NIS PROTOCOL (PRIMARY DATA COLLECTION)

TITLE:	**A NON-INTERVENTIONAL STUDY TO INVESTIGATE THE EFFECTIVENESS, SAFETY AND UTILIZATION OF COBIMETINIB AND VEMURAFENIB IN PATIENTS WITH AND WITHOUT BRAIN METASTASIS WITH BRAF V600 MUTANT MELANOMA UNDER REAL WORLD CONDITIONS (COVENIS)**
PROTOCOL NUMBER:	ML39302
VERSION NUMBER:	1.1
AUTHOR:	Dr. Carolin Bender [redacted]
EU PAS REGISTER NUMBER:	EUPAS18539
ACTIVE SUBSTANCES	L01XE38: cobimetinib L01XE15: vemurafenib
STUDIED MEDICINAL PRODUCTS :	cobimetinib, vemurafenib
PRODUCT REFERENCE NUMBERS:	Cobimetinib: EU/1/15/1048/001 Vemurafenib: EU/1/12/751/001
PROCEDURE NUMBER:	
JOINT PASS:	No
RESEARCH QUESTION AND OBJECTIVES:	The aim of this multi-center, non-interventional study is to provide data on effectiveness of cobimetinib plus vemurafenib with a special focus on OS, safety and utilization of the combination therapy in two different cohorts: patients with unresectable or metastatic BRAF V600 mutant malignant melanoma with or without cerebral metastases. **Primary** objective for this study is to estimate OS according to cohorts with cerebral and without cerebral metastases. The **safety** objectives for this study are the incidence of all adverse events (AEs) and serious adverse events (SAEs) in cobimetinib / vemurafenib treated

	patients.
COUNTRY OF STUDY POPULATION:	Germany
MARKETING AUTHORIZATION HOLDER (MAH):	Roche Registration Ltd 6 Falcon Way Shire Park Welwyn Garden City AL7 1TW United Kingdom
MAH CONTACT PERSON:	[redacted]
DATE FINAL:	23.01.2017

Based on protocol template Version 2.0 released on 20-Jan-2016

PROTOCOL FINALIZATION SIGNATURE PAGE

TITLE:	**A NON-INTERVENTIONAL STUDY TO INVESTIGATE THE EFFECTIVENESS, SAFETY AND UTILIZATION OF COBIMETINIB AND VEMURAFENIB IN PATIENTS WITH AND WITHOUT BRAIN METASTASIS WITH BRAF V600 MUTANT MELANOMA UNDER REAL WORLD CONDITIONS (COVENIS)**
PROTOCOL NUMBER:	ML39302
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EU PAS REGISTER NUMBER:	To be determined
STUDIED MEDICINAL PRODUCTS:	cobimetinib, vemurafenib
MARKETING AUTHORIZATION HOLDERS (MAH):	Roche Registration Ltd 6 Falcon Way Shire Park Welwyn Garden City AL7 1TW United Kingdom
DATE FINAL:	23.01.2017

This protocol was finalized on the date shown above.

Scientific Responsible Dr. Carolin Bender	Date
[redacted]	Date

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PROTOCOL ACCEPTANCE FORM

TITLE:	**A NON-INTERVENTIONAL STUDY TO INVESTIGATE THE EFFECTIVENESS, SAFETY AND UTILIZATION OF COBIMETINIB AND VEMURAFENIB IN PATIENTS WITH AND WITHOUT BRAIN METASTASIS WITH BRAF V600 MUTANT MELANOMA UNDER REAL WORLD CONDITIONS (COVENIS)**
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I agree to conduct the study in accordance with the current protocol.

Treating Physician's Name (print)

Treating Physician's Signature

Date

Please return a copy of this form to the contact provided below. Please retain the signed original for your study files.

[redacted]
Emil-Barell-Str. 1
79639 Grenzach-Wyhlen
Fax: [redacted]
Email: [redacted]

1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADO	Arbeitsgemeinschaft Dermatologische Onkologie
Abs	antibodies
AE	adverse event
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BM	Brain metastasis
BRAFi	BRAF inhibition
BRAFi/MEKi	BRAF/MEK inhibition
CI	Confidence interval
CNS	central nervous system
CPK	Creatine phosphokinase
CR	Complete remission
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated antigen-4
DDG	Deutsche Dermatologische Gesellschaft
DKG	German Cancer Society
DTIC	dacarbazine
ECG	electrocardiogram
ECOG	Eastern Co-operative Oncology Group
eCRF	Electronic Case Report Form
EDC	electronic data capture
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
eORR	Extracranial objective response rates
EU	European Union
FDA	Food and Drug Administration
GGT	gamma-glutamyl transpeptidase/transferase
GPP	Good Pharmacoepidemiological Practice
GVP	EU Guideline on Good Pharmacovigilance Practices
IEC	Independent Ethics Committee
EORTC	European Organisation for Research and Treatment of Cancer

IRB	Institutional Review Board
iORR	Intracranial objective response rates
LDH	Lactatdehydrogenase
LPLA	last patient, last assessment
LPLV	last patient, last visit
MAPK	Mitogen activated protein kinase
mM	malignant melanoma
MAH	marketing authorization holder
NCI	National Cancer Institute
NIS	Non-interventional study
[redacted]	[redacted]
ORR	objective response rates
OS	Overall survival
PAS	Post Authorization Safety
PD-1	programmed death-1
PFS	Progression free survival
PR	Partial remission
QLQ	Quality of life questionnaire
QoL	Quality of life
QPPV	Qualified Person for Pharmacovigilance
RAS	Rat sarcoma
RBC	red blood cell
RTL	Responsible Team Lead
SAE	Serious adverse event
SDV	Source data verification
SmPC	Summary of products characteristics

2. RESPONSIBLE PARTIES

Protocol Development Responsible

[redacted], Roche Pharma AG

Scientific Responsible

Dr. Carolin Bender, Roche Pharma AG

3. SYNOPSIS

TITLE:	**A NON-INTERVENTIONAL STUDY TO INVESTIGATE THE EFFECTIVENESS, SAFETY AND UTILIZATION OF COBIMETINIB AND VEMURAFENIB IN PATIENTS WITH AND WITHOUT BRAIN METASTASIS WITH BRAF V600 MUTANT MELANOMA UNDER REAL WORLD CONDITIONS (COVENIS)**
PROTOCOL NUMBER:	ML39302
VERSION NUMBER:	1.1
DATE OF SYNOPSIS:	17.11.2016
EU PAS REGISTER NUMBER:	
STUDIED MEDICINAL PRODUCTS:	Cobimetinib (Cotellic®), Vemurafenib (Zelboraf®)
SCIENTIFIC RESPONSIBLE	Carolin Bender
MAIN AUTHOR:	Carolin Bender, [redacted]
PHASE:	IV, non-interventional study
INDICATION:	Malignant Melanoma
MARKETING AUTHORIZATION HOLDER:	Roche Registration Ltd 6 Falcon Way Shire Park Welwyn Garden City AL7 1TW United Kingdom

Rationale and Background

Cutaneous malignant melanoma (mM) is a malignant disease of melanocytes which reside mainly in the basal layer of the epidermis (1). The incidence of mM has been increasing over the past decades. In 2014, around 20,000 new cases of malignant melanoma were diagnosed in Germany (2).Survival rates are dependent on the stage of the disease. Observed five-year survival rates of patients with AJCC stage IIIC or stage IV disease are as little as 40% or 15-20%, respectively, in times before introduction of new agents for treating advanced melanoma (3).

Until 2011, dacarbazine (DTIC), cisplatin and vindesine were the only approved systemic treatments for metastatic mM in Germany. Hence, besides treatment in clinical studies chemotherapy was the only treatment option with no proven benefit on OS (4). The recent introduction of new immunotherapeutic agents, such as cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibodies (Abs) and programmed death-1 (PD-1) Abs, as well as targeted therapies for patients with BRAF-mutated melanoma now offer potent treatment options to mM patients with increasing long-term benefit and significantly improved 2- and 3-year survival rates. An example for individualized, targeted therapy is BRAF inhibition (BRAFi) and more recently combined BRAF/MEK inhibition (BRAFi/MEKi) targeting the mitogen-activated protein kinase (MAPK) pathway. Mutations in the BRAF gene account for 40-60% of oncogenic driver mutations in melanoma (5, 6). These agents have shown significant clinical activity in patients with BRAF mutation positive advanced melanoma (7, 8). Treatment with vemurafenib and cobimetinib has shown superior efficacy compared to vemurafenib monotherapy with improved objective response rates (ORR) (70% vs. 50%, respectively) and survival (PFS: 12.3 months vs. 7.2 months & OS: 22.3 months vs. 17.4 months) in previously untreated patients with BRAF(V600)-mutant advanced melanoma (9).

The first approved immune checkpoint blocker ipilimumab significantly improved overall survival (OS), with a subset of patients experiencing long-term survival (10). More recently, pembrolizumab and nivolumab, monoclonal antibodies directed against PD-1, were shown to prolong progression-free survival (PFS) and OS in melanoma patients that was superior to CTLA-4 Ab monotherapy (11).

Malignant melanoma is the third most common disease to develop brain metastases. Up to 11% of all patients with cerebral metastases are diagnosed with mM (12).

Around 10 percent of initially diagnosed mM patients present with brain metastases (13, 14). Over the course of disease, the risk for brain metastasis increases. In a phase III trial recruiting patients without brain metastases comparing dacarbazine and temozolomide, 20 – 30% of patients had developed brain metastases at 12 months increasing to 30 - 40% after 3 years (15). Data from the central registry malignant melanoma shows around 30 percent of patients develops brain metastasis (BM) (16). Autopsy series have reported up to 75% of melanoma patients having brain metastases (17).

Before the advent of targeted therapies, OS for patients with brain metastases was about 4 months (20). Melanoma patients treated with single agent BRAF inhibitors have an OS ranging between 4.3 to 13 months (21, 22). In a pilot study, Dummer et al. (20) treated patients with BRAF V600 mutation–positive metastatic mM and previously treated, nonresectable BM, requiring corticosteroids for symptom control using vemurafenib monotherapy. Intracranial ORR was 16% with a median duration of response in the brain of 4.4 (2.1–4.6) months. Median OS was 5.3 months, and median PFS in the brain was 4.3 months.

Commonly, mM patients with central nervous system (CNS) involvement are excluded from clinical trials (21). Hence, no information from interventional clinical trials on activity of combined targeted therapy (BRAF and MEK inhibition) is available until present. Additionally, the pivotal study coBRIM has not included mM patients with brain metastases. Currently, there is one phase II trial (CONVERCE) for the treatment of brain metastases with vemurafenib and cobimetinib under investigation (22). The primary endpoint of this study is intracranial response. Radiological or stereo tactical treatment of brain metastases is only allowed prior to treatment start. CONVERCE evaluates the efficacy of vemurafenib and cobimetinib in brain metastases in a highly controlled setting.

Cobimetinib is approved for use in combination with vemurafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

To date no data are available on effectiveness, safety and, utilization of cobimetinib / vemurafenib in patients with mM in daily clinical routine in Germany.

Research Question and Objectives

The aim of this multi-center, non-interventional study is to provide data on effectiveness

of cobimetinib plus vemurafenib with a special focus on OS, safety and utilization of the combination therapy in two different cohorts: patients with unresectable or metastatic BRAF V600 mutant malignant melanoma with or without cerebral metastases.

Objectives

The **primary** objective for this study is as follows:

- to estimate OS according to cohorts with cerebral and without cerebral metastases

The **secondary** objectives for this study are as follows:
to estimate intermediate endpoints, including:

- PFS (investigator assessed)
- ORR (CR + PR) (investigator assessed)
- Intracranial ORR (iORR)
- Extracranial ORR (eORR)
- Time to CNS relapse in cohort with cerebral metastases / development of cerebral metastases in cohort with solely extracerebral metastases (investigator assessed)
- to describe clinical characteristics of patients overall, and according to both cohorts (i.e. demographic data, medical history, information on primary melanoma, ECOG performance status, serum LDH at baseline, number of extracranial metastatic sites at baseline; in case of brain metastasis: total number of brain metastases, diameter of largest metastasis, symptomatic/asymptomatic brain metastasis, leptomeningeal disease, concomitant therapy for brain metastasis)
- to describe utilization of cobimetinib / vemurafenib (type and number of previous adjuvant and palliative treatments, dosing schedules, treatment beyond progression, reason for discontinuation, subsequent therapies and concomitant medication)
- to describe utilization of cobimetinib / vemurafenib and treatment for brain metastasis (prior local treatment for brain metastases, concomitant radiotherapy or surgery, type of radiotherapy, steroid use prophylactic or therapeutic, use of anticonvulsiva)

- to describe patient reported outcome using the EORTC QLQ-C30 questionnaire

Safety Objectives

The safety objectives for this study are as follows:

The incidence of all adverse events (AEs) and serious adverse events (SAEs) in cobimetinib / vemurafenib treated patients.

- All protocol-specified adverse events (AEs) described in this section will be reported and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4 (CTCAE v4.03).
- Incidence, and outcomes of serious and non-serious AEs of interest (i.e., those AEs identified by Genentech/Roche as potential or known risks of cobimetinib and/or vemurafenib use)
- These AEs of interest for the combination of vemurafenib and cobimetinib include the following:
  - Any grade 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), clinical features consistent with rhabdomyolysis such as muscle pain, sings or renal failure, or dark red or brown urine)
  - Grade ≥ 3 hemorrhage event or any grade cerebral hemorrhage
  - Grade ≥ 3 rash
  - Grade ≥ 3 photosensitivity
  - Events suggestive of drug induced liver injury or other Grade ≥ 3 hepatotoxicity as defined by:
    - Grade ≥ 3 elevations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum bilirubin, gamma-glutamyl transpeptidase/transferase (GGT), OR cases of elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice

- AE potentially associated with prolongation of cardiac repolarization
- New or progression of RAS mutant malignancy, cutaneous squamous cell carcinoma, new primary melanoma, or basal cell carcinoma, or other new malignancies.

Study Design

This multi-center, two cohort non-interventional study does not influence the individually selected treatment scheme. The physicians´ choice for a particular type of therapy is not influenced. Only documentation of the chosen therapy is part of this study. Data collection during therapy with cobimetinib / vemurafenib should reflect clinical routine. Overall, the duration of patient inclusion will last until end of Q4 2018.

- Patients with:

  Cohort A: 157 patients with AJCC stage IIIC unresectable and stage IVa, b, c mM without cerebral metastases

  or

  Cohort B: 68 patients with AJCC stage IVc and cerebral metastases

  may be included

Description of Study

This prospective multi-center non-interventional study will include patients with an underlying diagnosis of BRAF V600 mutated unresectable or metastatic malignant melanoma, either with or without cerebral metastases. Data collection during therapy with Cobimetinib / Vemurafenib should reflect clinical routine. Study duration will be three years. Data from individual patients will be documented up to three years.

Population

Patients must meet the following criteria for study entry:

- Adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation according to SmPC
- Be willing and able to provide informed consent for the non-interventional study.
- Male or female patient being ≥ 18 years of age on day of signing informed consent.
- Histologically confirmed diagnosis of unresectable or metastatic mM (according to the cobimetinib label)
- Presence of BRAF mutation (V600) in tumor tissue prior to enrolment.

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

- Previous treatment with BRAF- and/or MEK inhibitors prior to study entry
- Hypersensitivity to the active substances or to any of the excipients listed in appendix 4.

Variables

Only variables, obtained according to routine clinical practice and follow objectives can and should be documented in this study.

Primary Variable

The primary variables for this study are as follows:

- OS

Secondary Variables

The secondary variables for this study are as follows:

- PFS
- ORR
- Time to CNS relapse / development of cerebral metastases
- Description of previous therapies and therapies after cobimetinib / vemurafenib discontinuation
- Description of Radiotherapy
- Description of Concomitant medication
- QoL

Primary Safety Variables

- Total adverse events
- Serious adverse events
- ≥ grade 3 adverse events
- Adverse events leading to treatment discontinuation
- Adverse Events of Special Interest

Data Sources

Patients' data will be recorded on eCRF. The degree of detail and completeness of data collected is dependent on local clinical practice. Data from patient notes should be entered on the eCRF as soon as they become available

Study data will be available from one source only:

Data from routine clinical visits at baseline and potentially, at subsequent visits will be collected and entered into an eCRF (see appendix 2).

Study Size

In this study 225 patients will be enrolled across 40 sites.

The following rates are expected for the two different populations:

- Cohort A: patients with AJCC stage IIIC unresectable and stage IVA, B, C mM without cerebral metastases: 70% (157 patients)
- Cohort B: patients with AJCC stage IVC and cerebral metastases: 30% (68 patients)

Data Analysis

All effectiveness and safety variables documented in this study will be analyzed by means of descriptive analyses.

Continuous data will be summarized using mean, standard deviation, median, minimum and maximum. Categorical variables will be expressed as absolute and relative number and 95% CI. Kaplan-Meier estimates and Cox-regression will be used to model data on time to disease progression and OS.

Definition of core analysis population

Analyses will include all patients who received at least one dose of cobimetinib and vemurafenib.

Other Analyses

Safety analyses

All patients who received at least once cobimetinib and vemurafenib will be part of the core analysis population. Safety will be assessed through summaries of adverse events. Descriptive statistics will be used to summarize all safety data. Adverse event data will be reported in listings and presented in frequency tables by Medical Dictionary for Regulatory Affairs (MedDRA) terms. All adverse events occurring after treatment will be summarized. Summaries of adverse events by grade, seriousness, and relationship to study treatment will be presented, as well as summaries of adverse events leading to death or to premature withdrawal from study treatment. Serious adverse events, including deaths, will be listed separately and summarized.

Effectiveness analyses

Effectiveness analyses will be based on all enrolled patients according to both defined cohorts:

Patients with:

Cohort A: patients with AJCC stage IIIC unresectable and stage IVA, B, C mM without cerebral metastases

or

Cohort B: patients with AJCC stage IVC and cerebral metastases

A data review meeting to designate patients to the different populations will be held before database closure.

Interim Analyses An interim analysis is not planned

Milestones

Start Date of Study:

The study start date will be the date of the first data collection: the date from which information on the first study subject is recorded in the study database. The planned start date is Q2/2017

End of Study

The end of the study will be the date from which the last information of the last subject is recorded in the study database. The planned end of study date is Q2/2020.

Length of Study

This study will last for 3 years. Patients will be recruited for 18 months and followed up to 18 months.

4. PROTOCOL AMENDMENTS AND UPDATES

Any protocol amendments will be prepared by the Marketing Authorization Holder or designee.

Protocol amendments will be submitted to the Institutional Review Board (IRB)/Ethics Committee (EC) and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes that involve logistical or administrative aspects only (e.g., change in Site Operations Representative or contact information).

Substantial protocol amendments/updates so far: none

Amendment/ Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
{Number}	{Date}	{Section no.}	{Short description}	{Reason}

5. MILESTONES

Study milestones are given in the following table.

Milestone	Planned Date
Registration of protocol in the EU PAS register	Q2/2017
Start of data collection	Q2/2017
End of data collection	Q2/2020
Study progress reports (from CRO)	monthly
Final report of study results	Q4/2020
Registration of the results in the EU PAS register	Q1/2021

6. RATIONALE AND BACKGROUND

6.1 STUDY BACKGROUND

Cutaneous malignant melanoma (mM) is a malignant disease of melanocytes which reside mainly in the basal layer of the epidermis (1). The incidence of mM has been increasing over the past decades. In 2014, around 20,000 new cases of mM were diagnosed in Germany (2). Survival rates are dependent on the stage of the disease. Observed five-year survival rates of patients with AJCC stage IIIC or stage IV disease are as little as 40% or 15-20%, respectively (3).

Until 2011, dacarbazine (DTIC), cisplatin and vindesine were the only approved systemic treatments for metastatic mM in Germany. Hence, besides treatment in clinical studies chemotherapy was the only treatment option with no proven benefit on OS (4). The recent introduction of new immunotherapeutic agents, such as cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibodies (Abs) and programmed death-1 (PD-1) Abs, as well as targeted therapies for patients with BRAF mutated mM now offer potent treatment options to patients. An example for individualized, targeted therapy is BRAF inhibition (BRAFi) and more recently combined BRAF/MEK inhibition (BRAFi/MEKi) targeting the mitogen-activated protein kinase (MAPK) pathway. Mutations in the BRAF gene account for 40-60% of oncogenic driver mutations in mM (5, 6). These agents have shown significant clinical activity in patients with BRAF mutation positive advanced mM (7, 8). Treatment with vemurafenib and cobimetinib has shown superior efficacy compared to vemurafenib monotherapy with improved objective response rates (ORR) (70% vs. 50%, respectively) and survival (PFS: 12.3 months vs. 7.2 months & OS: 22.3 months vs. 17.4 months) in previously untreated patients with BRAF V600-mutant advanced mM (9). Cobimetinib is approved for use in combination with vemurafenib for the treatment of adult patients with unresectable or metastatic mM with a BRAF V600 mutation.

The first approved immune checkpoint blocker ipilimumab significantly improved overall survival (OS), with a subset of patients experiencing long-term survival (10). More recently, pembrolizumab and nivolumab, monoclonal Abs directed against PD-1, were shown to prolong progression-free survival (PFS) and OS in mM patients that was superior to CTLA-4 Ab monotherapy (11).

Malignant melanoma is the third most common disease to develop brain metastases. Up to 11% of all patients with cerebral metastases are diagnosed with mM (12). Around 10 percent of initially diagnosed mM patients present with brain metastases (13, 14). Over the course of disease, the risk for brain metastasis increases. In a phase III trial recruiting patients without brain metastases comparing dacarbazine and temozolomide, 20 – 30% of patients had developed brain metastases at 12 months increasing to 30 - 40% after 3 years (15). Data from the central registry mM shows around 30 percent of patients develops brain metastasis (16). Autopsy series have reported up to 75% of mM patients having brain metastases (17).

Before the advent of targeted therapies, OS for patients with brain metastases was 4.3 months (18). Melanoma patients treated with single agent BRAFi have an OS of 4.3 to 13 months, but the outcome seems to be inferior to patients without brain metastases (19). In a pilot study, Dummer et al. (20) treated patients with BRAF V600 mutation–positive metastatic mM and previously treated, unresectable brain metastases, requiring corticosteroids for symptom control. Intracranial ORR was 16% with a median duration of response in the brain of 4.4 (2.1–4.6) months. Median OS was 5.3 months, and median PFS in the brain was 4.3 months.

According to current treatment guidelines in Germany (23), first line treatment for BRAF V600-mutated mM should be either combined BRAFi/MEKi or PD-1 Ab therapy or combined PD-1/CTLA-4 Ab therapy.

In patients with brain metastases, therapy guidelines differentiate between multiple, symptomatic brain metastases as opposed to limited brain metastasis. For the latter, surgery or stereotactic radiotherapy is recommended. For multiple, symptomatic brain metastases palliative whole brain radiotherapy is recommended, if life expectancy exceeds three months. To date, no guidance on adjuvant radiotherapy after R0-resection of brain metastases is given.

6.2 STUDY RATIONALE

Commonly, mM patients with CNS involvement are excluded from clinical trials (21). Hence, no information from interventional clinical trials on activity of combined targeted therapy (BRAFi/MEKi) is available until present. Additionally, the pivotal study of combined vemurafenib and cobimetinib treatment coBRIM has not included mM patients with brain metastases. Currently, there is one phase II trial (CONVERCE) for

the treatment of brain metastases with vemurafenib and cobimetinib under investigation (22). The primary endpoint of this study is intracranial response. Radiological or stereotactical treatment of brain metastases is only allowed prior to treatment start. CONVERCE evaluates the efficacy of vemurafenib and cobimetinib in brain metastases in a highly controlled setting.

To date no data are available on effectiveness, safety and, utilization of cobimetinib / vemurafenib in patients with mM in daily clinical routine in Germany

For information on the condition under observation please refer to the most recent version of the SmPC.

For information on vemurafenib /cobimetinib please refer to the most recent version of the SmPCs.

7. RESEARCH QUESTION AND OBJECTIVES

7.1 RESEARCH QUESTION

The aim of this multi-center, non-interventional study is to provide data on effectiveness of cobimetinib plus vemurafenib with a special focus on OS, safety and utilization of the combination therapy in two different cohorts: patients with unresectable or metastatic BRAF V600-mutated malignant melanoma with or without cerebral metastases.

7.2 OBJECTIVES

The primary objective for this study is as follows:

- to estimate OS according to cohorts with cerebral and without cerebral metastases (investigator assessed)

The secondary objectives for this study are as follows:

- to estimate intermediate endpoints, including:
  - PFS (investigator assessed)
  - ORR (CR + PR) (investigator assessed)
  - Intracranial ORR (iORR)
  - Extracranial ORR (eORR)
  - Time to CNS relapse in cohort with cerebral metastases / development of cerebral metastases in cohort with solely extracerebral metastases (investigator

assessed)

- to describe clinical characteristics of patients overall, and according to both cohorts (i.e. demographic data, medical history, information on primary mM, ECOG performance status, serum LDH at baseline, number of extracranial metastatic sites at baseline; in case of brain metastasis: number of brain metastases, largest diameter, symptomatic/asymptomatic brain metastasis, leptomeningeal disease, concomitant therapy for brain metastasis)
- to describe utilization of cobimetinib / vemurafenib (type and number of previous adjuvant and palliative treatments, dosing schedules, treatment beyond progression, reason for discontinuation, subsequent therapies and concomitant medication)
- to describe utilization of cobimetinib / vemurafenib and treatment for brain metastasis (prior local treatment for brain metastases, concomitant radiotherapy or surgery, type of radiotherapy, steroid use prophylactic or therapeutic, use of anticonvulsiva)
- to describe patient reported outcome using the EORTC QLQ-C30 questionnaire

Safety Objectives

The safety objectives for this study are as follows:

The incidence of all adverse events (AEs) and serious adverse events (SAEs) in cobimetinib / vemurafenib treated patients.

- All protocol-specified adverse events (AEs) described in this section will be reported and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4 (CTCAE v4.03).
- Incidence and outcomes of serious and non-serious AEs of interest (i.e., those AEs identified by Genentech/Roche as potential or known risks of cobimetinib and/or vemurafenib use)
- These AEs of interest for the combination of vemurafenib and cobimetinib include the following:
  - Any grade 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), clinical features consistent with rhabdomyolysis such as muscle pain, sings or renal failure, or dark red or brown urine)
- Grade ≥ 3 hemorrhage event or any grade cerebral hemorrhage
- Grade ≥ 3 rash
- Grade ≥ 3 photosensitivity
- Events suggestive of drug induced liver injury or other Grade ≥ 3 hepatotoxicity as defined by:
    - Grade ≥ 3 elevations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum bilirubin, gamma-glutamyl transpeptidase/transferase (GGT), OR cases of elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice
- AE potentially associated with prolongation of cardiac repolarization
- New or progression of RAS mutant malignancy, cutaneous squamous cell carcinoma, new primary melanoma, or basal cell carcinoma, or other new malignancies.

8. RESEARCH METHODS

8.1 STUDY DESIGN

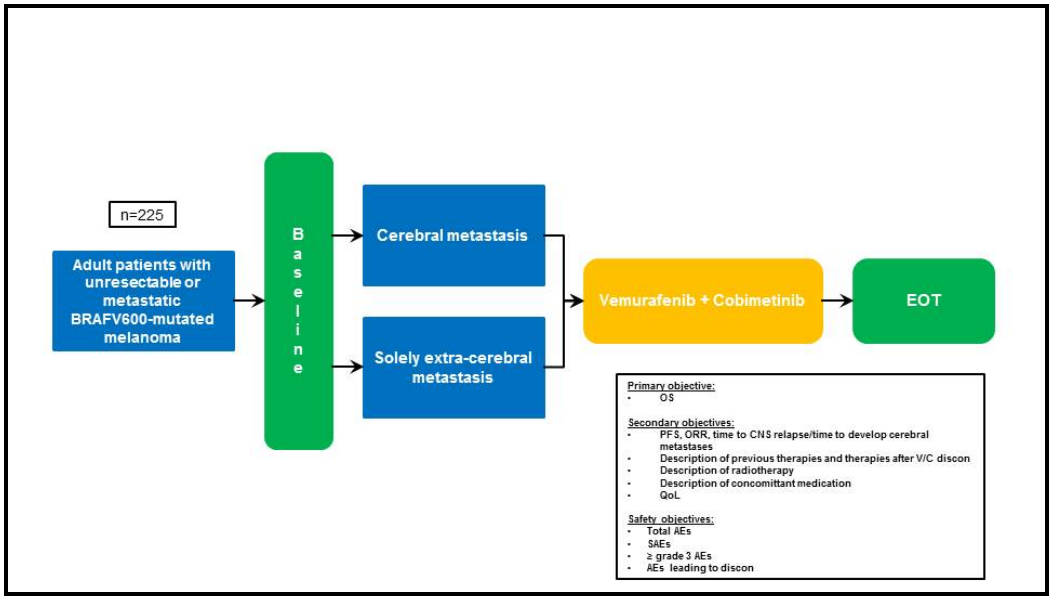
This multi-center, two cohort non-interventional study does not influence the individually selected treatment scheme. The physicians´ choice for a particular type of therapy is not influenced. Only documentation of the chosen therapy is part of this study. Data collection during therapy with cobimetinib / vemurafenib should reflect clinical routine. Overall, the duration of patient inclusion will last until end of Q4 2018.

- Patients with:

  Cohort A: 157 patients with AJCC stage IIIC unresectable and stage IVA, B, C mM without cerebral metastases

  or

  Cohort B: 68 patients with AJCC stage IVC and cerebral metastases may be included



Start Date of Study:

The study start date will be the date of the first data collection: the date from which information on the first study subject is recorded in the study database. The planned start date is Q2/2017.

End of Study:

The end of the study will be the date from which the last information of the last subject is recorded in the study database. The planned end of study date is Q2/2020.

Length of Study

This study will last for 3 years. Patients will be recruited for 18 months and followed up to 18 months.

A data collection overview is provided in Appendix 2.

8.1.1 Rationale for Study Design

8.2 SETTING

8.2.1 Centers

This study will be conducted at approximately 40 centers in one country (Germany).

Additional centers may be added or substituted if the ones stated above are underperforming.

8.2.2 Study Population

Patients receiving treatment for BRAF V600-mutated unresectable or metastatic mM with a combination of vemurafenib and cobimetinib according to standard of care and in line with the current summary of product characteristics (SmPC)/local labeling and who have no contraindication to a treatment with a combination of vemurafenib and cobimetinib therapy as per the local label are eligible for observation in this non interventional study if the following criteria applies.

Patients must meet the following criteria for study entry:

- Adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation according to SmPC
- Be willing and able to provide informed consent for the non-interventional study.
- Male or female patient being ≥ 18 years of age on day of signing informed consent.
- Histologically confirmed diagnosis of unresectable or metastatic mM (according to the cobimetinib label)
- Presence of BRAF mutation (V600) in tumor tissue prior to enrolment.

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

- Previous treatment with BRAF- and/or MEK inhibitors prior to study entry
- Hypersensitivity to the active substances or to any of the excipients listed in appendix 4.

Patient selection criteria are as broad as mentioned in the SmPC, with one exception:

Patients previously treated with BRAF- and/or MEK inhibitors are excluded. This may lower the number of patients available for recruitment in a further line setting.

8.2.3 Concomitant Medication and Treatment

Concomitant medication prescribed for concomitant diseases and treatment for mM at the beginning of the observation period or introduced during the observation period will be documented in the CRF from start of therapy with vemurafenib / cobimetinib until discontinuation of the treatment if applicable.

8.2.4 Dosage, Administration, and Compliance

Dosing and treatment duration of any studied medicinal products collected as parts of this non-interventional study are at the discretion of the physician in accordance with local clinical practice and local labeling.

8.3 VARIABLES

8.3.1 Primary Variable

The primary variable for this study is as follows:

- OS: Time interval between start of treatment and date of death for any cause

8.3.2 Secondary Variables

The secondary variables for this study are as follows:

- PFS
- ORR
- Time to CNS relapse / development of cerebral metastases
- Description of previous therapies and therapies after cobimetinib / vemurafenib discontinuation
- Description of Radiotherapy
- Description of Concomitant medication
- QoL

8.3.3 Primary Safety Variables

The primary safety variables for this study are as follows:

- Total adverse events
- Serious adverse events
- ≥ grade 3 adverse events
- Adverse events leading to treatment discontinuation
- Adverse events of special interest

8.4 DATA SOURCES

8.4.1 Collection of Data on the CRF

Patients' data will be recorded on eCRFs. The degree of detail and completeness of data collected is dependent on local clinical practice. Data from patient notes should be entered on the eCRF as soon as they become available.

8.4.2 Data Collected during the Observation Period

During therapy with a combination of vemurafenib and cobimetinib, laboratory assessments are routinely performed in accordance with current guidelines and local standard of care. When performed during the observational period, available results from the range of assessments described below will be documented on the CRF. Most data will be documented around the point in time or period during the treatment period when the respective assessments are usually performed according to standard of care. The proposed assessments and suggested timings for assessments in the protocol/observational plan are not mandatory. It is up to the treating physician to perform and document the assessments as performed in the real clinical setting.

At baseline the following items should be documented:

- Acceptance of inclusion / exclusion criteria
- Demographic data include age, sex, and self-reported race / ethnicity
- ECOG performance status
- Elevated LDH level within 1 month before cobimetinib / vemurafenib initiation
- Medical history including significant diseases within the previous 3 years, major surgeries.
- Melanoma history (including information on primary mM [date of diagnosis, histologic type, site, Breslow's thickness], BRAF mutation status, date of first diagnosis AJCC stage IIIC unresectable or stage IV, current AJCC stage; prior adjuvant and palliative therapies for melanoma, number of extracranial metastatic sites at baseline, presence of liver metastasis at baseline, in case of brain metastasis: date of first diagnosis of brain metastasis, prior local treatment for brain metastasis, number of brain metastases, largest diameter, symptomatic/asymptomatic brain metastasis, leptomeningeal disease, concomitant medication for brain metastases [i.e. steroids, anticonvulsants])
- Concomitant medication
- Start date of therapy with cobimetinib / vemurafenib

During observation period the following items should be documented (if applicable):

- Start and end date of treatment interruption (if appl.)
- Start and end date of dose modification (if appl.)
- Information on dose modification (if appl.). dosage and dosing schedule of cobimetinib / vemurafenib
- Reason for dose modification / treatment interruption (if appl.)
- Concomitant local treatment for brain metastasis (if appl.) Concomitant local treatment for brain metastasis (including type of treatment [i.e. surgery, radiotherapy], type of radiotherapy [i.e. whole brain radiotherapy, whole brain radiotherapy with boost, stereotactic radiotherapy], total dose and fraction of radiotherapy, number of metastases treated, steroid use prophylactic or therapeutic)
- Concomitant medication
- Tumor Response (CR, PR, SD, PD) according to clinical practice
- Elevated LDH level during therapy / follow up
- Date of disease progression
- Date of death
- Stop date of therapy with cobimetinib / vemurafenib
- Reason for Discontinuation: PD, AE/SAE, patient's wish, response, physician's decision
- AEs, SAE, AEs of interest, Pregnancies

In the routine care setting, patients are seen regularly by their treating physicians either for treatment or for regular assessment after treatment. Thus, no study-specific visits or evaluations are required by this protocol.

Please see Appendix 2 for the data collection overview (as per standard of care) during the treatment period.

8.4.3 Data Collected at Study Completion

For patients who complete the observation period, the study completion visit should be documented.

Please see Appendix 2 for the data collection overview at the study completion visit if available.

8.4.4 Data Collected during Follow-Up

After the study completion visit, adverse events (AEs) should be followed as outlined in Section 10.1.4.2.

Please see Appendix 2 for the data collection overview during follow-up.

8.4.5 Safety Data Collection

Clinical AEs, serious and non-serious, as well as safety data other than AEs as described in Section 8.3 will be recorded in the CRF during the total observation period. For clinical AEs, serious and non-serious, physician's assessment of severity (mild, moderate, severe or in oncology studies using the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE]) and relationship to therapy (i.e., related or unrelated) will be recorded as described in Appendix 3.

8.5 STUDY SIZE

In this study 225 patients will be enrolled across 40 sites.
The following rates are expected for the two different populations:

- Cohort A: patients with AJCC stage IIIC unresectable and stage IVa, b, c mM without cerebral metastases: 70% (157 patients)
- Cohort B: patients with AJCC stage IVC and cerebral metastases: 30% (68 patients)

The required sample size was estimated for Cohort B (brain metastases) and Cohort A (non-brain metastases). For the brain metastases group, a historical median OS of about 8 months is assumed under vemurafenib treatment (1-4). The aim was to find the required number of patients in order to estimate the median OS in such a way that the lower limit of the 95% confidence interval is at least 8 months. If a median OS of 12 months is assumed, a one-sample non-parametric survival analysis would yield in a confidence interval of [8.5 months ; 15.5 months], given the sample size was 68 (10% dropout rate included). For the non-brain metastases group, the aim was to set the number of patients in such a manner that the lower boundary of its associated median OS confidence interval does not overlap with the upper boundary of the brain metastasis group. If a median OS of 25 months is assumed, the 95% confidence interval for the median OS is [19; 31] months (5).

8.6 DATA MANAGEMENT

8.6.1 Data Quality Assurance

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

The CRO will produce a Data Quality Review Plan that describes the quality checking to be performed on the data.

The marketing authorization holder will perform oversight of the data management of this study, including approval of the CRO data management plans and guidance (including Data Quality Review Plan). Data will be periodically transferred electronically from the CRO to the marketing authorization holder, and the CRO's standard procedures will be used to handle and process the electronic transfer of these data.

CRFs and correction documentation will be maintained in the EDC system audit trail. System backups for data stored at the CRO and records retention for the study data will be consistent with the CRO standard procedures. The CRO will comply with the MAH's procedures regarding archiving and record management

8.6.2 Electronic Case Report Forms

CRFs are to be completed using a marketing authorization holder-designated electronic data capture (EDC) system. Sites will receive training and have access to a manual for appropriate CRF completion. CRFs will be submitted electronically to the marketing authorization holder and should be handled in accordance with instructions from the marketing authorization holder.

All CRFs should be completed by designated trained site staff. CRFs should be reviewed and electronically signed and dated by the physician or a designee.

At the end of the study, the physician will receive the data related to patients from his or her site in an electronically readable format (e.g., on a compact disc). Data must be kept with the study records. Acknowledgement of receipt of the data is required.

8.6.3 Source Data Documentation

Site Operations Representative will perform ongoing SDV as defined in the Trial Monitoring Plan to confirm that critical protocol data (i.e., source data) entered in the

CRF by authorized site personnel are accurate, complete, and verifiable from source documents.

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

Before study initiation, the types of source documents that contain study-relevant information will be clearly defined in the Trial Monitoring Plan. The Trial monitoring plan defines which kind of source data – if available from clinical routine - can be used for documentation into CRF. No additional source data creation beyond routine is allowed.

Source documents that are required to verify the validity and completeness of data entered in the CRF must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 8.6.5.

To facilitate SDV, the physicians and institutions must provide the marketing authorization holder direct access to applicable source documents and reports for study-related monitoring, marketing authorization holder audits, and IRB/EC review. The participating sites must also allow inspection by applicable health authorities.

8.7 DATA ANALYSIS

No statistical model will be used in the efficacy analysis and no formal hypothesis testing is planned. All effectiveness and safety variables documented in this study will be analyzed by means of descriptive analyses.

Continuous data will be summarized using mean, standard deviation, median, minimum and maximum. Categorical variables will be expressed as absolute and relative number and 95% CI. Kaplan-Meier estimates and Cox-regression will be used to model data on time to disease progression and OS.

Definition of core analysis population

Analyses will include all patients who received at least one dose of cobimetinib and vemurafenib.

A data review meeting to designate patients to the different populations will be held before database closure.

8.7.1 Safety Analyses

All patients who received at least once cobimetinib and vemurafenib will be part of the safety population which is identical to the core analysis population.

The analysis of safety outcomes/variables is based on the incidence and severity of all AEs, SAEs, AEs with NCI CTCAE version {4.0}.

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

8.7.2 Effectiveness Analyses

Effectiveness analyses will be based on all enrolled patients according to both defined cohorts:

Patients with:

Cohort A: patients with AJCC stage IIIC unresectable and stage IVA, B, C mM without cerebral metastases

or

Cohort B: patients with AJCC stage IVC and cerebral metastases

All effectiveness and variables documented in this study will be analyzed by means of descriptive analyses.

Continuous data will be summarized using mean, standard deviation, median, minimum and maximum. Categorical variables will be expressed as absolute and relative number and 95% CI. Kaplan-Meier estimates and Cox-regression will be used to model data on time to disease progression and OS.

All efficacy analyses will be performed separately for both groups.

The primary variable OS is defined as time interval from study start to death for any cause. Patients who have not died will be censored at the last date the patient was known to be alive. A 95% confidence interval will be calculated for the median overall survival.

PFS is defined as the interval between the start date of treatment and the date of progression or death for any cause, whichever comes first. Patients who have neither progressed nor died will be censored on the date of last evaluable tumor assessment.

Patients who had no post-baseline assessments and did not have an event will be censored OR is defined as a complete or a partial response documentation on the basis of investigator assessment.

Time to CNS relapse is defined as the interval between start date of treatment and the date of CNS relapse or death for any cause, whichever comes first.

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

8.7.3 Interim/Final Analysis and Timing of Analyses

An interim analysis is not planned.

At the end of the study the date from which the last information of the last subject is recorded in the study database the final analysis will be done.

8.8 QUALITY CONTOL

8.8.1 Study Documentation

The physician must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental notification. In addition, at the end of the study, the physician will receive

the patient data, which include an audit trail containing a complete record of all changes to data.

The Marketing Authorization Holder shall ensure that the dataset and statistical programs used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection.

8.8.2 Use of Site Computerized Systems

When clinical observations are entered directly into a participating site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

8.8.3 Retention of Records

Records and documents pertaining to the conduct of this study, including CRFs and Informed Consent Forms, must be retained by the physician for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

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

All supporting functional parties will comply with the MAH procedures regarding archiving and record management.

8.8.4 Site Audits and Inspections

Site visits will be conducted by the marketing authorization holder or an authorized representative for audit of study data, patients' medical records, and CRFs.

The physician will also permit national and local health authorities to inspect facilities and records relevant to this study.

8.8.5 Administrative Structure

For this non-interventional study, the Sponsor liaises with a contract research organization for site management and data management. The responsibility of the CRO includes:

- Preparation of all study documents and data repositories (including but not limited to patient information, informed consent, case report form, electronic data base)
- Initiation of participating sites, support of physicians throughout the study and site inspections
- Data analysis
- Reporting of results

No steering committee or expert advisory committee is involved in this study.

8.9 LIMITATIONS OF THE RESEARCH METHOD

As any observational research this study is subject to a series of risks of bias. The potential major ones have been taken into account as much as possible in the design and analysis of the non-interventional study.

The target population of this study is the population of patients treated with cobimetinib / vemurafenib, for metastatic melanoma in a real life setting in Germany. A representative sample of the target population will be drawn, Physicians from hospitals are to identify and recruit the patients. Sample representativeness may be compromised by selection biases.

Additionally the following limitations need to be considered:

- Patient representativeness
- Hospital representativeness
- Information bias
- Measurement errors
- Missing data
- Confounding
- Risk of underrecruiting or overrecruiting

To minimize the risk for the above mentioned biases, certain measurements will be performed. For example this will include, balancing the site selection according to

geography and demographics of melanoma patients in Germany. Minimization of patients lost to follow up will be attempted, by increasing efforts of physicians to contact such patients. Sensitivity analysis will be carried out to investigate bias.

As this is a non-interventional study, mandatory assessments must not be required. Nevertheless data reporting / collection will be conducted in a consistent way, to avoid bias in the data collection process.

This is the first collection of real world data of patients with BRAF mutated locally advanced or metastatic melanoma with or without brain metastases. Due to the unbalance between the two cohorts, and the uncertainity regarding the proportion of both cohorts it was decided to design the study based on two cohorts which will be analyzed separately.

8.10 OTHER ASPECTS

n/a

9. PROTECTION OF HUMAN SUBJECTS

9.1 PATIENT DISCONTINUATION

Patients have the right at any time and for any reason to withdraw their consent that their data are collected and used for the study. Reasons for discontinuation of treatment with the medicinal product or withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Patient is lost to follow-up.

9.1.1 Discontinuation from Treatment with Studied Medicinal Product

The decision for discontinuation from treatment lies with the treating physician in agreement with the patient's decision and is not regulated by this protocol.

The early termination visit should be completed by patients who discontinue treatment with vemurafenib / cobimetinib earlier than planned according to labeling. The primary reason for early treatment discontinuation should be documented on the appropriate CRF page. Every effort should be made to obtain information on patients who discontinue treatment.

9.1.2 Withdrawal from Study

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

9.1.3 Study and Site Discontinuation

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

- Patient enrollment is unsatisfactory

The marketing authorization holder will notify the physician if the study is placed on hold, or if the marketing authorization holder decides to discontinue the study.

The marketing authorization holder has the right to replace a site at any time. Reasons for replacing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the Guidelines for Good Pharmacoepidemiological Practices (GPP) or any other pertinent local law or guideline

9.2 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the Guidelines for GPP published by the International Society of Pharmacoepidemiology and the laws and regulations of the country in which the research is conducted.

The study will comply with national and European Union requirements for ensuring the well-being and rights of participants in non-interventional post-authorization safety studies.

9.3 INFORMED CONSENT

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

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

By signing the form, the patient confirms that he/she has been informed about the study and agrees to pseudonymous data collection, pooling of data with similar scientific data

(if applicable), and the possibility of monitoring activities. It is the responsibility of the physician to obtain written informed consent from each patient participating in the study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. The physician must also explain that the patient is completely free to refuse to enter the study or to withdraw from it at any time, for any reason and without losing the benefit of any medical care to which the patient is entitled or is presently receiving.

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

9.4 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Site Operations Representative in consultation with the Scientific Responsible and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

In addition to the requirements for collecting and reporting all AEs, adverse events of special interest (AESI), and SAEs to the marketing authorization holder, physicians must comply with requirements for AE reporting to the local health authority and IRB/EC.

9.5 CONFIDENTIALITY

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

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

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

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

By signing the protocol, the participating physician commits to complying with all related applicable local laws and regulations, as well as any applicable EU regulations, such as the EU Data Privacy Act.

9.6 FINANCIAL DISCLOSURE

Physicians will provide the marketing authorization holder with sufficient, accurate financial information in accordance with local regulations to allow the marketing authorization holder to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Physicians are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., LPLV).

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ ADVERSE REACTIONS

10.1 SAFETY REPORTING REQUIREMENTS FOR STUDIED MEDICINAL PRODUCTS

10.1.1 Safety Parameters and Definitions

The reporting requirements in this section apply to all studied medicinal products (observational products of interest, as specifically stated in the study Objectives). For safety reporting requirements for non-studied medicinal products, see Section 10.2.

Safety assessments will consist of monitoring and recording SAEs and non-serious AEs (including AEs of special interest), performing safety laboratory assessments, measuring vital signs, and conducting other tests that are deemed critical to the safety evaluation of the study as per standard medical practice.

10.1.1.1 Adverse Events

According to the International Conference of Harmonisation (ICH), an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Appendix 3
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., electrocardiogram [ECG], X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study medicine.

10.1.1.2 Assessment of Serious Adverse Events (Immediately Reportable to the Marketing Authorization Holder), Non-serious Adverse Events of Special Interest (AESI) and Other Non-serious Adverse Events

Serious Adverse Events

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

- Is fatal (i.e., the AE actually causes or leads to death)
- Is life-threatening (NOTE: The term "life-threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires or prolongs inpatient hospitalization (see A)
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study medicine
- Is a significant medical event in the physician's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE criteria; see Appendix 3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each AE recorded on the CRF (for detailed instructions, see Appendix 3).

Adverse Events of Special Interest

AEs of special interest for this study include the following:

- Cases of potential medicine-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Appendix 3).
- Suspected transmission of an infectious agent by the study medicine, 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 only applies when a contamination of the study medicine is suspected.

- Photosensitivity Grade $\geq$ 3
- Grade$\geq$ 3 rash
- Retinal vein occlusion (RVO), Grade $\geq$ 2
- Visual disturbance, Grade $\geq$ 3
- QTc interval prolongation, Grade $\geq$ 3
- Grade 4 elevations in liver function tests (LFTs)
- Any non-cutaneous primary malignancy will be reported as a **serious** adverse event of special interest
- Any cutaneous primary malignancy, including squamous cell carcinoma (SCC), keratoacanthoma (KA), basal cell carcinoma (BCC), new primary melanoma

The occurrence of any cutaneous primary malignancy, including SCC, KA, BCC, new primary melanoma will be considered a Grade 3 adverse event in this study.

Non-Serious Adverse Events other than Adverse Events of Special Interest

All non-serious AEs (in addition to AEs of special interest) must be collected for this study.

10.1.2 Methods and Timing for Capturing and Assessing Safety Parameters

The physician is responsible for ensuring that all AEs collected as per protocol (see Section 10.1.1.1 for definition) are recorded in the AE section of the CRF and reported to the marketing authorization holder in accordance with instructions provided in this section and in Section 10.1.3.

For each AE recorded in the AE section of the CRF, the physician will make an assessment of seriousness (see Section 10.1.1.2), severity (see Appendix 3), and causality (see Appendix 3).

10.1.2.1 Adverse Event Reporting Period

Physicians will seek information on AEs at each patient contact. All AEs subject to the collecting and reporting requirements outlined in this protocol, whether reported by the

patient or noted by study personnel, will be recorded in the patient's medical record and in the AE section of the CRF.

Once the patient is enrolled in the study, AEs will be collected until the end of his or her observation period. After this period, the physician is not required to actively monitor patients for AEs but if the treating physician becomes aware of any related AEs to any medicinal product they should be notified to the competent authority in the Member State where the reactions occurred or to the marketing authorization holder of the suspected medicinal product, but not to both (to avoid duplicate reporting).

10.1.2.2 Procedures for Recording Adverse Events

Physicians should use correct medical terminology/concepts when recording AEs in the AE section of the CRF. Colloquialisms and abbreviations should be avoided.

Only one AE term should be recorded in the event field of the CRF.

See Appendix 3 for further specific instruction regarding:

- Diagnosis versus signs and symptoms
- Adverse Events occurring secondary to other Adverse Events
- Persistent or recurrent Adverse Events
- Abnormal Laboratory Values
- Abnormal Vital Sign Values
- Abnormal Liver Function Tests
- Deaths
    - All events with an outcome or consequence of death should be classified as serious adverse events (SAEs) and reported to the marketing authorization holder immediately. All deaths that occur during the protocol-specified AE reporting period, regardless of relationship to study medicine, must be recorded in the AE section of the CRF and immediately reported to the marketing authorization holder
- Pre-existing Medical Conditions
- Lack of Therapeutic Efficacy or worsening of Malignant Melanoma
- Hospitalization or Prolonged Hospitalization
- Overdoses, Misuses, Abuses, Off-Label Use, Occupational Exposure, or Medication Error
- Drug Interactions
- Quality Defects and Falsified Medicinal Products

10.1.3 Reporting Requirements from Physician to Marketing Authorisation Holder

10.1.3.1 Immediate Reporting Requirements from Physician to Marketing Authorization Holder

Certain events require immediate reporting to allow the Marketing Authorization Holder and the regulatory authorities to take appropriate measures to address potential new risks associated with the use of the medicine. The physician must report such events to the marketing authorization holder immediately; under no circumstances should reporting take place more than 24 hours after the physician learns of the event. The following is a list of events that the physician must report to the marketing authorization holder within 24 hours after learning of the event, regardless of relationship to study medicine:

- SAEs
- Non-serious AEs of special interest
- Pregnancies

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

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

For reports of SAEs and non-serious AEs of special interest, including follow-up, physicians should record all case details that can be gathered immediately (i.e., within 24 hours) in the AE page of the CRF and submit the report via the EDC system.
A report will be generated and sent to Roche Drug Safety by the EDC system.

In the event that the EDC system is temporarily unavailable, please refer to Section 10.1.3.3.

Physicians must also comply with local requirements for reporting SAEs to the local health authority and IRB/EC.

10.1.3.2 Reporting Requirements for Non-Serious Adverse Events

For all non-serious AEs, including follow-up reports, physicians must record all case details that can be gathered within 30 calendar days of learning of the event on the AE section of the CRF and submit the report via the EDC system. A report will be generated and sent to Roche Drug Safety or the relevant marketing authorization holder (for non-Roche studied products) to allow appropriate reporting to relevant competent authorities.

In the event that the EDC system is temporarily unavailable please refer to Section 10.1.3.3.

10.1.3.3 If EDC System is Temporarily Unavailable or not Used

In the event that the EDC system is {temporarily unavailable} a completed paper reporting form and fax coversheet should be faxed/scanned to Roche Drug Safety or its designee immediately (i.e., no more than 24 hours after learning of the event) or within 30 days for non-serious AEs if not AEs of special interest, using the fax number or email address provided to physicians.

Once the system is available again, all information should additionally be entered and submitted via the EDC system.

10.1.3.4 Reporting Requirements for Pregnancies/Breastfeeding Pregnancies/Breastfeeding in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the physician if they become pregnant during the study or within 30 daysafter the last dose of medicine. A Pregnancy Report should be completed by the physician immediately (i.e., no more than 24 hours after learning of the pregnancy and sent to Roche Drug Safety. Pregnancy should not be recorded on the AE CRF. The physician should discontinue Cobimetinib and Vemurafenib andcounsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any SAEs associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the AE section of the CRF.

Suspected adverse reactions that occur in infants following exposure to a medicinal product from breast milk should be reported to Roche Drug Safety.

Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the physician if their partner becomes pregnant during the study or within 30 days after the last dose of study medicinal product. A Pregnancy Report should be completed by the physician immediately (i.e., no more than 24 hours after learning of the pregnancy) and sent to Roche Drug Safety. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study medicine. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report with additional information on the course and outcome of the pregnancy. A physician who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

Abortions

Any abortion should be classified as an SAE (as the marketing authorization holder considers abortions to be medically significant), recorded in the AE section of the CRF, and reported to the marketing authorization holder immediately (i.e., no more than 24 hours after learning of the event; see Section 10.1.3.1).

Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to the medicine {or the female partner of a male patient exposed to the medicine} should be classified as an SAE, recorded in the AE section of the CRF, and reported to the marketing authorization holder immediately (i.e., no more than 24 hours after learning of the event; see Section 10.1.3.1).

10.1.3.5 Reporting Requirements for Adverse Events originating from Patient Reported Outcomes

Although sites are not expected to review the PRO data, if physician/study personnel become aware of a potential adverse event during site review of the PRO questionnaire data, he/she will determine whether the criteria for an adverse event have been met and, if so, these must be reported using the Adverse Event (e)CRF.

10.1.4 Follow-Up of Patients after Adverse Events

10.1.4.1 Physician Follow-Up

The physician should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the physician, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all SAEs considered to be related to studied medicinal product until a final outcome can be reported.

During the study period, resolution of AEs (with dates) should be documented in the AE section of the CRF and in the patient's medical record to facilitate SDV.

All pregnancies reported during the study should be followed until pregnancy outcome.

10.1.4.2 Marketing Authorization Holder Follow-Up

For all AEs, the Marketing authorization holder or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

10.2 SAFETY REPORTING REQUIREMENTS FOR NON-STUDIED MEDICINAL PRODUCTS

Although adverse event information is not being actively solicited for non-studied medicinal products, the physician/consumers are reminded to report any adverse reactions (for which they suspect a causal role of a medicinal product) that come to their attention to the marketing authorization holder of the suspected medicinal product, or to the concerned competent authorities via the national spontaneous reporting system.

In addition, the following should also be reported if occurring during exposure to a marketed medicinal product, even in the absence of adverse events:

- Pregnancy
- Breastfeeding
- Abnormal laboratory findings
- Overdose, abuse, misuse, off-label use, medication error or occupational exposure
- Reports of lack of efficacy
- Product quality defects and falsified medicinal products
- Data related to a suspected transmission of an infectious agent via a medicinal product

· Drug interactions (including drug/drug, drug/food, drug/device and drug/alcohol)

When a patient is not exposed to a marketed medicinal product, but the physician/consumer becomes aware of the potential for a medication error, or an intercepted medication error, this should also be reported.

11. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a study, the marketing authorization holder is dedicated to openly providing information on the study to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The marketing authorization holder will comply with all requirements for publication of study results.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the physician must agree to submit all manuscripts or abstracts to the marketing authorization holder prior to submission for publication or presentation. This allows the marketing authorization holder to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the physician.

In accordance with standard editorial and ethical practice, the marketing authorization holder will generally support publication of multicenter studies only in their entirety and not as individual center data. In this case, a coordinating physician will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors' authorship requirements. Any formal publication of the study in which contribution of marketing authorization holder personnel exceeded that of conventional monitoring will be considered as a joint publication by the physician and the appropriate marketing authorization holder personnel.

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

[redacted]

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Appendix 1
List of Stand-Alone Documents Not Included in the Protocol

List of contact details of responsible parties:

- Dr. Carolin Bender, Medical Manager
  Roche Pharma AG, Emil-Barell-Str. 1, 79639 Grenzach-Wyhlen
  E-Mail: [redacted] Phone: 07624 / 14 2148
- [redacted],
  Roche Pharma AG, Emil-Barell-Str. 1, 79639 Grenzach-Wyhlen,
  E-Mail: [redacted], Phone: [redacted]
- [redacted],
  Roche Pharma AG, Emil-Barell-Str. 1, 79639 Grenzach-Wyhlen,
  E-Mail: [redacted], Phone: [redacted]
- [redacted], Biostatistics and Epidemiology
  Roche Pharma AG, Emil-Barell-Str. 1, 79639 Grenzach-Wyhlen,
  E-Mail: [redacted], Phone: [redacted]
- [redacted],
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Appendix 2
Data Collection Overview (as per Standard of Care)

Data Collection (available data will be collected; no additional diagnostic or monitoring procedures shall be applied to the patients outside of routine clinical practice)	Baseline	Data Collected during Observational Period	End of Treatment	Data Collected during Follow-Up
Inclusion/exclusion criteria [a]	x			
Demographic data [b]	x			
ECOG PS	x	x	x	x
Elevated LDH level within 1 month before cobimetinib / vemurafenib initiation	x			
Quality of Life (EORTC QLQ C30)	x	x	x	
Medical history [c]	x			
Melanoma history [d]	x			
Concomitant medication	x	x	x	
Start date of therapy with cobimetinib / vemurafenib	x			
Start and end date of treatment interruption (if appl.)		x	x	
Start and end date of dose modification (if appl.)		x	x	
Information on dose modification [e] (if appl.)		x	x	
Reason for dose modification / treatment interruption (if appl.)		x	x	
Concomitant local treatment for brain metastasis [f] (if appl.)		x	x	
Tumor Response (CR, PR, SD, PD) [g]		x	x	
Elevated LDH level during therapy / follow up		x	x	x
Date of disease progression		x	x	
Stop date of therapy with cobimetinib / vemurafenib		x	x	
Reason for Discontinuation [h]		x	x	
AEs, SAE, AEs of interest, Pregnancies		x	x	x
Therapy following cobimetinib / vemurafenib (if appl.)				x
Tumor Response to following therapy (CR, PR, SD, PD) [g]				x
Date of death		x	x	x
Reason for death [i]		x	x	x

[a] Inclusion criteria: Date of informed consent, age ≥ 18 years, date of histologically confirmed malignant melanoma, AJCC stage IIIC unresectable or IV, date of positive BRAF V600 mutation analysis; exclusion criteria: no previous with BRAF- and/or MEK inhibitors prior to study entry, no Hypersensitivity to the active substances or to any of the excipients listed in appendix 4

[b] Demographic data include age, sex, and self-reported race/ethnicity.

[c] Medical history including significant diseases within the previous 3 years, major surgeries.

[d] Melanoma history (including information on primary melanoma [date of diagnosis, histologic type, site, Breslow's thickness], BRAF mutation status, date of first diagnosis AJCC stage IIIC unresectable or stage IV, current AJCC stage; prior adjuvant and palliative therapies for melanoma, number of extracranial metastatic sites at baseline; in case of brain metastasis: date of first diagnosis of brain metastasis, prior local treatment for brain metastasis, number of brain metastases, largest diameter, symptomatic/asymptomatic brain metastasis, leptomeningeal disease, concomitant medication for brain metastases [i.e. steroids, anticonvulsants])

[e] dosage and dosing schedule of cobimetinib / vemurafenib

[f] Concomitant local treatment for brain metastasis (including type of treatment [i.e. surgery, radiotherapy], type of radiotherapy [i.e. whole brain radiotherapy, whole brain radiotherapy with boost, stereotactic radiotherapy], total dose and fraction of radiotherapy, number of metastases treated, steroid use prophylactic or therapeutic)

[g] according to clinical practice

[h] PD, AE/SAE, patient's wish, response, physician's decision

[i] Due to melanoma (yes/no/unknown)

Appendix 3
Methods for Assessing and Recording Adverse Events

3.1 Assessment of Severity of Adverse Events

3.2 Assessment of Causality of Adverse Events

3.3 Procedures for recording Adverse Events

Appendix 3.1 Assessment of Severity of Adverse Events

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

Adverse Event Severity Grading Scale

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

Note: Based on the NCI CTCAE (v4.0), which can be found at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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

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

[c] If an event is assessed as a "significant medical event," it must be reported as an SAE (see Section 10.1.3.1 for reporting instructions), per the definition of SAE in Section 10.1.1.2.1.

[d] Grade 4 and 5 events must be reported as SAEs (see Section 10.1.3.1 for reporting instructions), per the definition of SAE in Section 10.1.1.2.1.

Appendix 3.2 Assessment of Causality of Adverse Events

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

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

For patients receiving combination therapy, causality will be assessed individually for each of the medicinal product.

Appendix 3.3 Procedures for recording Adverse Events

Appendix 3.3.2 Diagnosis versus Signs and Symptoms

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

Appendix 3.3.3 Adverse Events Occurring Secondary to Other Events

In general, AEs that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary AE that is separated in time from the initiating event should be recorded as an independent event in the AE section of the CRF. For example:

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

All AEs should be recorded separately in the AE section of the CRF if it is unclear as to whether the events are associated.

Appendix 3.3.4 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once in the AE section of

the CRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent AE becomes more severe, the most extreme severity should also be recorded in the AE section of the CRF. If the event becomes serious, it should be reported to the marketing authorization holder immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 10.1.3.1 for reporting instructions). The AE section of the CRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to SAEs.

A recurrent AE is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an AE should be recorded separately in the AE section of the CRF.

Appendix 3.3.5 Abnormal Laboratory Values

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

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the physician's judgment

Note: For oncology studies, certain abnormal values may not qualify as AEs.

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

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 ´ the upper limit of normal [ULN] associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded in the AE section of the eCRF.

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

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once in the AE section of the eCRF (see Appendix 3.3.4 for details on recording persistent AEs).

Appendix 3.3.6 Abnormal Vital Sign Values

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

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

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

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded in the AE section of the CRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once in the AE section of the CRF (see Appendix 3.3.4 for details on recording persistent AEs).

Appendix 3.3.7 Abnormal Liver Function Tests

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

- Treatment-emergent ALT or AST > 3 ´ ULN in combination with total bilirubin > 2 ´ the ULN
- Treatment-emergent ALT or AST > 3 ´ ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded in the AE section of the CRF (see Appendix 3.3.5) and reported to the marketing authorization holder immediately (i.e., no more than 24 hours after learning of the event) either as an SAE or a non-serious AE of special interest (see Section 10.1.3.1).

Appendix 3.3.8 Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 10.1.2.1), regardless of relationship to study medicine, must be recorded in the AE section of the eCRF and immediately reported to the marketing authorization holder (see Section 10.1.3.1).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the AE section of the CRF. Generally, only one such event should be reported. The term **"sudden death"** should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the AE section of the CRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

Appendix 3.3.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions in the CRF.

A preexisting medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events in the AE section of the CRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

Appendix 3.3.10 Lack of Therapeutic Efficacy

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. These data will be captured as effectiveness assessment data only. In most cases, the expected pattern of progression will be based on clinical criteria In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE. This exception from reporting includes events of disease progression with a fatal outcome which are clearly attributable to disease progression.

Appendix 3.3.11 Hospitalization or Prolonged Hospitalization

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE (per the definition of SAE in Section 10.1.1.2), except as outlined below.

The following hospitalization scenarios are not considered to be SAEs:

- Hospitalization for respite care
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.
  - The patient has not suffered an AE.

Hospitalization due solely to progression of the underlying cancer.The following hospitalization scenarios are not considered to be SAEs but should be reported as AEs instead:

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

Appendix 3.3.12 Overdoses, Misuses, Abuses, Off-Label Use, Occupational Exposure, or Medication Error

Any overdose, misuse, abuse, off-label use, occupational exposure, medication error (including intercepted or potential), or any other incorrect administration of medicine under observation should be noted in the Drug Administration section of the CRF. Any overdose, misuse, abuse, off-label use, occupational exposure or medication error (including intercepted or potential) reports must be forwarded to the marketing authorization holder with or without an AE.

Reports with or without an AE should be forwarded to the marketing authorization holder as per non-serious timelines. If the associated AE fulfills the seriousness criteria, the event should be reported to the marketing authorization holder immediately (i.e., no more than 24 hours after learning of the event, see Section 10.1.3.1).

For the purpose of reporting cases of suspected adverse reactions, an occupational exposure to a medicine means an exposure to a medicine as a result of one's professional or non-professional occupation.

Appendix 3.3.13 Quality Defects and Falsified Medicinal Products

Reports of suspected or confirmed falsified medicinal product or quality defect of a medicinal product, with or without an associated AE, should be forwarded to the marketing authorization holder as per non-serious timelines. If the associated AE fulfills the seriousness criteria, the event should be reported to the marketing authorization holder immediately (i.e., no more than 24 hours after learning of the event, see Section 10.1.3.1).

Appendix 3.3.14 Drug Interations

Reports of suspected or confirmed drug interactions, including drug/drug, drug/food, drug/device and drug/alcohol interactions should be forwarded to the marketing authorization holder as per non-serious timelines. If the associated AE fulfills the seriousness criteria, the event should be reported to the marketing authorization holder immediately (i.e., no more than 24 hours after learning of the event, see Section Section 10.1.3.1)

Appendix 3.3.15 Safety data other than Adverse Events

Safety data other than AEs (see section 8.3 Variables) should be recorded in an appropriate section of the CRF and reviewed on an ongoing basis.

Appendix 4
List of excipients

4.1 Cotellic

Tablet core	Film coating
Lactose monohydrate	Polyvinyl alcohol
Microcrystalline cellulose (E460)	Titanium dioxide (E171)
Croscarmellose sodium (E468)	Macrogol 3350
Magnesium stearate (E470b)	Talc (E553b)

4.2 Zelboraf

Tablet core	Film coating
Croscarmellose sodium	Polyvinyl alcohol
Colloidal anhydrous silica	Titanium dioxide (E171)
Magnesium stearate	Macrogol 3350
Hydroxypropylcellulose	Talc
	Iron oxide red (E172)