirolo

Translational Study Coordinator: Prof. Giuseppe Palmieri

Design and Statistical analysis: Dott. Paolo Bruzzi[1]

Scientific Committee:
Dr. Paola Queirolo[1]
Dr. Del Vecchio[2]
Dr.ssa Chiarion[3]
Prof. Palmieri[4]
Dott. Paolo Bruzzi[1]

1. IRCCS AOU San Martino - IST, Genova
2. Istituto Nazionale dei Tumori, Milano
3. Istituto Oncologico Veneto, Padova
4. ICB-CNR, Sassari

The trial will be conducted in accordance with the Declaration of Helsinki, the Guideline for Good Clinical Practice of the international conference on Harmonization (ICH E6-R2) and all applicable laws and regulations.

List of abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BORR	Best Overall Response Rate
CAP	Chest Abdomen Pelvis
CMP	Clinical Monitoring Plan
CPK	Creatine Phosphokinase
CrCl	Creatinine Clearance
CRO	Contract Research Organization
cSCC	Cutaneous Squamous Cell Carcinoma
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
HR	Hazard Ratio
IEC	Independent Ethics Committee
IWRS	Interactive Web Response System
LLN	Lower Limit of Normal
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical dictionary for regulatory activities
MUGA	Multiple Gated Ejection Acquisition
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
PPS	Per Protocol Set
RECIST	Response Evaluation Criteria In Solid Tumors
RVO	Retinal Vein Occlusion
SAE	Serious Adverse Event
SCC	Squamous Cell Carcinoma
SD	Stable Disease
SmPC	Summary of Product Characteristics
ULN	Upper Limit of Normal
WHO	World Health Organization

Synopsis

Protocol Title: An evaluation of the efficacy beyond progression of vemurafenib combined with cobimetinib associated with local treatment compared to second-line treatment in patients with $BRAF^{v600}$ mutation-positive metastatic melanoma in focal progression with first-line combined vemurafenib and cobimetinib
Country: Italy
Study Coordinator: Paola Queirolo
Study Phase: II
Study Design: This is a randomized, open-label, multicenter, phase II study. All patients will initially be treated with first-line vemurafenib + cobimetinib. After focal progression, defined as the appearance or dimensional increase of lesions that can be treated with surgery or radiotherapy, patients will be randomized to either continue receiving vemurafenib and cobimetinib along with local management (i.e. surgery, radiotherapy), or switch to a standard second-line treatment. In the latter patients, local treatment may be provided based on the Investigator's judgment to ensure patient safety and good clinical practice. Patients with non-focal progression of disease will not be randomized but will switch to second-line therapy and will be followed up for survival only. Second-line treatment consists of immunotherapy with anti-PD-1 antibodies (pembrolizumab or nivolumab). All patients will be followed up for 24 months after randomization or last dose of vemurafenib and cobimetinib (for non-randomized patients). Treatments will continue until the development of progressive disease (non-focal), unacceptable toxicity, consent withdrawal, death, reasons deemed appropriate by the treating physician or study termination by the Sponsor.
Primary Objective: The primary objective of the study is to evaluate the efficacy, in terms of overall survival, of vemurafenib combined with cobimetinib associated with local treatment compared with second-line therapy in patients with $BRAF^{V600}$ mutation-positive metastatic melanoma in focal progression with first-line combined vemurafenib and cobimetinib.
Treatment: The study treatment is a combination of vemurafenib and cobimetinib. Vemurafenib is taken on a 28-day cycle. Each dose consists of four 240 mg (960 mg) tablets twice daily for 28 consecutive days. The first dose should be taken in the morning and the second dose in the evening approximately 12 hours later. Each dose can be taken with or without a meal. Vemurafenib tablets should be swallowed whole with a glass of water and should not be chewed or crushed. Cobimetinib is taken on a 28-day cycle. Each dose consists of three 20 mg tablets (60 mg) and should be taken orally, once daily for 21 consecutive days (Days 1 to 21-treatment period), followed by a 7-day break (Days 22 to 28-treatment break). Each subsequent treatment cycle should start after the 7-day treatment break has elapsed. The dose should be taken in the morning.
Primary Endpoint: The primary endpoint is Overall Survival (OS) for patients with focal progression
Secondary Endpoints: The secondary endpoints are the following: ● Progression Free Survival (PFS) for patients with focal progression ● OS for patients with non-focal progression ● Prognostic role in terms of OS of focal compared with non-focal progressive disease ● Safety based on the following variables: o Nature, frequency, severity, and timing of adverse events and serious adverse events. o Changes in vital signs, physical findings and clinical laboratory results during and following vemurafenib + cobimetinib administration.
Sample Size Justification and Statistics: **Sample size**: The present phase II study is aimed at providing the rationale for a phase III efficacy trial of adequate

size assessing the efficacy of dual target inhibition beyond focal progression. Consequently, an alfa error rate of 0.2 (two-sided) will be used. The expected OS of patients with BRAF+ metastatic melanoma after a 1st focal progression is difficult to estimate due to the lack of published data on this specific subset of patients. However, the survival experience of these patients can be reasonably considered to be intermediate between that of BRAF+ patients in first-line treatment with combined BRAF and MEK inhibition and the post-progression survival of the same patients, i.e. at approximately 1.5 years of median survival. With 120 patients enrolled over a period of 12 months, and a total of 60-70 patients randomized into the second-line study in patients with focal progression, at least 38 deaths are expected in both groups combined with a 2-year of follow-up after last dose of vemurafenib and cobimetinib. With 38 events, the study has 80% power to detect, with an alfa error rate of 0.2 (two-sided), a statistical significance difference in favor of the experimental arm corresponding to a Hazard Ratio of 0.5. The final analysis will take place after the observation of 38 deaths in the randomized cohorts or after 24 months since randomization of the last patient, whichever first.

Analysis of efficacy:

- Overall survival of patients with focal progression will be compared between treatment groups using a log-rank test procedure with a two-sided $\alpha = 0.2$ level. The OS function for each treatment group will be estimated using the Kaplan-Meier product-limit method. Median and corresponding two-sided 80% confidence intervals will be computed by treatment group. Kaplan-Meier plots of OS will be presented. A Cox proportional hazard model for OS with treatment arm as single factor will be used to estimate the hazard ratio of vemurafenib and cobimetinib plus local treatment to Standard of Care (SOC) second-line treatment and its corresponding 80% confidence interval.
- Progression free survival will be compared between treatment groups using a log-rank test procedure with a two-sided $\alpha = 0.2$ level. The PFS function for each treatment group will be estimated using the Kaplan-Meier product-limit method. Median and two-sided 80% confidence intervals (CI) for median PFS will be computed by treatment group. Kaplan-Meier plots of PFS will be presented. A Cox proportional hazard model for PFS with treatment arm as single factor will be used to estimate the hazard ratio of vemurafenib and cobimetinib plus local treatment to SOC second-line treatment and its corresponding 80% confidence interval.
- Overall survival results of patients with non-focal progression will be descriptively compared with OS results of patients with focal progression (i.e. primary efficacy endpoint). No statistical test is foreseen for this comparison.

Analysis of safety

AEs and laboratory parameters will be assessed according to the Common Terminology Criteria for AEs (CTCAE version 4). Other safety data analyzed: ECGs, physical examinations, vital signs and ECOG PS will be listed and summarized by treatment arm.

Main Inclusion Criteria:

- Patients with histologically confirmed melanoma, either unresectable Stage IIIc or Stage IV metastatic melanoma, as defined by the American Joint Committee on Cancer 7th edition.
- Patients previously untreated for metastatic melanoma.
- Documentation of $BRAF^{V600}$ mutation-positive status in melanoma tumor tissue (archival or newly obtained tumor samples) by a validated mutational test.
- Adequate performance status to receive vemurafenib and cobimetinib therapy as determined by treating physician.

Planned Timelines: About 12 centers will enroll a total of 120 patients. The study will have an enrolment period of 12 months and a follow-up period of 24 months. The end of the study will occur when all patients have been followed up for survival for 24 months after the last patient has been randomized or after the last dose of vemurafenib and cobimetinib (for non-randomized patients).

Table of contents

Amendment 1

This amendment was drawn up to align the protocol with the recommendations of the Ethics Committee concerning the definition of second-line therapy. The protocol now states that patients with general progression of disease, as well as those with focal progression randomized to second-line treatment, will be treated with anti-PD 1 immunotherapy, i.e. nivolumab or pembrolizumab. Both agents are approved by the FDA and EMA thanks to their favorable efficacy and toxicity profiles and represent new standard of care for the treatment of advanced melanoma.

The amendment also draws attention to the fact that since all patients are likely to undergo general disease progression, the switch to second-line therapy in patients randomized to local treatment plus continuation of BRAF+MEK inhibitors will only be delayed, but because of that allow a study of the activity of combination treatment beyond local progression.

Finally, a correction has been made regarding the storing conditions of vemurafenib.

Changes to the protocol are shown in the track changes version using strike through font for deletions and underlined font for insertions.

1. BACKGROUND AND RATIONALE

Nearly half of the patients with advanced melanoma harbor a valine to glutamine substitution (V600E) in codon 600 of the serine-threonine kinase BRAF (*Davies et al 2002*). Less common BRAF mutations such as lysine (V600K) or arginine substitutions (V600R) have also been reported (*Eroglu et al 2016*). In the past 5 years, two BRAF inhibitors that target these mutations, vemurafenib and dabrafenib, have been approved by the US Food and Drug Administration (FDA). These drugs have shown high rates of rapid response, with rates ranging from 48% to 59% in phase II and III trials (*Chapman et al. 2011*; *Ascierto et al. 2013*; *Hauschild et al. 2012*). Duration of responses is however limited in the majority of patients due to the development of acquired resistance, with median progression-free survival (PFS) in these patients ranging from 5.1 to 6.8 months (*Sosman et al. 2012*; *Hauschild et al. 2012*).

Mechanisms of resistance to BRAF inhibitor therapy are diverse and include the reactivation of the mitogen-activated protein kinase (MAPK) pathway in over two-thirds of tumors, along with promotion of parallel signaling networks such as the PI3K–PTEN–AKT pathway (*Shi et al. 2014*; *Rizos et al. 2014*; *Wagle et al. 2011*). Sequential therapy with a MEK inhibitor following progression on a BRAF inhibitor has not shown benefit, as no responses and a PFS of only 1.8 months was observed in a study of 40 patients, suggesting that resistance to BRAF inhibitors also confers resistance to MEK inhibitors (*Kim et al. 2013*). Therefore, the premise behind the subsequent clinical trials combining inhibitors of both MEK

and mutant BRAF kinase was that they would help to delay resistance and result in higher rates and longer duration of responses and reduced toxicity respect to BRAF inhibitor monotherapy *(Eroglu et al 2016)*.

Vemurafenib and cobimetinib

Patients with advanced $BRAF^{V600}$ mutated melanoma who were either BRAF inhibitor naïve ($n = 63$) or had recently progressed on vemurafenib ($n = 66$) were included in the phase Ib BRIM7 trial (*Ribas et al. 2014*). In the dose escalation phase, patients received vemurafenib 720 or 960 mg BID continuously and cobimetinib 60, 80 or 100 mg QD for 14 days on and 14 days off, or 21 days on and 7 days off or continuously. The maximum tolerated dose was established as vemurafenib 960 mg BID in combination with cobimetinib 60 mg for 21 days on, 7 days off. The Overall Response Rate (ORR) rate was 87% in the 63 BRAF inhibitor naïve patients, with a median PFS of 13.7 months (95% CI: 10·1–17·5). ORR was 15% in the 66 patients who had already progressed on vemurafenib, with a median PFS of 2.8 months (95% CI: 2.6–3.4). The study results were updated with an additional 11 months of follow up; a median Overall Survival (OS) of 28.5 months in the vemurafenib-naïve and 8.4 months in the vemurafenib-progressing patients was reported, with 2-year OS rates of 61.1% and 15.1% respectively (*Pavlick et al. 2015)*.

In the coBRIM trial, the addition of cobimetinib (60 mg QD for 21 of 28 days) to vemurafenib (960 mg BID) led to an improvement in median PFS of 9.9 in the 247 patients versus 6.2 months in the 248 patients who received vemurafenib with placebo. Hazard Ratio (HR) for death or disease progression was 0.51 ($p < 0.001$) (*Larkin et al. 2014*). The ORR was 68% in the combination arm compared to 45% in the control arm and was associated with a nonsignificant higher incidence of grade 3 or 4 Adverse Events (AE) compared with vemurafenib and placebo (65% versus 59%).There was no significant difference in the rate of study drug discontinuation. Toxicities observed more frequently with the combination were serous retinopathy, diarrhea, nausea or vomiting, photosensitivity, elevated aminotransferase levels and an increased creatine kinase level. As expected, the incidence of secondary cutaneous squamous cell cancers decreased with the combination therapy compared with vemurafenib alone (down from 11% to 2%). Study results were updated with an 8-months additional follow up, with a PFS of 12.3 months for the combination arm compared with 7.3 for monotherapy, HR 0.58, and an ORR of 70% versus 50% respectively. Median OS for patients treated with the combination was 22.3 (*Eroglu et al 2016)*. The overall survival benefit for cobimetinib and vemurafenib observed in the coBRIM trial underlines the positive impact that the combination of these two therapies can have on the

treatment of advanced $BRAF^{V600}$ mutation-positive melanoma. The data from these studies confirm the clinical benefit of cobimetinib combined with vemurafenib and support the use of the combination as a standard first-line approach to improve survival in patients.

Although the addition of cobimetinib to vemurafenib is associated with a significant improvement in outcomes among patients with BRAF V600-mutated metastatic melanoma, patients treated with the combination treatment eventually experience progression of disease. In this setting, the use of anti-PD 1 immunotherapy with agents such as nivolumab or pembrolizumab has proved to be effective.

Nivolumab

Nivolumab is a fully human IgG4 PD-1 immune checkpoint inhibitor antibody approved by the FDA in 2014 for the treatment of patients with unresectable or metastatic melanoma and disease progression after ipilimumab therapy and, if the patient is positive for a *BRAF* V600 mutation, after treatment with a BRAF inhibitor.

The approval of nivolumab was based on the results of trials Checkmate-037 and Checkmate 066. Checkmate 037 was a phase 3 randomized, controlled, open-label study of nivolumab versus investigator's choice chemotherapy (ICC) in patients who had unresectable or metastatic melanoma, and progressed after ipilimumab, or ipilimumab and a BRAF inhibitor if they were $BRAF^{V\ 600}$ mutation-positive. Primary endpoints were the proportion of patients who had an objective response and overall survival. Objective responses were assessed after 120 patients had been treated with nivolumab and had a minimum follow-up of 24 weeks, and safety in all patients who had had at least one dose of treatment.

A total of 405 patients were randomised to receive either nivolumab (n = 272) or chemotherapy (n = 133), which consisted of the investigator’s choice of either dacarbazine or carboplatin and paclitaxel. Confirmed objective responses were reported in 38 (31.7%, 95% CI 23.5–40.8) of the first 120 patients in the nivolumab group versus five (10.6%, 3.5–23.1) of 47 patients in the ICC group. Grade 3–4 adverse events related to nivolumab included increased lipase (three [1%]), increased alanine aminotransferase, anemia, and fatigue (two [1%] each); for ICC, these included neutropenia (14 [14%]), thrombocytopenia (six [6%]), and anemia (five [5%]). Grade 3–4 drug-related serious adverse events were noted in 12 (5%) nivolumab-treated patients and nine (9%) patients in the ICC group. No treatment-related deaths occurred.

The study concluded that nivolumab led to a greater proportion of patients achieving an objective

response and fewer toxic effects than with alternative available chemotherapy regimens for patients with advanced melanoma that had progressed after ipilimumab or ipilimumab and a BRAF inhibitor (*Weber et al., 2015*).

In an updated analysis (24-month follow-up), ORR was 27.2% (95% CI: 22.0, 32.9) in the nivolumab group and 9.8% (95% CI: 5.3, 16.1) in the chemotherapy group. Median durations of response were 31.9 months (range: 1.4+-31.9) and 12.8 months (range: 1.3+-13.6+), respectively. The PFS HR for nivolumab vs. chemotherapy was 1.03 (95% CI: 0.78, 1.36). There was no statistically significant difference between nivolumab and chemotherapy in the final OS analysis. The primary OS analysis was not adjusted to account for subsequent therapies, with 54 (40.6%) patients in the chemotherapy arm subsequently receiving an anti-PD1 treatment. OS may be confounded by dropout, imbalance of subsequent therapies and differences in baseline factors. More patients in the nivolumab arm had poor prognostic factors (elevated LDH and brain metastases) than in the chemotherapy arm (*nivolumab Summary of Product Characteristics*).

Checkmate 066 was conducted in patients with previously untreated metastatic melanoma (and without *BRAF* mutations). The results showed a 1-year survival rate of 73% with nivolumab vs 42% with dacarbazine, with a hazard ratio of 0.42 ($P < .0001$).

The FDA has expanded the frontline melanoma indications for nivolumab as a single agent and in combination with ipilimumab (Yervoy) to include patients with *BRAF* V600 mutations, based on data from the phase III Checkmate-067 trial.

In the pooled dataset of nivolumab 3 mg/kg as monotherapy across tumor types (n = 2227), the most frequent adverse reactions (≥ 10%) were fatigue (30%), rash (17%), pruritus (12%), diarrhea (12%), and nausea (12%). Most adverse reactions were mild to moderate (Grade 1 or 2) (*nivolumab SmPC*).

Pembrolizumab

Pembrolizumab is another PD-1 immune checkpoint inhibitor antibody approved by the FDA and EMA for the treatment of patients with unresectable or metastatic melanoma. Approval was based on results of two randomized, open-label, active-controlled clinical trials.

In the PN-006 trial, patients with unresectable stage III/IV melanoma who had received no more than one previous systemic therapy were assigned to receive on a 1:1:1 ratio pembrolizumab at 10 mg/kg every 2 weeks, pembrolizumab at 10 mg/kg every 3 weeks, or 4 doses of ipilimumab at 3 mg/kg every 3

weeks. Primary end points were PFS and OS. A total of 834 patients were enrolled with 65% treatment naïve, and 18% of having received a BRAF inhibitor (representing 50% of patients who had a *BRAF*V^{600} mutation). ORRs were 33.7% for the 2-weekly pembrolizumab group (P < 0.001 *vs.* ipilimumab), 32.9% for the 3-weekly pembrolizumab (P < 0.001), and 11.9% for the ipilimumab group. Rates of CR were 5.0%, 6.1%, and 1.4% respectively. The estimated 6-month PFS was superior in the pembrolizumab groups (2-weekly: 47.3%; 3-weekly: 46.4%) as compared with the ipilimumab group (26.5%) (P < 0.001 for both pembrolizumab groups *versus* ipilimumab). Estimated 12-month OS was also superior in the pembrolizumab groups (2-weekly: 74.1%, P=0.0005; 3-weekly: 68.4%, P = 0.0036) as compared with the ipilimumab group (58.2%). At a median follow-up of 7.9 months, responses were still ongoing in 89.4%, 96.7%, and 87.9% of patients respectively. Grade 3–5 AEs were lower in the pembrolizumab groups (13.3% and 10.1%) than in the ipilimumab group (19.9%) (*Robert et al., 2015*).

In the PN-002 trial, patients with confirmed progressive melanoma within 24 weeks of ≥2 ipilimumab doses and, if *BRAF*^{V600} mutant-positive, previous treatment with a BRAF or MEK inhibitor or both, were recruited on a 1:1:1 basis to receive pembrolizumab at 2 mg/kg every 3 weeks, pembrolizumab at 10 mg/kg every 3 weeks, or investigator-choice chemotherapy (paclitaxel plus carboplatin, paclitaxel, carboplatin, dacarbazine, or oral temozolomide). Crossover to pembrolizumab was allowed for patients progressing on chemotherapy. A total of 540 patients were enrolled with 48% crossing over to pembrolizumab on progression). More than two thirds of patients had ≥2 lines of prior systemic therapy including ipilimumab in all patients. About 25% of the patients had BRAF or MEK inhibitors, and about 50% had chemotherapy. With central review, the response was 21% in the pembrolizumab 2 mg/kg group, 25% in the pembrolizumab 10 mg/kg group, and 4% in the chemotherapy group (p < 0.0001 for each pembrolizumab dose *versus* chemotherapy). The primary endpoint of PFS was improved in the pembrolizumab 2 mg/kg group (P < 0.0001) and the pembrolizumab 10 mg/kg group (P < 0.0001) compared with the chemotherapy group, with 6-month PFS at 34%, 38% and 16% respectively. More than 85% of pembrolizumab-induced responses were maintained at the time of PFS analysis. Median duration of response had not been reached (*Ribas et al., 2015*).

The adverse drug reactions reported for patients being treated with pembrolizumab appear to be mostly of low grade and manageable. It was noted that immunological ADRs include skin, gastrointestinal, endocrine, hepatic, pulmonary and renal events. These are managed appropriately with the recommendations as stated in the SmPC (*pembrolizumab SmPC*).

Rationale

Patterns of progression with combined therapy are heterogeneous and progressive lesions often represent only a small amount of the total tumor burden. In this setting, a local treatment of progressing lesions can be provided without modifications of the ongoing systemic treatment. Moreover, even when a local treatment cannot be delivered, retrospective evidence in the BRAF monotherapy setting supports continuation of therapy in order to maintain partial inhibition of the pathway.

The activity of treatment beyond progression with combination treatment has never been evaluated in a prospective trial. The aim of this trial is to evaluate the impact of combined cobimetinib and vemurafenib treatment beyond progression associated with local treatment of progressive lesions in terms of OS improvement in patients affected by metastatic melanoma with $BRAF^{V600}$ mutation treated with vemurafenib in combination with cobimetinib who experienced focal progression.

Patients with focal progression who are randomized to local treatment plus BRAF+MEK inhibitor treatment beyond progression will receive second line treatment with an anti-PD-1 agent in case of systemic progressive disease. Therefore, the switch to second-line treatment is only postponed until systemic progressive disease and all patients will ultimately receive a second line treatment with an anti-PD-1 agent.

2. STUDY AIMS AND DESIGN

2.1 Objectives of the study

Primary Objective

The primary objective of the study is to evaluate the efficacy, in terms of overall survival, of vemurafenib combined with cobimetinib associated with local treatment compared with second-line therapy, in patients with $BRAF^{V600}$ mutation-positive metastatic melanoma in focal progression with first-line combined vemurafenib and cobimetinib.

Secondary Objectives

- To compare progression-free survival of patients receiving treatment beyond focal progression vs second-line treatment.
- To compare the adverse event profiles in patients receiving treatment beyond progression vs. second-line treatment.
- To evaluate the prognostic role of focal *versus* non-focal progressive disease

Exploratory objective

A translational study aims to identify positive and negative biomarkers predictive of clinical outcomes in paired tumor DNA specimens from the same patients (tumor biopsies and peripheral blood), taken before therapy with BRAF+MEK inhibitors and after progression.

2.2 Endpoints of the study

Primary Endpoint

The primary endpoint of the study is OS computed from the day of randomization to the day of death from any cause.

Secondary Endpoints

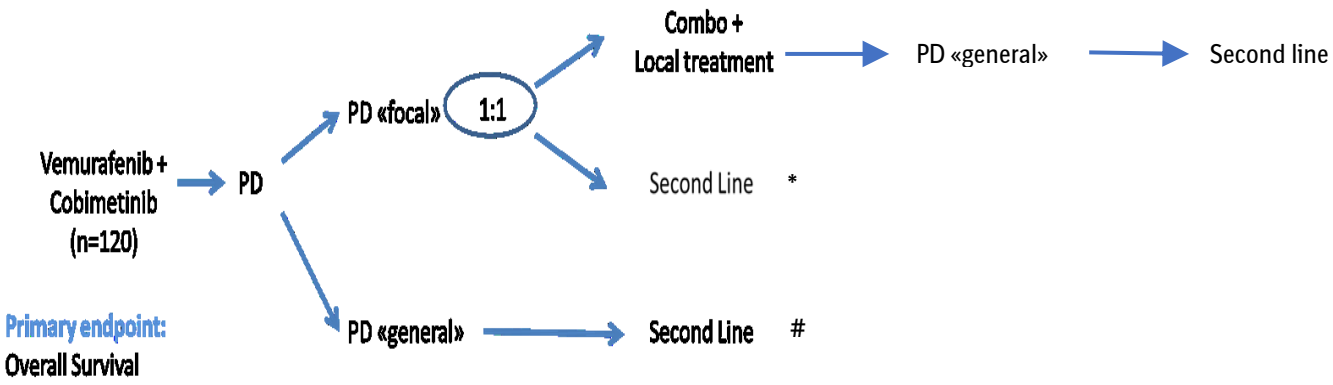
- PFS computed from the day of randomization to the day of disease progression or death from any cause
- OS for patients with non-focal progression
- Prognostic role in terms of OS of focal compared with non-focal progressive disease
- Safety evaluated on the basis of the following variables:
  - Nature, frequency, severity, and timing of adverse events and serious adverse events.
  - Changes in vital signs, physical findings and clinical laboratory results during and following vemurafenib + cobimetinib administration

2.3 Study Design

This is a randomized, open-label, multicenter, phase II study. The study will enroll approximately 120 melanoma patients at about 12 sites located in Italy. All patients will initially be treated with first-line vemurafenib and cobimetinib. After focal progression, defined as the appearance or dimensional increase of lesions that can be treated with surgery or radiotherapy, patients will be randomized to either continue receiving vemurafenib and cobimetinib along with local management (i.e. surgery, radiotherapy), or switch to a second-line treatment with an anti-PD-1 agent (nivolumab or pembrolizumab). In the latter patients, local treatment may be provided based on the Investigator's judgment to ensure patient safety and good clinical practice.

Patients with non-focal progression of disease will not be randomized but will switch to second-line therapy with an anti-PD-1 agent (nivolumab or pembrolizumab), as per local practice, and will be followed up for survival only. All patients will be followed up for 24 months after randomization or last dose of vemurafenib and cobimetinib (for non-randomized patients). Treatments will continue until the development of progressive disease (non-focal), unacceptable toxicity, consent withdrawal, death, reasons deemed appropriate by the treating physician or study termination by the Sponsor.

The study will have an enrolment period of 12 months and a follow-up period of 24 months. The end of the study will occur when all patients have been followed up for survival for 24 months after the last patient has been randomized, or after the last dose of vemurafenib and cobimetinib (for non-randomized patients).



* Local treatment may be provided based on the Investigator's judgment to ensure patient safety and good clinical practice.

Patients with non-focal (general) progression after first-line treatment with vemurafenib and cobimetinib will not be randomized and will only be followed for survival status.

* # Second line treatment with an anti-PD-1 agent (nivolumab or pembrolizumab)

2.4 Schedule of Assessments and Procedures

The visit and assessment schedule is shown in Table 1. The Table reports assessments to be performed on all patients prior to randomization or general progression and on patients with focal progression following randomization. Following general progression of disease, both randomized and non-randomized patients will be followed for survival status only. Most screening/baseline assessments must be performed within 28 days prior to the first administration of study drugs on Day 1, with the exception of the serum pregnancy test to be done within 7 days and other laboratory exams to be done within 14 days. Results of tests or examinations performed as standard of care before obtaining informed consent and within the 28 days prior to commencing study drugs may be used. All assessments during the study must be performed within a window of -4/+1 days of the day indicated on the assessment schedule, except for tumor evaluations, which will have a window of +/- 5 days. Eligibility for the study will be determined by the investigator from the screening/baseline assessments according to the study inclusion/exclusion criteria. Patients who discontinue study drugs for any reason (e.g. AEs) other than disease progression will continue to be followed until disease progression. Follow-up will continue for 24 months after randomization or last dose of vemurafenib and cobimetinib (for non-randomized patients).

2.4.1 Screening Examination and Eligibility Screening Form

Written informed consent must be obtained before any study specific assessments or procedures are performed. Patients who fulfill all the inclusion and none of the exclusion criteria will be eligible for the study.

2.4.2 Procedures for Enrollment of Eligible Patients

A patient who fulfils entry criteria will be given a unique identifying number. A patient number will not be reused if the patient leaves the study. Under no circumstances the patients who will be enrolled in this study and completed treatment as specified will be permitted to re-enroll in the study. A Patient Enrollment and Identification Code List must be maintained by the investigator.

Table 1. Schedule of visits and assessments

	Screening[1]	Treatment[2]: 28-day cycles Visit window during the treatment period is -4/+ 1 days	End of treatment EOT (discontinuation of treatment)[3]	Post treatment FU[4]	Survival follow-up Every 12 weeks [19]
Days	**-28 to -1**	**Day 1 of each 28-day cycle**			
Informed consent[5]	X				
Demography	X				
Inc./Exc. criteria	X				
Medical history	X				
BRAF mutational status	X				
Physical examination, height, weight[6]	X	X	X	X	
Vital signs	X	X	X	X	
Performance status (ECOG)	X	X	X	X	
Tumor assessment[7]	X	Every 8 weeks for the first 16 weeks, and then as standard of care with a minimum of every 12 weeks	X		
Tumor biopsy for ancillary study[8]	A fresh biopsy should be obtained at baseline and upon progression if feasible				
Cardiac imaging MUGA/ECHO	X	On Day 1 of cycle 2 and every 3 treatment cycles thereafter or as clinically indicated until discontinuation	X		
ECG[9]	X	As clinically indicated	X		
Hematology[10]	X	X	X	X	
Clinical chemistry[10]	X	X	X	X	
Blood sample for ancillary study[11]	Blood samples are to be taken at baseline and upon progression				
Serum pregnancy test[12]	X	X	X		
Dermatological evaluation[13]	X	Every 12 weeks	X	X	X
Ophthalmological exam	X	Every 3 months	X		
AEs, SAEs and AESIs[14]	X	Throughout the study	X	X	X
Concomitant medication[15]	X	Throughout the study	X		
Drug dispensing[16]		X			
Treatment accountability[17]		X	X		
Drug diary[18]		X	X		
Randomization		After “focal” disease progression on treatment with first-line vemurafenib and cobimetinib			

Notes:

Day 1 = first dose of vemurafenib and cobimetinib

[1] All screening/baseline assessments must be performed -28 to -1 days prior to the first administration of study drugs on Day 1. Results of tests or examinations (including tumor assessments) performed before obtaining informed consent and within 28 days prior to Day 1 may be used.

[2] All patients will be treated initially with first-line vemurafenib and cobimetinib. Upon disease progression, patients with non-focal progression will switch to second-line therapy with an anti-PD-1 agent (nivolumab or pembrolizumab). Patients with focal progression will be randomized to receive either vemurafenib + cobimetinib associated with local management (i.e. surgery, radiotherapy) or second-line treatment with an anti-PD-1 agent (nivolumab or pembrolizumab). Patients of both arms will have visits every 28 days. A window of 4 days prior to the scheduled visit date and 1 day after the scheduled visit date (- 4 days / + 1 days) is allowed for each visit from Cycle 2 onwards.

[3] End of Treatment Visit (EOT) will be performed when the patient discontinues treatments regardless of when it occurs.

[4] Follow up visit is to be performed within 28 days from discontinuation of treatments.

[5] Informed consent must be obtained prior to any study procedure including screening/baseline assessments.
[6] Height is measured only at screening.
[7] Radiological tumor assessments (CT/MRI chest/abdomen/pelvis along with brain CT/MRI for assessment of brain metastasis will be performed at baseline and every 8 weeks for the first 16 weeks of treatment, and then as per institutional standard of care thereafter but at a minimum of every 12 weeks and at the end of study visit. A window of +/- 5 days of scheduled visit is allowed to complete tumor assessments. If at any time during treatment phase there is suspicion of disease progression based on clinical or laboratory findings before the next scheduled assessment, an unscheduled tumor assessment should be performed.
[8]At baseline, tumor tissues may be obtained from archived samples for patients that cannot be biopsied.
[9] A 12-lead ECG is to be performed at screening, during the study and end of study visit and as clinically indicated.
[10] Hematology and biochemistry assessments do not need to be repeated on Day 1 if performed within 7 days; if the tests need to be repeated, the results must be known before the patient receives treatments to ensure that inclusion/exclusion criteria related to these tests are met.
[11] Blood samples are to be obtained before therapy with BRAF+MEK inhibitors and after progression.
[12] Serum pregnancy test to be performed within 7 days prior to Day 1, and on Day 1 of every cycle.
[13] Dermatology evaluation by a dermatologist must be performed at screening every 12 weeks, at the end of study visit if not performed within the previous 12 weeks and at the follow-up visit.
[14] During screening, AEs are not recorded in the eCRF unless they are SAEs related to protocol-mandated procedures. ALL AEs (including SAEs and AESIs) must be recorded from the time of first treatment administration. After the last treatment, any new, non-serious AEs that the investigator considers may be related to treatments should be reported up to 28 days after last dose. Any SAEs reported after last dose that the investigator considers may be related to treatments should be reported until the end of the study.
[15] All concomitant medications during the study started within 14 days prior to the screening visit and up to the end of study visit must be recorded.
[16] Drug dispensing applies only to patients taking vemurafenib and cobimetinib. Patients randomized to the control arm will be treated with second-line treatment as per clinical practice.
[17] Vemurafenib, cobimetinib and second-line treatment accountability will be performed at every study visit from Cycle 2 onwards and at the End of Study Visit.
[18] Patients will keep a diary to record ONLY those occasions when a dose of vemurafenib and/or cobimetinib was missed (morning or evening, each day of treatment). The patient will bring this diary with him/her to each study visit to allow missed doses to be recorded by the investigator.
[19]All patients will be followed up for 24 months after randomization or last dose of vemurafenib and cobimetinib (for non-randomized patients).

2.4.3 Clinical Assessments and Procedures

The following clinical assessments and procedures must be completed for all patients enrolled in this study at screening/baseline and/or during study visits. From Cycle 2 onwards, all assessments except for tumor evaluations must be performed within a window of 4 days prior to the scheduled visit date to one day after the scheduled visit date (- 4 days / + 1 day). A window of +/- 5 days will be applied to tumor evaluations. The visit and assessment schedule is shown in Table 1. Patients should be assessed prior to each cycle, and as necessary throughout participation in the study. Each treatment cycle has a duration of 28 days. The clinical assessments and procedures are outlined below and a schedule of when they are to be performed is shown in Table 1. Patients with non-focal progression will be followed for survival status only.

Screening/Baseline:

- Informed Consent
- Medical history (including demographics, relevant medical history, previous and current diseases, prior skin cancer history, therapies and procedures, all medications started within 14 days prior to screening visit). History should include any visual disturbances or symptoms
- Physical examination, height and weight
- Dermatological evaluation for Squamous Cell Carcinoma (SCC)
- Vital signs (blood pressure, heart rate, temperature, respiratory rate)
- Eastern Cooperative Oncology Group (ECOG) performance status
- Hematology and clinical chemistry
- Serum pregnancy test (within 7 days prior to commencement of dosing) for women of childbearing potential
- Tumor assessments including measurable and non-measurable lesions [baseline brain CT or MRI, CT/MRI Chest/Abdomen/Pelvis (CAP), bone scan if clinically indicated]
- BRAF V^{600} mutational status (if not already available) with a validated mutational test.
- 12-lead ECG
- Cardiac imaging
- Ophthalmological exam
- Concomitant therapy

- AEs, SAEs and AESIs
- Tumor tissue and peripheral blood samples for ancillary study (optional). Baseline tumor tissues will be obtained from fresh baseline biopsies performed in patients with easily accessible biopsy sites. Tumor tissues may be obtained from archived samples for patients that cannot be biopsied.

Treatment period

All patients will be treated initially with first-line vemurafenib and cobimetinib. During treatment with vemurafenib and cobimetinib, patients should undergo tumor assessments consisting of CT or MRI scans of the chest, abdomen, and pelvis. A brain CT/MRI should also be performed for assessment of brain metastasis. For patients with palpable/superficial lesions, clinical disease assessments by physical examination should be performed.

Patients with focal progression will be randomized to either continue treatment with vemurafenib and cobimetinib in addition to a local treatment (e.gs surgery, radiotherapy) or start treatment with a second-line treatment with an anti-PD-1 agent (nivolumab or pembrolizumab). Focal Progression is defined as the appearance or dimensional increase of new lesions that can be locally treated with surgery or radiotherapy. Randomized patients with focal progression will continue to be evaluated as indicated in Table 1. Patients with non-focal disease progression will switch to a second-line treatment with an anti-PD-1 agent (nivolumab or pembrolizumab) and will be followed-up for survival.

Patients who discontinue study drugs for any reason (e.g. AEs) other than disease progression will continue to be followed until disease progression. Follow-up will continue for 24 months after randomization or last dose of vemurafenib and cobimetinib (for non-randomized patients).

Patients will be given a diary on which to record ONLY those occasions when a dose of vemurafenib and/or cobimetinib will be missed (morning or evening, each day of treatment). The patient will bring this diary with him/her to each study visit to allow missed doses to be recorded by the investigator.

The following clinical assessments and procedures will be completed during the treatment periods (first line and following focal progression):

- Physical exam
- Dermatological evaluation
- Vital signs (blood pressure, heart rate, temperature, respiratory rate)
- ECOG PS

- Hematology and clinical chemistry
- Brain CT/MRI for assessment of brain metastasis. Radiological tumor assessments (CT/MRI chest/abdomen/pelvis and bone scan if clinically indicated) to assess extent of disease
- 12-lead ECG
- Cardiac imaging
- Ophthalmological exam
- Concomitant therapy throughout the study
- AEs, SAEs and AESIs
- Drug accountability throughout the study
- Serum pregnancy test

End of Treatment Visit (when patient discontinues study drugs)

The End of Study Visit (EOS) will be performed when the patient discontinues treatments regardless of when it occurs and the following assessments will be performed:

- Physical examination
- Dermatological evaluation
- Vital signs (blood pressure, heart rate, temperature, respiratory rate)
- ECOG performance status
- Hematology and clinical chemistry
- Serum pregnancy test
- Tumor assessments if not performed within the previous 8 weeks (CT/MRI CAP, CT/MRI of brain as clinically indicated) including assessment of any tumor lesions accessible by physical examination
- 12-lead ECG (if clinically indicated)
- Cardiac imaging (if not performed within the previous 16 weeks)
- Ophthalmological evaluation (if not performed within the previous 16 weeks)
- Concomitant therapy

- AEs, SAEs and AESIs

Follow up visit within 28 days from discontinuation of study drugs

The following assessments will be performed during the follow up visit:

- Physical examination
- Vital signs
- Hematology and clinical chemistry
- ECOG performance status
- Monitoring of AEs and SAEs
- Dermatological evaluation for evaluation of cutaneous SCC
- Follow up for disease progression for those patients who have discontinued study drug for any reason (i.e. AE) other than disease progression
- New anti-cancer therapy
- AEs, SAEs and AESIs

Survival follow-up

Patients will be followed up for survival every 12 weeks for up to 24 months after the last patient has been randomized. Patients who are not randomized will be followed up for survival every 12 weeks until the end of the study (i.e. 24 months after the last dose of vemurafenib and cobimetinib).

2.4.4 Tumor Response Criteria

Disease should be assessed at each visit, and until documented non-focal progression ascertained by the Investigator.

Tumor evaluation will be assessed by means of CT or MRI of the chest, abdomen and pelvis (CAP) and brain at screening/baseline (between Day -28 and -1), every 8 weeks for the first 16 weeks of treatment, and then as per institutional standard of care thereafter but at a minimum of every 12 weeks and at the end of study visit. A window of +/- 5 days of scheduled visit is allowed to complete tumor assessments.

Documentation of $BRAFV^{600}$ mutation-positive status in melanoma tumor tissue (archival or newly obtained tumor samples) must be obtained at screening by means of a validated mutation test.

Tumor responses will be assessed by the investigator according to Response Evaluation Criteria In Solid

Tumors (RECIST) (version 1.1) Criteria. Both measurable and non-measurable lesions will be assessed by the investigator. In case of Stable Disease (SD), measurements must indicate SD for at least 6 weeks. For assessing response in patients with measurable disease, the preferred radiologic tumor response assessment is a CT scan with oral and IV contrast. If IV contrast is contraindicated, a non-contrast chest CT will be done with abdominal/pelvic contrast enhanced MRI. If contrast enhanced MRI is contraindicated, then non-contrast MRI will suffice. CT/MRI scans of extremities may be done as appropriate in individual patients. PET scan, bone scan, and ultrasound are not adequate for RECIST response assessment. Patients should be assessed at designated times using a consistent imaging modality. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. If more than one method of assessment is used at baseline, select the most accurate method according to RECIST when recording data; in addition, this method should again be performed in all subsequent evaluations. Tumor measurements should be made by the same investigator/radiologist for each patient during the study to the extent that this is feasible. Objective responses by RECIST (Version 1.1) should be confirmed by repeat assessments at least 4 weeks after initial documentation of response. Clinical lesions will be considered measurable only when they are superficial and > 10 mm diameter as assessed using calipers (e.g. skin nodules). For skin lesions, documentation by color photography with ruler is required. A CT scan is the preferred modality for skin lesions and should be used whenever possible. For patients with palpable/superficial lesions, clinical disease assessments by physical examination should be performed throughout study treatment as clinically indicated.

After disease progression during treatment with vemurafenib and cobimetinib, patients will undergo tumor assessments: CT or MRI scans of the chest, abdomen, and pelvis should be performed. For patients with palpable/superficial lesions, clinical disease assessments by physical examination should be performed.

Focal Progression will be defined as the appearance or dimensional increase of lesions that can be treated locally with surgery or radiotherapy. Patients in focal progression will be randomized to either continue with treatment with vemurafenib and cobimetinib in addition to local treatment (e.g. surgery, radiotherapy) or start a second-line treatment.

2.4.5 Clinical Safety Assessments

Safety evaluations include assessments of Adverse Events (AE), clinical laboratory tests, vital sign measurements, physical examination, assessment of Eastern Cooperative Oncology Group (ECOG) performance status, dermatology evaluations, cardiac imaging, ECG, ophthalmic examination. The NCI CTC-AE (Version 4) will be used to evaluate the clinical safety of the treatments in this study. See Table

1 for a schedule of all safety assessments.

- **Adverse events**

Monitoring for adverse events will take place continuously throughout the study, starting from informed consent until the end of the study. Patients should be assessed for AEs throughout the study. During screening, AEs are not recorded in the eCRF unless they are SAEs related to protocol-mandated procedures.

- **Clinical laboratory tests**

Laboratory assessments for safety will be performed at local laboratories and are listed below:

- Hematology: hemoglobin, WBC, ANC, platelet count.
- Biochemistry: glucose, uric acid, creatinine, creatinine-clearance, sodium, potassium, bicarbonate (if routinely performed on venous blood samples), total bilirubin with direct and indirect fractions (if total bilirubin is elevated), alkaline phosphatase, Aspartate Aminotransferase (AST) [SGOT], Alanine Aminotransferase ALT [SGPT]) and LDH.
- Serum Pregnancy Test in women of childbearing potential (within 7 days prior to first administration of study drug).

- **Vital signs**

Vital signs consist of body temperature, seated blood pressure and heart rate, and respiratory rate. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes prior to dosing.

- **Physical examination**

A full physical examination will be performed at screening visit, whereas targeted exams will occur during the treatment and post-treatment periods according to the Investigator's observations and/or subject complaints on new or changed conditions. Patients should be asked specifically about skin and vision changes. For patients with palpable/superficial lesions, clinical disease assessments by physical examination should be performed throughout study treatment as clinically indicated.

Significant findings that were present prior to the signing of informed consent must be included in the Medical History CRF page. Significant new findings that begin or worsen from the time of first treatment administration must be recorded on the Adverse Event page of the eCRF.

- **ECOG performance status**

Eastern Cooperative Oncology Group (ECOG) performance status should be evaluated prior to any study-related procedures or assessments.

- **Dermatological evaluations**

Dermatological evaluation for Squamous Cell Carcinoma (SCC). Any suspicious lesions should be biopsied or resected and sent for pathologic examination. Please refer to vemurafenib Summary of Product Characteristics (SmPC) for details on dermatologic monitoring. Evaluations are to be performed at screening, every 12 weeks thereafter, at end of treatment and during follow-up.

- **ECG**

As vemurafenib is associated with concentration-dependent QTc prolongation, patients should undergo 12-lead ECG monitoring at screening/baseline, during the study and end of study as clinically indicated.

- **Cardiac imaging**

Decreases in Left Ventricular Ejection Fraction (LVEF) from baseline have been reported in patients receiving cobimetinib, with median time to first onset of events at 4 months (0.7-7 months). All patients should therefore undergo evaluation of LVEF, either by echocardiography (ECHO) or multiple gated ejection acquisition scan (MUGA) prior to treatment start and around day 1 of cycle 2, and at least every 3 treatment cycles thereafter or as clinically indicated until treatment discontinuation. Decrease in LVEF from baseline can be managed using treatment interruption, dose reduction or with treatment discontinuation.

- **Ophthalmological exam**

Serous retinopathy has been reported in patients treated with cobimetinib. Patients should be monitored for ocular toxicity every 3 months. Most events observed in clinical trials resolved or improved to asymptomatic Grade 1 following dose interruption or reduction.

Patients with a history of visual disturbances or symptoms at baseline need to undergo ophthalmologic examination prior to treatment start to evaluate the presence of retinal pathology, which may exclude these patients from this program. Ophthalmologic examination must be performed by a qualified ophthalmologist.

For patients reporting new or worsening visual disturbances during treatment with cobimetinib, an ophthalmologic examination is also required. If serous retinopathy is diagnosed, cobimetinib treatment should be withheld until visual symptoms improve to Grade ≤ 1. Serous retinopathy can be managed with treatment interruption, dose reduction or with treatment discontinuation (see section 5.4).

2.4.6 Ancillary biomarker study

The optional ancillary biomarker study will be performed on tumor tissue biopsies and peripheral blood samples.

- Tumor biopsies:

Tumor biopsies for this ancillary study will be required at baseline and upon progression when feasible. At baseline, tumor tissues will be obtained from fresh baseline biopsies performed in patients with easily accessible biopsy sites (subcutaneous and lymph nodes) and from archived samples for patients that cannot be biopsied.

Upon progression, fresh biopsies will be obtained for patients with accessible tumor lesions provided they have given their consent to participate in the biomarker study. Accessible lesions are defined as tumor lesions that can be easily biopsied i.e. cutaneous, sub-cutaneous and palpable lymph nodes. Failure to obtain sufficient tumor sample, after making best efforts, will not be considered a protocol violation. Lesions with the biggest change in size, based on interval evaluation, should be excised at time of progressive disease. See Appendix 2 for full details.

- Peripheral blood samples:

Peripheral blood mononuclear cell samples will be collected for the biomarkers study before therapy with BRAF+MEK inhibitors (baseline) and after progression.

Response/resistance to targeted agents will be measured by mutation analysis on circulating tumor DNA to assess new peripheral blood biomarkers. See Appendix 2 for full details.

3. STUDY POPULATION

3.1 Inclusion Criteria

A subject is eligible for the study if all of the following criteria are met:

Disease-specific inclusion criteria

1. Patients with histologically confirmed melanoma, either unresectable Stage IIIc or Stage IV metastatic melanoma, as defined by the American Joint Committee on Cancer 7th edition.
2. Patients previously untreated for metastatic melanoma.
3. Documentation of BRAF^{V600} mutation-positive status in melanoma tumor tissue (archival or newly obtained tumor samples) by a validated mutational test.

4. Adequate performance status to receive vemurafenib and cobimetinib therapy as determined by treating physician.

General inclusion criteria

5. Male or female patient aged ≥18 years
6. Able to participate and willing to give written informed consent prior to any treatment-related procedures and to comply with treatment guidance.
7. Adequate end-organ function, defined by the following laboratory results obtained within 14 days prior to the first dose of program drug treatment:
   a) Bilirubin ≤ 1.5 · the upper limit of normal (ULN).
   b) AST, ALT, and alkaline phosphatase ≤ 3 · ULN, with the following exceptions:
      - Patients with documented liver metastases: AST and/or ALT ≤5 · ULN.
      - Patients with documented liver or bone metastases: alkaline phosphatase ≤ 5 · ULN.
   c) Serum creatinine ≤1.5 · ULN or creatinine clearance (CrCl) ≥ 40 mL/min based on measured CrCl from a 24-hour urine collection or Cockroft-Gault glomerular filtration rate estimation.
8. Female patients of childbearing potential and male patients with partners of childbearing potential must agree to always use two effective forms of contraception during program therapy and for at least 6 months after completion of program therapy.
      - Please note that potential interactions between vemurafenib and hormonal contraceptives may decrease the effectiveness of hormonal contraceptives.
9. Negative serum pregnancy test prior to commencement of dosing in women of childbearing potential.
10. Patient should be able to swallow tablets.
11. Absence of any psychological, familial, sociological, or geographical condition that potentially hampers compliance with the treatment regimen; these conditions should be discussed with the patient before program entry.
12. Patient does not currently participate in other clinical trials.

3.2 Exclusion Criteria

A subject is excluded from the study if any of the following criteria are met:

Cancer-related exclusion criteria

1. Palliative radiotherapy within 7 days prior to the first dose of program treatment.
2. Patients with active malignancy (other than BRAF-mutated melanoma) or a previous malignancy within the past 3 years except for patients with resected melanoma, resected BCC, resected cutaneous SCC, resected melanoma *in situ*, resected carcinoma *in situ* of the cervix, and resected carcinoma *in situ* of the breast.

Exclusion criteria based on organ function

Ocular

3. Evidence of retinal pathology on ophthalmologic examination that is considered a risk factor for neurosensory retinal detachment / central serous chorioretinopathy (CSCR), retinal vein occlusion (RVO), or neovascular macular degeneration.
4. Systemic risk factor for RVO including uncontrolled glaucoma, uncontrolled hypercholesterolemia, hypertriglyceridemia or hyperglycemia.

Cardiac

5. History of clinically significant cardiac dysfunction, including the following:
   a) Current unstable angina.
   b) Symptomatic congestive heart failure of New York Heart Association class 2 or higher.
   c) History of congenital long QT syndrome or mean (average of triplicate measurements) QTcF ≥ 450 msec at baseline; presence of clinically significant ventricular or atrial dysrhythmias ≥ Grade 2.
   d) Uncontrolled hypertension ≥ Grade 2 (patients with a history hypertension controlled with anti-hypertensives to ≤ Grade 1 are eligible).
   e) Left ventricular ejection fraction (LVEF) below institutional lower limit of normal (LLN) or below 50%, whichever is lower.

General exclusion criteria

6. Current severe, uncontrolled systemic disease.
7. Major surgery or traumatic injury within 14 days prior to first dose of program treatment.
8. History of malabsorption or other condition that would interfere with absorption of program drugs.

9. Hypersensitivity to the active substance or to any of the excipients.

10. Pregnant or breastfeeding women.

3.3 Criteria for Premature Withdrawal

Every patient has the right to discontinue study participation at any time, for any reason. When applicable, patients should be informed of the circumstances under which their participation may be terminated by the investigator without their consent. The investigator may withdraw patients from the study in the event of intercurrent illness, AEs, treatment failure after a prescribed procedure, lack of compliance with the study and/or study procedures (e.g., dosing instructions, study visits), or any reason where it is felt by the investigator that it is in the best interest of the patient to be discontinued from the study. Any administrative or other reasons for withdrawal must be documented and explained to the patient.

Handling of Participant Withdrawals or Termination

Patients who discontinue from the study will be asked to return to the clinic within 28 days of the last dose of treatment for the follow-up visit and to be contacted every 12 weeks for at least 12 months for survival follow-up. If 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. A complete final evaluation at the time of the patient's withdrawal should be made with an explanation of why the patient is withdrawing from the study.

If the reason for removal of a patient from the study is an AE, the event is to be recorded on the CRF and the patient should be followed until the AE has resolved, if possible. All patients will be followed for safety for 28 days following the last dose of study medication until the end of the study.

4. INVESTIGATIONAL MEDICINAL PRODUCTS

4.1 Formulation, appearance, packaging and labeling

This is an open-label study and all study treatments, along with their packaging and labelling, have been approved by local Health Authorities.

- Vemurafenib (Zelboraf®)

Study drug packaging will bear a label with the identification required by local law, the protocol number, drug identification and dosage. Vemurafenib is supplied in 240 mg film-coated tablets for oral administration packed in blisters contained in boxes. For additional batch-specific instructions and

information see the packaging.

- Cobimetinib (Cotellic®)

Study drug packaging will bear a label with the identification required by local law, the protocol number, drug identification and dosage. Cobimetinib is supplied in 20 mg film-coated tablets for oral administration packed in blisters contained in boxes. For additional batch-specific instructions and information see the packaging.

- Control

Patients randomized to second-line treatment will be treated with an anti-PD-1 agent (nivolumab or pembrolizumab).

4.2 Product storage and stability

Investigational treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all investigational treatment should be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Medication labels will be in the local language and comply with the legal requirements of each country.

Vemurafenib is to be stored in a dry place in its original packaging and with the container kept tightly closed, as indicated on the study drug label. Patients will be requested to store vemurafenib at the recommended storage conditions noted on the label, out of the reach of children or other vulnerable persons.

Cobimetinib does not require any particular storage conditions.

4.3 Dosing and administration

Vemurafenib

Vemurafenib is taken on a 28-day cycle. Each dose consists of four 240 mg (960 mg) tablets twice daily for 28 consecutive days. The first dose should be taken in the morning and the second dose should be taken in the evening approximately 12 hours later. Each dose can be taken with or without a meal. Vemurafenib tablets should be swallowed whole with a glass of water and should not be chewed or crushed.

Missed doses

If a dose is missed, it can be taken up to 4 hours prior to the next dose to maintain the twice-daily regimen. Both doses should not be taken at the same time.

Cobimetinib

Cobimetinib is taken on a 28-day cycle. Each dose consists of three 20 mg tablets (60 mg) and should be taken orally, once daily for 21 consecutive days (Days 1 to 21-treatment period), followed by a 7-day break (Days 22 to 28-treatment break). Each subsequent treatment cycle should start after the 7-day treatment break has elapsed.

The dose should be taken in the morning with or without meal

4.4 Dose adjustments/modifications/delays

- **Vemurafenib**

Management of symptomatic adverse drug reactions (e.g. arthralgia, fatigue, rash, etc.) may require temporary interruption and/or dose reduction of vemurafenib. When dose reduction is needed, the dose is reduced from 960 mg twice daily to 720 mg twice daily initially, and to 480 mg twice daily if additional dose reduction is required. Posology adjustments resulting in a dose below 480 mg twice daily are not recommended. Dose escalation after dose reduction is generally not recommended unless under special circumstances i.e. increased likelihood of clinical benefit for the dose increase and no safety concerns. Dose increases above 960 mg twice daily will not be allowed. Dose modification will follow the indications in the table below.

Dose Interruption/Modification Criteria for Vemurafenib for any AEs

Grade (CTC-AE) [a]	**Recommended dose modification**
Grade 1 or Grade 2 (tolerable)	Maintain Vemurafenib at a dose of 960 mg twice daily.
Grade 2 (intolerable) or Grade 3	
1st occurrence of any grade 2 or 3 AE	Interrupt treatment until grade 0 – 1. Resume dosing at 720 mg twice daily (or 480 mg twice daily if the dose has already been lowered).
2nd occurrence of any grade 2 or 3 AE or persistence after treatment interruption	Interrupt treatment until grade 0 – 1. Resume dosing at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480 mg twice daily).
3rd appearance of any grade 2 or 3 AE or persistence after 2nd dose reduction	Discontinue permanently.
Grade 4	
1st occurrence of any grade 4 AE	Discontinue permanently or interrupt Vemurafenib treatment until grade 0 – 1. Resume dosing at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480 mg twice daily).
2nd occurrence of any grade 4 AE or persistence of any grade 4 AE after 1st dose reduction	Discontinue permanently.

[a] The intensity of clinical adverse events graded by the Common Terminology Criteria for Adverse Events v4.0 (CTC-AE).

For Grade 1 and tolerable grade 2 toxicities, patients may continue full dose. For intolerable Grade 2 toxicities or Grade 3 toxicities, dosing will be interrupted until resolution to Grade 1 or less and dose reductions in 240 mg decrements are required. On the third appearance of intolerable Grade 2 or Grade 3 toxicity despite two dose reductions, it is recommended that patients discontinue vemurafenib.

Exception will be granted for reversible laboratory abnormalities with no clinical sequelae and/or clinical significance in the opinion of the Investigator. For Grade 4 toxicities, patients should discontinue study treatment or, based on investigator judgement, interrupt until resolution to Grade 1 or less with dose reduction of 50% upon restarting study drug.

Patients who develop cutaneous Squamous Cell Carcinoma (cSCC) or any other skin lesions during the trial may choose to continue or discontinue from the trial in consultation with the investigator. If the patient elects to continue in the trial, definitive treatment (i.e. surgical excision) of any SCC is required.

Special consideration must be taken with any patient on study with an increase in QTc > 500 ms or change from baseline > 60 ms. If QTc exceeds 500 ms or the change from baseline is greater than 60 ms, vemurafenib treatment should be temporarily interrupted. QTc interval should be monitored weekly until it is less than 500 ms. Appropriate electrolyte (K+, Mg++, Ca++) evaluation should be performed, with any necessary corrections done, and cardiac risk factors (e.g. congestive heart failure, bradyarrhythmias) controlled. When QTc decreases to less than 500 ms, re-initiation of treatment may occur at one reduced dose level from 960 mg b.i.d. to 720 mg b.i.d. If a subsequent increase in QTc to >500 ms or change from baseline greater than 60 ms is observed, vemurafenib may be reduced to 480 mg bid. Permanent discontinuation of vemurafenib is recommended if QTc increase meets both criteria of >500 ms and >60 ms change from pre-treatment values or if QTc > 500 ms or change from baseline > 60 ms is observed on 2 separate prior occasions.

If a patient's dose has been interrupted for > 4 weeks due to an AE, the patient will be considered to have discontinued from the study. However, a temporary interruption of study drug of up to 8 weeks is allowed in case of tumor surgery or other safety or elective procedures in the best interest of the patient.

Treatment with vemurafenib must be interrupted prior to tumor surgery, radiotherapy or other procedures.

- **Cobimetinib**

Dose modification of cobimetinib is independent of vemurafenib dose modification. The Table below provides general guidance for cobimetinib dose modification.

Recommended cobimetinib dose modifications

Grade (CTC-AE)	**Recommended cobimetinib dose**
Grade 1 or Grade 2 (tolerable)	No dose reduction. Maintain dose of 60 mg once daily.
Grade 2 (intolerable) or Grade 3/4	
1st occurrence	Interrupt treatment until grade ≤ 1. Resume treatment at 40 mg (2 tablets) once daily.
2nd occurrence	Interrupt treatment until grade ≤ 1. Resume treatment at 20 mg (1 tablet) once daily.
3rd appearance	Consider permanent discontinuation.

Dose modification advice for left ventricular dysfunction

Permanent discontinuation of cobimetinib treatment should be considered if cardiac symptoms are attributed to the drug and do not improve after temporary interruption. Recommended dose modifications in patients with left ventricular ejection fraction (LVEF) decrease from baseline are shown in the table below.

Recommended dose modifications for cobimetinib in patients with (LVEF) decrease from baseline

Patient	**LEFV value**	**Dose modification**	**LVEF value following treatment break**	**Recommended daily dose**
Asymptomatic	≥ 50% (or 40-49% and < 10% absolute decrease from baseline)	Continue at current dose	NA	NA
	< 40% (or 40-49% and ≥ 10% absolute decrease from baseline)	Interrupt treatment for 2 weeks	< 10% absolute decrease from baseline	1st occurrence: 40 mg
				2nd occurrence: 20 mg
				3rd occurrence: permanent discontinuation
			< 40% (or ≥ 10% absolute decrease from baseline)	Permanent discontinuation
Symptomatic	NA	Interrupt treatment for 4 weeks	Asymptomatic and < 10% absolute decrease from baseline	1st occurrence: 40 mg
				2nd occurrence: 20 mg

				3rd occurrence: permanent discontinuation
			Asymptomatic and < 40% (or ≥ 10% absolute decrease from baseline)	Permanent discontinuation
			Symptomatic regardless of LVEF	Permanent discontinuation

Vemurafenib treatment can be continued when cobimetinib treatment is modified, if clinically indicated.

- **Dose modification advice for cobimetinib when used with vemurafenib**

Liver laboratory abnormalities

For Grade 1 and 2 liver laboratory abnormalities, cobimetinib and vemurafenib should be continued at the prescribed dose.

Grade 3: Cobimetinib should be continued at the prescribed dose. The dose of vemurafenib may be reduced as clinically appropriate. Please refer to the vemurafenib SmPC.

Grade 4: Cobimetinib treatment and vemurafenib treatment should be interrupted. If liver laboratory abnormalities improve to Grade ≤1 within 4 weeks, cobimetinib should be restarted at a dose reduced by 20 mg and vemurafenib at a clinically appropriate dose, per its SmPC.

Cobimetinib treatment and vemurafenib treatment should be discontinued if liver laboratory abnormalities do not resolve to Grade ≤1 within 4 weeks or if Grade 4 liver laboratory abnormalities recur after initial improvement.

Creatine phosphokinase (CPK) elevations

Cobimetinib dosing does not need to be modified or interrupted to manage asymptomatic CPK elevations.

Photosensitivity

Grade ≤2 (tolerable) photosensitivity should be managed with supportive care. Grade 2 (intolerable) or Grade ≥3 photosensitivity: cobimetinib and vemurafenib should be interrupted until resolution to Grade ≤1. Treatment can be restarted with no change in cobimetinib dose. Vemurafenib dosing should be reduced as clinically appropriate, please refer to its SmPC for further information.

Rash

Rash events may occur with either cobimetinib or vemurafenib treatment. The dose of cobimetinib and/or

vemurafenib may be either temporarily interrupted and/or reduced as clinically indicated. Additionally, Grade ≤2 (tolerable) rash should be managed with supportive care and cobimetinib dosing can be continued without modification. Grade 2 (intolerable) or Grade ≥3 acneiform rash: general dose modification recommendations in the AE Table above for cobimetinib should be followed. Vemurafenib dosing can be continued when cobimetinib treatment is modified (if clinically indicated). Grade 2 (intolerable) or Grade ≥3 non-acneiform or maculopapular rash: cobimetinib dosing can be continued without modification if clinically indicated. Vemurafenib dosing may be either temporarily interrupted and/or reduced, please refer to its SmPC for further information.

QT prolongation

If during treatment the QTc exceeds 500 msec, please refer to the vemurafenib SmPC (section 4.2) for dose modifications for vemurafenib. No dose modification of Cotellic is required when taken in combination with vemurafenib.

See the Summary of Product Characteristics for more details about vemurafenib and cobimetinib.

4.5 Duration of Therapy

Treatment with study drug continues until general (non-focal) disease progression or unacceptable toxicity (adverse event related to study drug), or the subject meets other criteria for discontinuation of study drug outlined in the previous section.

4.6 Accountability, assessment of compliance and destruction of the drugs

The investigator is responsible for the control of drugs under investigation. Adequate records for the receipt (e.g. Drug Receipt Record) and disposition (e.g. Drug Dispensing Log) of the study drug must be maintained. Accountability and patient compliance will be assessed by maintaining adequate "drug dispensing" and return records.

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

- Documentation of drug shipments received from Roche (date received, quantity and batch number)
- Disposition of unused study drug not dispensed to patient

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

- Identification of the patient to whom the study medication was dispensed

- Date(s), quantity and batch number of the study medication dispensed to the patient
- Date(s), quantity and batch number of the study medication returned by the patient

All records and drug supplies must be available for verification by the Monitor at every monitoring visit. Patients will be asked to return all used and unused drug supply containers at the end of each cycle of treatment as a measure of compliance.

This inventory must be available for verification by the Monitor. Patient compliance will be assessed by maintaining adequate study drug dispensing records. The investigator is responsible for ensuring that dosing is administered in compliance with the protocol.

Used and unused investigational product will be destroyed locally/returned to Roche.

5. STATISTICAL CONSIDERATIONS

5.1 Statistical and analytical plan

The final analysis will be performed when randomized patients have been followed up for survival for a minimum of 24 months after the last patient has been randomized or after the observation of the 38th death in the randomized cohorts, whichever occurs first.

5.2 Statistical hypotheses

The primary efficacy endpoint is OS in patients with focal progression.

The distribution of OS will be estimated using the Kaplan-Meier method. The median OS along with 80% confidence intervals will be presented by treatment group. The primary efficacy analysis will be the comparison of the distribution of OS between the two treatment groups using a log-rank test at two-sided 20% level of significance, i.e.,

H_0: $S_{\text{Combo+Local treatment}}(t) = S_{\text{Second Line}}(t)$

will be tested against the one-sided alternative hypothesis

H_{a1}: $S_{\text{Combo+Local treatment}}(t) > S_{\text{Second Line}}(t)$,

where $S_{\text{Combo+Local treatment}}(t)$ is the survival distribution function of OS in the vemurafenib and cobimetinib plus local treatment arm and $S_{\text{Second Line}}(t)$ is the survival distribution function of OS in the SOC second line. A Cox proportional hazard model will be used to estimate the hazard ratio (HR) of OS, along with 80% confidence interval (see Section 6.4.2).

5.3 Analysis datasets

Full Analysis Set

The Full Analysis Set (FAS) comprises all patients with focal progression to whom treatment has been assigned by randomization. According to the intent to treat principle, patients will be analyzed according to the treatment they have been assigned to during the randomization procedure.

Per Protocol Set

The Per-Protocol Set (PPS) consists of a subset of patients in the FAS who received at least one dose of the randomized treatment and had no major protocol deviation. Protocol deviations leading to exclusion from the PPS will be defined in the Statistical Analysis Plan.

Safety Set

The Safety Set consists of all patients with focal progression who received at least one dose of study treatment or second-line treatment after randomization. Patients who did not take at least one dose of study treatment or second-line treatment will not be included in the safety set. Patients will be analyzed according to the treatment they actually received.

Non-focal Progression Set

The Non-focal Progression set consists of all patients who received at least one dose of vemurafenib + cobimetinib treatment in first-line treatment, experienced a non-focal progression and were therefore not randomized.

5.4 Description of statistical methods

All data collected in this study will be listed and summarized as appropriate as described below. Data from all sites will be pooled and summarized.

Continuous data will be summarized by mean, standard deviation (SD), median, first and third quartiles, minimum and maximum. Categorical data will be presented by absolute and relative frequencies (n and %) or contingency tables.

All statistical tables, listings, figures and analyses will be performed by means of SAS® release 9.4 or later (SAS Institute, Inc., Cary, NC, USA).

Two-sided alpha level 0.2 will be considered. No alpha level adjustment will be carried out for primary and secondary outcome variables.

5.4.1 Analysis of the primary efficacy endpoint

The efficacy analysis will be performed based on the FAS as primary analysis and on the PPS as supportive analysis.

Overall Survival (OS)

Overall survival of patients with focal progression is defined as the time, in months, from randomization to the date of death from any cause. If a patient is not known to have died, survival time will be censored at the date of last contact ("last known date alive").

Overall survival will be compared between treatment groups using a log-rank test procedure with a two-sided α =0.2 level. The OS function for each treatment group will be estimated using the Kaplan-Meier product-limit method. Median and corresponding two-sided 80% confidence intervals will be computed by treatment group. Kaplan-Meier plots of OS will be presented.

A Cox proportional hazard model for OS with treatment arm as single factor will be used to estimate the hazard ratio of vemurafenib and cobimetinib plus local treatment to second-line SOC and its corresponding 80% confidence interval.

5.4.2 Analysis of the secondary efficacy endpoints

Progression Free Survival (PFS)

The PFS analysis will be performed on the FAS.

Progression free survival of patients with focal progression is defined as the time, in months, from randomization to the date of the first documented tumor progression or death due to any cause, whichever comes first. Clinical deterioration will not be considered progression. For subjects who neither progress nor die, time will be censored at the date of their last tumor assessment. For subjects who start a new anti-tumor treatment, time will be censored at the date of the start of the new treatment. For a randomized subject who does not have any post-randomization tumor assessments and who has not died, time will be censored at the randomization date.

Progression free survival will be compared between treatment groups using a log-rank test procedure with a two-sided α =0.2 level. The PFS function for each treatment group will be estimated using the Kaplan-Meier product-limit method. Median and two-sided 80% confidence intervals (CI) for median PFS will be computed by treatment group. Kaplan-Meier plots of PFS will be presented.

A Cox proportional hazard model for PFS with treatment arm as single factor will be used to estimate the hazard ratio of vemurafenib and cobimetinib plus local treatment to second-line SOC and its corresponding

80% confidence interval.

Absolute frequencies and proportions of patients with tumor progression or all-cause death will also be provided.

Overall Survival (OS) of patients with non-focal progression

The survival analysis of patients with non-focal progression will be performed on the Non-focal Progression Set.

Overall survival of patients with non-focal progression is defined as the time, in months, from date of non-focal progression to first-line to the date of death from any cause. If a patient is not known to have died, survival time will be censored at the date of last contact ("last known date alive"). The OS function will be estimated using the Kaplan-Meier product-limit method. Median and corresponding two-sided 80% confidence intervals will be computed. A Kaplan-Meier plot of OS will be presented.

Overall survival results of patients with non-focal progression will be descriptively compared with OS results of patients with focal progression (i.e. primary efficacy endpoint). No statistical test will be foreseen for this comparison.

5.4.3 Safety analysis

Safety analyses will be conducted on the Safety Set and will be reported by actual treatment group and on the Non-focal Progression Set.

Adverse events

AEs will be assessed according to the Common Terminology Criteria for AEs (CTCAE version 4).

The incidence of AEs will be tabulated by MedDRA System Organ Class and Preferred Term. The incidence of AEs will also be summarized by system organ class, preferred term and severity (based on CTCAE grades). The same analysis will be repeated for SAEs regardless of drug relationship, for drug related SAEs, AEs with CTCAE grade 3 or 4, AEs of special interest, AEs leading to discontinuation of study treatment and for drug related AEs. AEs for which relationship to study drug is not specified will be considered treatment-related. Deaths reportable as SAEs will be listed by patient and tabulated by type of AE.

Laboratory parameters

Categorization of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4 or according to normal ranges for those parameters without available CTCAE grading. The calculation of CTCAE grades will be based purely on the observed

laboratory values; clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests where grades are not defined by CTCAE v4, results will be graded by the low/normal/high (low and high) classifications based on laboratory normal ranges.

The following by-treatment summaries will be generated separately for hematology, biochemistry and urinary laboratory tests:

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each patient will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value.
- Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value for laboratory tests where CTCAE grades are not defined.

Listings of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges will also be generated.

Other safety data

ECGs, physical examinations, vital signs and ECOG PS will be listed and summarized by treatment arm.

ECG

- Shift table baseline to worst on-treatment result
- Listing of ECG evaluations for all patients with at least one abnormality
- Change from baseline QTcF

Physical examination

- Shift table baseline to worst on-treatment result

Vital signs

- Table with descriptive statistics at baseline, one or several post-baseline time points and change from baseline to this/these post-baseline time points

ECOG PS

- Shift tables comparing the baseline PS with the worst post-baseline result

5.4.4 Baseline descriptive statistics

All data about patient demographics and baseline characteristics will be summarized, overall and by treatment group, by means of descriptive statistics for all patients enrolled in the study (i.e. patients who received at least one dose of first-line vemurafenib and cobimetinib treatment).

A complete description of patient disposition will be provided, overall and by treatment group specifying the number of randomized patients, number of patients at each visit, completed and discontinued patients, and the reason for the discontinuation.

The analysis populations will be described and the reasons for excluding the patient from any analysis set will be provided with the number of protocol violators per each criterion.

Medical history data will be presented by MedDRA System Organ Class and Preferred Term.

5.4.5 Treatments

The Safety set and the Non-focal progression Set will be used for the following analyses.

Investigational treatment

Duration of study treatment, cumulative dose, average daily dose, actual dose intensity and relative dose intensity of each of the components of study treatment will be summarized. The number of patients with dose changes/interruptions will be presented along with the reasons for the dose change/interruptions.

Concomitant treatments

Concomitant medications or procedures and significant non-drug therapies taken concurrently with the study treatment will be listed and summarized by WHO Anatomical Therapeutic Chemical (ATC) Class, Preferred Term and treatment arm. These summaries will include medications starting on or after the start of study treatment or medications starting prior to the start of study treatment and continuing after the start of study treatment. Any prior medication or significant non-drug therapy starting and ending prior to the start of study treatment will be listed.

5.4.6 Planned interim analyses

No formal interim analysis is planned.

5.4.7 Exploratory analysis

For sequencing and point mutation calling, coverage and sequencing statistics will be determined using Picard CalculateHsMetrics and Picard CalculateInsertSizeMetrics. Non-synonymous mutations will be annotated using Oncotator (http://www.broadinstitute.org/oncotator/). Associations with clinical and

pathological variables will be evaluated using either Fisher's exact tests or Freeman–Halton tests. P-values less than 0.05 will be considered statistically significant. All the analyses will be carried out using the statistical software STATA 12® (StataCorp LP, Texas, USA).

5.5 Sample size

The present phase II study is aimed at providing the rationale for a phase III efficacy trial of adequate size assessing the efficacy of dual target inhibition beyond focal progression. Consequently, an alfa error rate of 0.2 (two-sided) will be used. The expected OS of patients with BRAF+ metastatic melanoma after a 1st focal progression is difficult to estimate due to the lack of published data on this specific subset of patients. However, the survival experience of these patients can be reasonably considered to be intermediate between that of BRAF+ patients in 1st line treatment with combined BRAF and MEK inhibition and the post-progression survival of the same patients, i.e. at approximately 1.5 years of median survival. With 120 patients enrolled over a period of 12 months, and a total of 60-70 patients randomized into the II line study in patients with focal progression, 38 deaths are expected in both groups combined with a 2-year follow-up after randomization. With 38 events, the study has 80% power to detect, with an alfa error rate of 0.2 (two-sided), a statistical significance difference in favor of the experimental arm corresponding to a Hazard Ratio of 0.5.

5.6 Enrollment and randomization

Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.) that is assigned by the system automatically when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. Once assigned, the Subject No. must not be reused for any other subject and the Subject No. for that individual must not be changed.

Treatment assignment/randomization

Patients will be assigned, after focal progression, to one of the two treatment arms (i.e. vemurafenib and cobimetinib plus local treatment or SOC second line treatment) in a 1:1 ratio.

The randomization numbers will be generated using procedures that ensure that treatment assignment is unbiased. A patient randomization list will be produced using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms.

After focal progression, patients will be randomized via an Interactive Web Response System (IWRS) to

one of the treatment arms. The IWRS will assign a randomization number to the patient, which will be used to link the patient to a treatment arm. The randomization number will be used by the system only to assign patients to the treatment arms but will not be communicated to the user.

6. CLINICAL MONITORING

Clinical site monitoring will be conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial complies with the currently approved protocol, with GCP, and with applicable regulatory requirements.

Monitoring for this study will be performed by a Contract Research Organization (CRO).

Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

Independent audits may be conducted to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the CMP.

7. SAFETY INSTRUCTIONS AND GUIDANCE

7.1 Warning and precautions

Investigators and patients should be aware of the risks of photosensitivity reactions and squamous cell carcinoma (SCC).

Mild to severe photosensitivity was reported in several patients in the Phase I study who received doses of Vemurafenib that ranged from 240 to 1120 mg b.i.d. All patients should be advised to avoid prolonged sun exposure while taking Vemurafenib and for at least 5 days after study drug discontinuation. Patients should also be advised to use a broad-spectrum sunscreen of at least SPF >30 to help protect against sunburn. For acneiform rash, investigators should consider treatment with minocycline.

A detailed surveillance plan for SCC is foreseen, which includes a thorough skin evaluation by a dermatologist for all patients who participate in the study. A full skin examination is requested at baseline and every 12 weeks while on study, when patient discontinues study drug and at the follow-up visit (28 days after discontinuing study drug and every 12 weeks for 12 months for long-term follow-up).

Any lesion at baseline or during treatment clinically suspected of representing cutaneous Squamous Cell Carcinoma (cSCC), basal cell carcinoma, actinic keratosis, keratoacanthoma or other skin conditions

identified by the dermatologist should be treated as per local standard of care.

Owing to the possible tumor biopsy requirement (for screening or evaluation of suspicious skin lesions) in this study, risks such as infection of the surgical site, excessive bleeding, or injury to adjacent tissues, should be considered for patients who undergo tumor tissue biopsies.

Concomitant medications

Due to the underlying illness and the frequency of co-existent medical conditions in this patient population, all concomitant medication or treatment required by the patient will be at the discretion of the treating physician. Potential drug–drug interactions during treatment with vemurafenib and/or cobimetinib are however possible and are discussed here below.

- Vemurafenib

Medications primarily metabolized by CYP450 1A2, 3A4 and 2C9 enzymes, as well as those that strongly inhibit or induce the CYP 3A4 enzyme, should be used with caution when co- administered with Vemurafenib.

Appendix 1 includes a non-exhaustive list of typical examples of CYP1A2 and CYP3A4 substrates and CYP3A4 inducers and inhibitors.

Results from an *in vivo* drug-drug interaction study in patients with cancer demonstrated that vemurafenib is a moderate CYP1A2 inhibitor, a weak CYP2D6 inhibitor and a CYP3A4 inducer. Coadministration of vemurafenib increased the AUC of caffeine (CYP1A2 substrate) 2.6-fold and increased the AUC of dextromethorphan (CYP2D6 substrate) by 47%, while it decreased the AUC of midazolam (CYP3A4 substrate) by 39%. Concomitant use vemurafenib with agents with narrow therapeutic windows that are metabolized by CYP1A2, CYP2D6 and CYP3A4 is not recommended as vemurafenib may alter their concentrations. If coadministration cannot be avoided, exercise caution and consider a dose reduction of the concomitant CYP1A2 and CYP2D6 substrate drug.

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

Based on *in vitro* data, vemurafenib is a substrate of CYP3A4, and therefore concomitant administration of strong CYP3A4 inhibitors or inducers may alter vemurafenib concentrations. Strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) and inducers (e.g., phenytoin, carbamazepine, rifampin,

rifabutin, rifapentine, phenobarbital) should be used with caution when coadministered with vemurafenib.

- Cobimetinib

Concurrent use of strong CYP3A inhibitors during treatment with Cobimetinib should be avoided. Caution should be exercised if a moderate CYP3A4 inhibitor is co-administered with cobimetinib. If concomitant use with a strong or moderate CYP3A inhibitor is unavoidable, patients should be carefully monitored for safety and dose modifications applied if clinically indicated.

7.2 Adverse Events and Laboratory Abnormalities

7.2.1 Adverse Events (AEs)

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

7.2.2 Severity

Severity of all AEs will be graded according to the NCI Common Terminology Criteria for Adverse Events v 4.0 (CTCAE v 4.0; most recent sub-version) on a five-point scale (Grade 1 to 5) and reported in detail on the CRF.

CTCAE grades are as follows:

Grade 1 Mild Discomfort noticed but no disruption of normal daily activity

Grade 2 Moderate Discomfort sufficient to reduce or affect daily activity. No treatment or medical intervention is indicated although this could improve the overall well-being or symptoms of the patient

Grade 3 Severe Inability to work or perform normal daily activity; treatment or medical intervention is indicated in order to improve the overall wellbeing or symptoms; delaying the onset of treatment is not putting the survival of the patient at direct risk.

Grade 4 Life threatening/disabling. An immediate threat to life or leading to a permanent mental or physical conditions that prevents work or performing normal daily activities; treatment or medical intervention is required in order to maintain survival.

Grade 5 Death AE resulting in death.

7.2.3 Drug AE relationship

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

Yes or No

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

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

– Reasonable temporal association with drug administration

– It may or may not have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.

– Known response pattern to suspected drug

– Disappears or decreases on cessation or reduction in dose

– Reappears on re-challenge

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

– It does not follow a reasonable temporal sequence from administration of the drug.

– It may readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.

– It does not follow a known pattern of response to the suspected drug.

– It does not reappear or worsen when the drug is re-administered.

7.2.4 Serious Adverse Events

A serious adverse event (SAE) is any experience that suggests a significant hazard, contraindication, side effect or precaution. An SAE is any AE that at any dose fulfills at least one of the following criteria:

– is fatal; (results in death; NOTE: death is an outcome, not an event)

– is Life-Threatening (NOTE: the term "Life-Threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe).

– required in-patient hospitalization or prolongation of existing hospitalization;

– results in persistent or significant disability/incapacity;

– is a congenital anomaly/birth defect;

– is medically significant or requires intervention to prevent one or other of the outcomes listed above

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

Adverse Events of Special Interest (Immediately reportable to the Sponsor)

The following Adverse Events of Special Interest (AESI) even if assessed as non-serious must be reported to Sponsor within 24h of the Investigator becoming aware of the event (expedited reporting as described in Section 7.5.2).

Combined list of cobimetinib plus vemurafenib AESI:

- Grade 1-4 serous retinopathy
- Any Grade retinal vein occlusion
- Grade ≥ 2 Left ventricular dysfunction
- Rhabdomyolysis/Grade ≥3 CPK elevation including elevations of CPK-MM in conjunction with other laboratory evidence (aldolase and urine myoglobin), and clinical feature consistent with rhabdomyolysis (such as muscle pain, signs of renal failure, dark red or brown urine)
- Grade ≥3 hemorrhage event, or any Grade cerebral hemorrhage
- Grade ≥3 Rash
- Grade ≥3 Diarrhea
- Grade ≥3 Photosensitivity
- Events suggestive of Drug Induced Liver Injury or other Grade ≥3 hepatotoxicity
- AEs potentially associated with prolongation of cardiac repolarization
- Non-cutaneous squamous cell carcinoma
- Skin cancers
- Gastrointestinal polyps
- Any new or worsening malignancy including progression of RAS mutant malignancy, cuSCC, new primary melanoma, basal cell carcinoma (with or without radiation sensitization determined per protocol

design or inclusion/exclusion)

- Potential drug-induced liver injury as defined by Hy's Law:
  - Treatment-emergent ALT or AST > 3 × baseline value in combination with total bilirubin > 2 × ULN (of which ≥ 35% is direct bilirubin)
  - Treatment-emergent ALT or AST > 3 × baseline value in combination with clinical jaundice
- Suspected transmission of an infectious agent by the study treatment, as defined below:

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

7.2.5 Progression of Underlying Malignancy

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

Symptomatic deterioration may occur in some patients. In this situation, progression is evident in the patient's clinical symptoms, but is not supported by the tumor measurements, or the disease progression is so evident that the investigator may elect not to perform further disease assessments. In such cases, the determination of clinical progression is based on symptomatic deterioration. These determinations should be a rare exception, as every effort should be made to document the objective progression of underlying malignancy. If there is any uncertainty about an AE being due only to the disease under study, it should be reported as an AE or SAE

7.3 Follow-up of AEs (28 days post discontinuation of study drugs and every 12 weeks until 24 months for long term follow up)

After 28 days from the last dose of study drugs, continue to follow up AEs as follows:

Related AEs: Follow until one of the following occurs:

– Resolved or improved to baseline

– Relationship is reassessed as unrelated

– Death

– Start of new anti-cancer regimen

– Investigator confirms that no further improvement can be expected

– Clinical or safety data is no longer collected, or final database closure

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

– Resolved or improved to baseline

– Severity improved to Grade 2

– Death

– Start of new anti-cancer regimen

– Investigator confirms that no further improvement can be expected

– Clinical or safety data is no longer collected, or final database closure

Unrelated Grade 1 or Grade 2 AEs: follow up until 28 days after last dose of study drugs and every 12 weeks until 12 months for long-term follow up. The outcome of each AE must be recorded on the CRF.

Long Term Safety Follow up Visits

After treatment discontinuation, patients will continue to be followed for the occurrence of second primary malignancies and survival status every 12 weeks for 24 months after the last patient is randomized, or until the occurrence of one of the following: death, withdrawal of consent, or lost to follow up.

The following information will be collected in the CRFs every 12 weeks during this follow-up:

- Date of follow up assessment for a second primary malignancy
- Type of malignancy
- Histology of malignancy
- Date of diagnosis (histologically confirmed locally)
- Survival status

This information can be collected during a routine clinic visit, from the patient medical records, or by

telephone (call from treating physician (investigator in the study) to the patient and/or other health care providers involved in the patient's care).

7.4 Laboratory Test abnormalities

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

Any laboratory result abnormality fulfilling the criteria for an SAE/AESI should be reported as such, in addition to being recorded as an AE in the CRF.

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

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

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

7.4.1 Follow-up of Abnormal Laboratory Test Values

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

7.5 Handling of Safety Parameters

7.5.1 Reporting of AEs

Information about all adverse events, whether volunteered by the patient, discovered by investigator questioning, or detected through physical examination, laboratory test or other means will be collected on the Adverse Event CRF page, documented in the patient's medical records, and followed as appropriate.

7.5.2 Reporting of SAEs/AESI (immediately reportable)

Any SAEs / AESIs (as defined in section above) which occurs during the course of the study from the

enrollment visit (start of study screening procedures), including long term follow-up must be reported to the sponsor within 24 hours of the investigator becoming aware of the event (expedited reporting). The following proviso applies:

- During the screening period, after written informed consent has been signed but prior to initiation of study drug, only SAEs related to protocol procedures will be reported.
- From the first administration of vemurafenib and cobimetinib, all SAEs and AESIs must be reported until 28 days after the last dose of study drug. Related SAEs must be collected and reported regardless of the time elapsed from the last study drugs administration, even if the study has been closed.

The investigator must complete the SAE Reporting Form on the eCRF or, in case of technical issues, send it via fax or email to the Pharmacovigilance Officer delegated by Sponsor indicated below within 24 hours after learning of the event.

CRO Pharmacovigilance Officer: Dr Riccardo Chisci, OPIS s.r.l. Email: all_phv@opis.it Fax: +39 0362 633622

7.6 Pregnancy

A female patient must be instructed to stop taking vemurafenib and cobimetinib immediately inform the investigator if she becomes pregnant during the study. The investigator should report all pregnancies within 24 hours using the pregnancy section of the eCRF or, in case of technical issues, by sending it to the Pharmacovigilance Officer indicated in Section 7.5.2. The investigator should counsel the patient and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

Pregnancies occurring up to 6 months after the completion of the study medication must also be reported to the Pharmacovigilance Officer. Pregnancy occurring in the partner of a male patient participating in the study should be reported to the Pharmacovigilance Officer immediately (no more than 24 hours after learning of the pregnancy). The partner should be counseled, the risks of continuing the pregnancy should be discussed, as well as the possible effects on the fetus. Monitoring of the pregnant partner should continue until conclusion of the pregnancy.

8. SOURCE DOCUMENTS AND ACCESS TO DATA/SOURCE DOCUMENTS

Each participating site will maintain appropriate medical and research records for this trial, in compliance

with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants. Each site will permit authorized representatives of Regulatory Agencies to examine (and when permitted by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant files and records kept at the pharmacy, at the laboratories, and medical-technical departments involved in the clinical trial.

The eCRF will not be the only record of the patient's participation in the study in order to ensure that anyone who accessed the patient's medical record would have adequate knowledge that the patient is participating in the trial.

9. QUALITY ASSURANCE AND QUALITY CONTROL

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The investigational site will provide direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.

10. ETHICS

This clinical study shall be implemented and reported in accordance with the ICH Guidelines for Good Clinical Practice, all applicable local regulations and with the ethical principles laid down in the Declaration of Helsinki.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the relevant Independent Ethics Committee (IEC) and Competent Authority (CA) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IEC and or CA before

the changes are implemented to the study. All changes to the consent form will be IEC and/or CA approved; a determination will be made regarding whether previously consented participants need to be re-consented.

10.1 Informed consent

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to enrolment in the trial and before any study related procedure takes place.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IEC-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.2 Participant and data confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the Sponsor and their representatives. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

The study monitor, other authorized representatives of the Sponsor, representatives of the IEC or pharmaceutical company supplying study product(s) may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and

pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IEC and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will not include the participant's contact details or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites will be secured and password protected.

10.3 Research Use of Stored Human Samples, Specimens or Data

Samples and data collected under this protocol may be used to study melanoma, unless otherwise defined by the local laws and legislation of the participating countries.

Samples and data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.

Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

10.4 Insurance

Prior to the start of the trial, the Sponsor will ensure that adequate insurance for patients is in place covering losses due to death or injury resulting from the trial, in accordance with applicable laws and regulations. In addition, the Sponsor will ensure that adequate insurance is in place for both investigator(s) and Sponsor to cover liability pertaining to death or injury resulting from the trial. The Investigator(s) will remain responsible towards the Sponsor of any fault or misconduct regarding the performance of the Study.

11. DATA HANDLING AND RECORD KEEPING

11.1 Data collection and management

- Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Form (eCRF) using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the Electronic Data Capture (EDC) system until they are trained.

Web-based software will be used and no installation procedure is needed. Each site-qualified personnel will be allowed to access the eCRF by means of a 'login mask' requiring Username and Password and may read, modify and update only the information reported at his or her site. Each page reports site code and patient code.

On-line validation programs will check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer to the CRO working on behalf of the Sponsor. The Investigator will certify that the data entered in the eCRF are complete and accurate.

After database lock, the investigator will receive a CD-ROM of patient data for archiving at the investigational site.

- Database management and quality control

The CRO working on behalf of the Sponsor will review the data entered in the eCRF by investigational staff for completeness and accuracy and instruct site personnel to make any necessary corrections or additions. The Data Manager will perform the cleaning session by reviewing the warning messages raised by on-line checks and by running post-entry checks by means of validation programs and data listings specific for the study. If clarifications are needed, the Data Manager will raise queries by means of data query forms through the web application. Designated investigator site staff will be required to respond to queries and the Data Manager will make the correction to the database according to the responses.

Data collection and query flows as well as the on-line and off-line checks are detailed in the Data Management Plan and Data Validation documents.

Concomitant medications and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA).

Randomization codes and data about the study drug are tracked using the eCRF. The system is supplied by OPIS, who also manages the database.

The occurrence of any protocol deviations will be checked and the database will be locked and made available for data analysis after these actions have been completed and the database has been declared complete and accurate.

11.2 Study records retention

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6-R2 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than twenty five (25) years from the completion of the study unless the Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines. The subjects' medical files will be archived in accordance with the national laws.

11.3 Protocol deviations

A protocol deviation is any noncompliance with the clinical trial protocol or GCP requirements. The noncompliance may be on the part of either the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site to use continuous vigilance to identify and report deviations. All deviations must be addressed in study source documents.

12. PUBLICATION

This study will ensure that the public has access to the published results of the research.
The International Committee of Medical Journal Editors (ICMJE) policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies.

13. References

- Ascierto P., Minor D., Ribas A et al. (2013) Phase II trial (BREAK-2) of the BRAF inhibitor dabrafenib (GSK2118436) in patients with metastatic melanoma. J Clin Oncol; 31: 3205–3211.
- Chapman P., Hauschild A., Robert C et al. (2011) Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med; 364: 2507–2516
- Davies H., Bignell G., Cox C. et al. (2002) Mutations of the BRAF gene in human cancer. Nature; 417: 949–954.
- Eroglu Z, Ribas A. (2016) Combination therapy with BRAF and MEK inhibitors for melanoma: latest evidence and place in therapy. Ther Adv Med Oncol; 8(1): 48–56.
- Hauschild A., Grob J., Demidov L. et al. (2012) Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet; 380: 358–365.
- Kim K., Kefford R., Pavlick A. et al. (2013) Phase II study of the MEK1/MEK2 inhibitor trametinib in patients with metastatic BRAF-mutant cutaneous melanoma previously treated with or without a BRAF inhibitor. J Clin Oncol; 31: 482–489.
- Larkin J., Ascierto P., Dreno B. et al. (2014) Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med; 371: 1867–1876. [
- Pavlick A., Ribas A., Gonzalez R. et al. (2015) Extended follow-up results of phase Ib study (BRIM7) of vemurafenib (VEM) with cobimetinib (COBI) in BRAF-mutant melanoma. J Clin Oncol; 33: 9020.
- Ribas A., Gonzalez R., Pavlick A. et al. (2014) Combination of vemurafenib and cobimetinib in patients with advanced BRAF (V600)-mutated melanoma: a phase 1b study. Lancet Oncol; 15: 954–965.
- Ribas A., Puzanov I., Dummer R. et al. (2015) Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. Lancet Oncol; 16(8) 908-18.
- Rizos H., Menzies A., Pupo G. et al. (2014) BRAF inhibitor resistance mechanisms in metastatic melanoma: spectrum and clinical impact. Clin Cancer Res; 20: 1965–1977.
- Robert C, Schachter J, Long GV et al., (2015) Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med; 372(26): 2521-32.
- Shi H., Hugo W., Kong X. et al. (2014) Acquired resistance and clonal evolution in melanoma during BRAF inhibitor therapy. Cancer Discov; 4: 80–93.

- Sosman J., Kim K., Schuchter L. et al. (2012) Survival in BRAF V600–mutant advanced melanoma treated with vemurafenib. N Eng J Med; 366: 707–714.
- Wagle N., Emery C., Berger M.et al. (2011) Dissecting therapeutic resistance to RAF inhibition in melanoma by tumor genomic profiling. J Clin Oncol; 29: 3085–3096.
- Weber JS, D'angelo SP, Minor D et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol; 2015 (16): 375-384.

Appendix 1. Impact of Vemurafenib on Concomitant Medications

Substrates		
CYP 1A21	CYP 2C91	CYP3A42
Amitriptyline caffeine clomipramine clozapine cyclobenzaprine estradiol fluvoxamine haloperidol imipramine N-DeMe mexilletine naproxen olanzapine ondansetron phenacetin_ acetaminophen propranolol riluzole ropivacaine tacrine theophylline tizanidine verapamil (R)warfarin zileuton zolmitriptan	**NSAIDs:** diclofenac ibuprofen lornoxicam meloxicam S-naproxen_Nor piroxicam suprofen **Oral Hypoglycemic:** tolbutamide glipizide Angiotensin II Blockers: losartan irbesartan Sulfonylureas: glyburide glibenclamide glipizide glimepiride tolbutamide amitriptyline celecoxib fluoxetine fluvastatin glyburide nateglinide phenytoin-4-OH2 rosiglitazone tamoxifen torsemide S-warfarin	**Macrolide antibiotics:** clarithromycin erythromycin telithromycin Anti-arrhythmics: quinidine_3OH **Benzodiazepines:** alprazolam diazepam_3OH midazolam triazolam **Immune Modulators:** cyclosporine tacrolimus (FK506) HIV Antivirals: indinavir nelfinavir ritonavir saquinavir Prokinetic: cisapride **Antihistamines:** astemizole chlorpheniramine terfenadine **Calcium Channel Blockers:** amlodipine diltiazem felodipine lercanidipine nifedipine2 nisoldipine nitrendipine verapamil **HMG CoA Reductase Inhibitors:** atorvastatin cerivastatin

Substrates		
CYP 1A21	CYP 2C91	CYP3A42
		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 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.

Impact of Concomitant Medications on Vemurafenib3	
CYP 3A4 Inhibitors1	CYP 3A4 Inducers2
Indinavir nelfinavir ritonavir clarithromycin itraconazole ketoconazole nefazodone saquinavir telithromycin aprepitant erythromycin fluconazole grapefruit juice verapamil diltiazem cimetidine amiodarone chloramphenicol ciprofloxacin delaviridine diethyldithiocarbamate fluvoxamine gestodene imatinib mibefradil mifepristone norfloxacin norfluoxetine star fruit voriconazole	Efavirenz nevirapine barbiturates carbamazepine efavirenz glucocorticoids modafinil nevirapine oxcarbazepine phenobarbital phenytoin pioglitazone rifabutin rifampin St. John's wort troglitazone

- 1 Concomitant administration of these drugs may increase Vemurafenib exposure
- 2 Concomitant administration of these drugs may reduce Vemurafenib exposure

Appendix 2. Translational biomarker study

- Tumor biopsies

The ancillary study requires tumor biopsies at baseline and upon progression for all enrolled patients when feasible.

At baseline, tumor tissues will be obtained from fresh baseline biopsies performed in patients with easily accessible biopsy sites (subcutaneous and lymph nodes) and from archived samples for patients that cannot be biopsied. Tissue sample will remain in 10% neutral buffered formalin for a minimum of 24-48 hours but no more than 96 hours. A matched paraffin embedded (FFPE) tissue block will then be stored at room temperature at the site until shipment. Path assessments will be regularly performed to ensure that collected samples are of good quality.

Upon progression, fresh biopsies will be obtained for patients with accessible tumor lesions provided they have given their consent to participate in the biomarker study. Accessible lesions are defined as tumor lesions that can easily biopsied i.e. cutaneous, sub-cutaneous and palpable lymph nodes. Failure to obtain sufficient tumor sample, after making best efforts, will not be considered a protocol violation. Lesions with the biggest change in size should be excised at time of progressive disease.

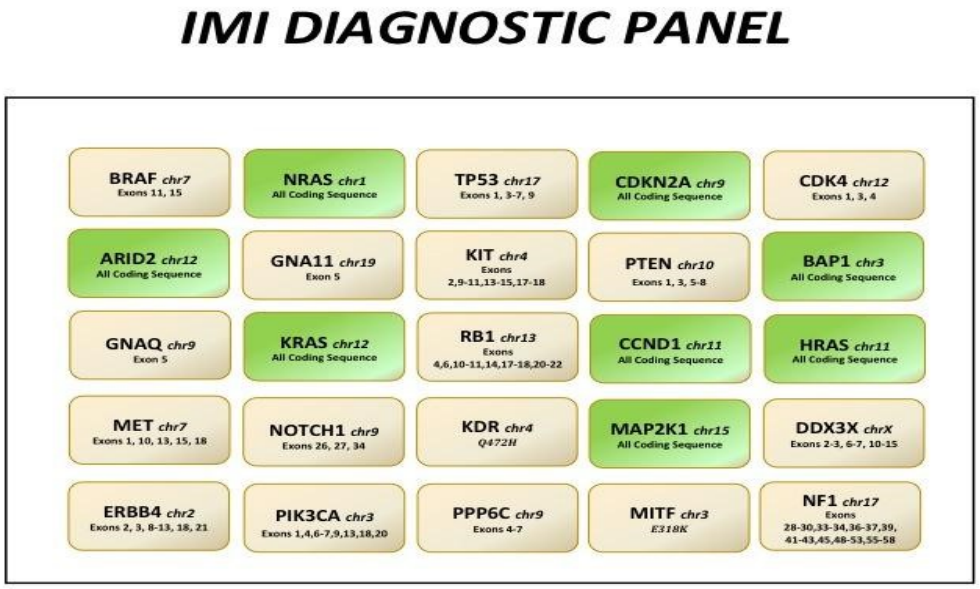
A minimum of 10-15 x 5-6 micron-thick tissue sections will be collected for each patient/time point. Biopsies will be immediately transferred into the provided vials filled with formalin. The biopsies will be fixed for 24±2 hours, transferred into 70% ethanol and then (still in ethanol) shipped to a central pathology lab for paraffin embedding.

As tumor tissue biomarkers, aberrations in main molecular pathways involved in melanoma pathogenesis (i.e., MAPK, CDKN2A-CDK4/6, PI3K-AKT) will be measured through gene panels. Using Ion Torrent technology, the following gene-panels - already tested on DNA samples from FFPE tissues - will be used for assessing the alterations in the main gene pathway candidates:

1) Hotspot regions in *Ion Ampliseq Cancer Hotspot panel* (~2,800 mutations of 50 oncogenes and tumor suppressor genes): 1 pool (10-15 ng per DNA sample).

ABL1	*EGFR*	*GNAS*	*KRAS*	*PTPN11*
AKT1	*ERBB2*	*GNAQ*	*MET*	*RB1*
ALK	*ERBB4*	*HNF1A*	*MLH1*	*RET*
APC	*EZH2*	*HRAS*	*MPL*	*SMAD4*
ATM	*FBXW7*	*IDH1*	*NOTCH1*	*SMARCB1*
BRAF	*FGFR1*	*JAK2*	*NPM1*	*SMO*
CDH1	*FGFR2*	*JAK3*	*NRAS*	*SRC*
CDKN2A	*FGFR3*	*IDH2*	*PDGFRA*	*STK11*
CSF1R	*FLT3*	*KDR*	*PIK3CA*	*TP53*
CTNNB1	*GNA11*	*KIT*	*PTEN*	*VHL*

2) Exons within melanoma-associated genes from *IMI Somatic DNA panel*: 3 pools (10-15 ng per pool, 30-45 ng per DNA sample).



- Peripheral blood samples:

Approximately 10 ml of peripheral venous blood samples must be collected in EDTA tubes and immediately centrifuged at 1900 x g (4000 rpm) for 15 minutes at room temperature, for about 5 ml of plasma separation; this is a crucial step, because circulating tumor DNA has a very short half-life, ranging from 15-30 minutes to a maximum of two hours. Samples will be collected before therapy with BRAF+MEK inhibitors and after progression.

Aspirated supernatant plasma must be transferred in polypropylene tubes (RNase, DNase and pyrogen-free, for cryopreservation use) as 1ml aliquots and stored at -80°C (plasma is stable at this temperature for

a long time).
Samples will be shipped on ice dry, avoiding freeze-thaw cycles.

Libraries were generated starting from 10-15 ng of DNA per primer pool using the Ion AmpliSeq Library Kit 2.0, barcoded with Ion Xpress Barcode Adapters (Life Technologies), purified with Agencourt Ampure XT Beads, diluted at a final concentration of 50 pM, pooled together, placed into the Ion Chef for emulsion PCR and Chip (316™ v2 BC) loading steps, then subsequently sequenced on the Ion PGM using the Ion Hi-Q™ Sequencing Chemistry.