Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

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Vemurafenib in Multiple Nonmelanoma *BRAF*^{V600}-Mutated Cancers

Hyman DH, Puzanov I, Vivek Subbiah V et al.

This supplement contains the following items:

Roche

F. HOFFMANN-LA ROCHE LTD

CLINICAL STUDY PROTOCOL

PROTOCOL NUMBER MO28072

An open-label, phase II study of vemurafenib in patients with BRAF V600 mutation-positive cancers

RO5185426
VEMURAFENIB

IND NUMBER 73,620

EUDRACT NUMBER 2011-004426-10

Sponsor: F. Hoffmann-La Roche LTD
Grenzacherstrasse 124,
4070 Basel, Switzerland

PROTOCOL APPROVAL

Protocol Number / Version: MO28072 / Version 1

Date: 30NOV2011

Protocol approved by:

Luisa Veronese MD (International Medical Leader) Maria Luisa Veronese

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This protocol is intended for use in a life-threatening indication: Yes x No ☐

SYNOPSIS OF PROTOCOL MO28072

TITLE	An open-label, phase II study of vemurafenib in patients with BRAF V600 mutation-positive cancers
SPONSOR	F. Hoffmann-La Roche Ltd CLINICAL PHASE II
INDICATION	Patients with cancers (excluding melanoma and papillary thyroid cancer) harboring BRAF V600 mutations as identified by the routinely performed mutation analysis assays at each individual participating site
OBJECTIVES	Primary objective: • To evaluate the efficacy of vemurafenib in patients with cancers harboring BRAF V600 mutations as response rate (RR) at Week 8 determined by the Investigator using Response Evaluation Criteria In Solid Tumors, Version 1.1 (RECIST, v1.1) or International Myeloma Working Group (IMWG) uniform response criteria and to identify tumor types for further development Secondary objectives: • To evaluate the safety and tolerability of vemurafenib in this patient population. • To evaluate in solid tumors and multiple myeloma (MM) overall response rate (ORR), clinical benefit rate (Clinical response (CR) or Stringent Complete Response (sCR)), partial response (PR) or very good partial response (VGPR) and stable disease [SD]) of vemurafenib, duration of response (DOR), time to response, time to tumor progression (TTP), progression free survival (PFS) and overall survival (OS). Exploratory objective: • To evaluate the Roche Companion Diagnostic (CoDx) cobas® 4800 BRAF V600 Test for the detection of BRAF V600 in tumor samples.
TRIAL DESIGN	Open-label, multicenter, multinational, phase II study exploring the efficacy and safety of vemurafenib in a diverse population of patients with cancers (excluding melanoma and papillary thyroid cancer) known to harbor BRAF V600 mutations and for whom vemurafenib is deemed the best treatment option in the opinion of the Investigator. Patients with BRAF V600 mutation-positive cancers will be identified through mutation analysis assays, as routinely performed at each participating site. BRAF V600 mutation and test used for the detection of the BRAF mutation assay will be recorded in the eCRFs. The presence of BRAF V600 mutation will be retrospectively confirmed by the cobas® 4800 BRAF V600 Mutation Test. The trial will consist of a Screening Period (Day –28 to −1), a Treatment Period, an End-of-Treatment Visit occurring when vemurafenib is discontinued for any reason, a Safety-Follow-Up

	visit occurring 28 days after the last dose of vemurafenib, and a Survival Follow-Up Period lasting for a maximum of 12 months for each patient after their last dose of study medication to monitor survival status. Day 1 of the study (baseline) will be defined as the first day a patient receives vemurafenib. One cycle of therapy will be defined as 28 days of treatment. Patients will be asked to attend clinic visits at regular intervals during the study for safety and efficacy assessments. The study will include 8 cohorts of patients with the following cancers: Cohort 1. Non-small cell lung cancer (NSCLC) Cohort 2. Ovarian cancer Cohort 3 Colorectal cancer Cohort 4. Cholangiocarcinoma/cancer of the biliary tract Cohort 5. Breast cancer Cohort 6. Prostate cancer Cohort 7. Multiple myeloma (MM) Cohort 8. Solid tumors other than the above Recruitment/enrollment in any of the above cohorts may present some challenges due to the low frequency of BRAF V600 mutations in the specific disease settings. Therefore, if no patients are enrolled within any of the cohorts after one year from the start of the study, then that particular cohort will be closed and enrollment for that cohort will be stopped. Cohort 8 will be closed to enrollment when all other cohorts are closed, regardless of the number of patients recruited at that time. This cohort is quite heterogeneous and will be examined primarily to seek efficacy signals in the relatively rare BRAF V600 mutation-positive tumors. Enrolled patients will receive continuous oral dosing of vemurafenib at 960 mg twice daily (b.i.d) until the development of progressive disease (as per Investigator assessment), unacceptable toxicity, withdrawal of consent, protocol violation endangering the patient's safety, death, reasons deemed critical by the treating physician, or study termination by the Sponsor. Patients who develop disease progression but, in the opinion of the Investigator, would still benefit from continuing vemurafenib may continue treatment with vemurafenib after discussion with the Sponsor.
NUMBER OF PATIENTS	It is estimated that approximately 104-152 patients with solid tumors or multiple myeloma will be enrolled in this study. Approximately 13–19 patients per indication (Cohort) will be included. The number of patients can be less than 104 if a cohort is closed earlier as a result of stopping rules for the cohort.

TARGET POPULATION	Adult patients with BRAF V600 mutation-positive cancers (excluding melanoma and papillary thyroid cancer). BRAF V600 mutations will be identified by mutation analysis assays as routinely performed at each individual participating site. **Eligibility Criteria** <u>For solid tumors only</u>: 1. Histologically confirmed cancers (excluding melanoma and papillary thyroid cancer) that harbor a BRAF V600 mutation and are refractory to standard therapy or for which standard or curative therapy does not exist or is not considered appropriate by the Investigator 2. Measurable disease according to RECIST, v1.1 3. Adequate hematologic function, as defined by the following laboratory values; test performed within 7 days prior to the first dose of vemurafenib: a. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L b. Platelet count $\geq 100 \times 10^9$/L <u>For multiple myeloma only</u>: 4. Patients with a confirmed diagnosis of MM harboring a BRAF V600 mutation 5. Patients must have received at least one line of prior systemic therapy for the treatment of MM. A line of treatment is sequential treatment without interruption for response and subsequent progression 6. Patients treated with local radiotherapy (with or without concomitant exposure to steroids for pain control or management of cord/nerve root compression); two weeks must have elapsed since the last date of radiotherapy, which is recommended to be a limited field. Patients who require concurrent radiotherapy should have entry into the Study deferred until the radiotherapy is completed and two weeks have passed since the last date of therapy 7. Patients must have relapsed and/or refractory MM with measurable disease, defined as disease that can be measured either by serum or urinary evaluation of the monoclonal component or by serum assay of free light chain (FLC) of at least one of the following three parameters: a. Serum M-protein > 0.5 g/dL b. Urine M-protein > 200 mg per 24 hours c. Involved FLC level > 10 mg/dL (> 100 mg/L)provided serum FLC ratio is abnormal 8. Adequate hematologic function as defined by the following laboratory values performed within 7 days prior to the first dose of vemurafenib:

a. Absolute neutrophil count (ANC) ≥ 1.0 x 109/L
b. Platelets count ≥ 50 x 109/L

For all patients (solid tumors and MM):

9. Signed written informed consent approved by the relevant Independent Ethics Committee (IEC) / Institutional Review Board (IRB) must be obtained prior to performing any study-related procedures
10. Male or female ≥ 18 years of age
11. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2
12. Must have recovered from all side effects of their most recent systemic or local treatment
13. Able to swallow pills
14. Adequate hematologic, renal and liver function as defined by the following laboratory values; tests performed within 7 days prior to the first dose of vemurafenib:
    a. Hemoglobin ≥ 9 g/dL
    b. Serum creatinine ≤ 1.5 times upper limit of normal (ULN) or creatine clearance (CrCl) > 50 mL/min by Cockroft–Gault formula (Protocol Appendix 1)
    c. Aspartate aminotransferase (AST [SGOT]) and alanine aminotransferase (ALT [SGPT]) ≤ 2.5 times ULN (≤ 5 times ULN if considered due to primary or metastatic liver involvement)
    d. Serum bilirubin ≤ 1.5 times ULN
    e. Alkaline phosphatase ≤ 2.5 times ULN (≤ 5 times ULN if considered due to tumor)
15. Negative serum pregnancy test within 7 days prior to commencement of dosing in premenopausal women. Women of non-childbearing potential may be included without serum pregnangy test if they are either surgically sterile or have been postmenopausal for ≥ 1 year
16. Fertile men and women must use an effective method of contraception during treatment and for at least 6 months after completion of treatment as directed by their physician. Effective methods of contraception are defined as those which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly (for example implants, injectables, combined oral contraception or intra-uterine devices). At the discretion of the Investigator, acceptable methods of contraception may include total abstinence in cases where the lifestyle of the patient ensures compliance. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods] and withdrawal

are not acceptable methods of contraception.)

17. Absence of any psychological, familial, sociological, or geographical conditions potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before trial entry

Exclusion Criteria

1. Melanoma, papillary thyroid cancer or hematological malignancies (with the exception of multiple myeloma)
2. Uncontrolled concurrent malignancy (early stage or chronic disease is allowed if not requiring active therapy or intervention and is under control)
3. For MM, solitary bone or solitary extramedullary plasmacytoma as the only evidence of plasma cell dyscrasia
4. Active or untreated CNS metastases. Patients with brain metastasis are eligible if asymptomatic, off corticosteroid therapy, and without evidence of disease progression in brain for $\geq$ 2 months
5. History of or known carcinomatous meningitis
6. Concurrent administration of any anti-cancer therapies (e.g., chemotherapy, other targeted therapy, experimental drug, etc.) other than those administered in this study
7. Known hypersensitivity to vemurafenib or another BRAF inhibitor
8. Prior treatment with a BRAF or MEK inhibitor (prior sorafenib is allowed)
9. Pregnant or lactating women
10. Refractory nausea and vomiting, malabsorption, external biliary shunt or significant bowel resection that would preclude adequate absorption.
11. Any of the following within the 6 months prior to first vemurafenib administration:
    - Myocardial infarction, severe/unstable angina, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack
12. Pulmonary embolism within 30 days prior to first vemurafenib administration

	13. Hypertension not adequately controlled by current medications within 30 days prior to first vemurafenib administration 14. History or presence of clinically significant ventricular or atrial dysrhythmias ≥ Grade 2 (National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 [NCI CTCAE, v4.0]) 15. Corrected QT (QTc) interval ≥ 450 msec at baseline or history of congenital long QT syndrome 16. Uncontrolled medical illness (such as infection requiring treatment with intravenous [IV] antibiotics) 17. Other severe, acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or vemurafenib administration or may interfere with the interpretation of study results which, in the judgment of the Investigator, would make the patient inappropriate for entry into this study 18. Unwillingness to practice effective birth control 19. Inability to comply with other requirements of the protocol
LENGTH OF STUDY	The trial will consist of a Screening Period (Day –28 to −1), a Treatment Period, an End-of-Treatment Visit occurring when vemurafenib is discontinued for any reason, a Safety-Follow-Up Visit occurring 28 days after the last dose of vemurafenib and a Survival Follow-Up period lasting for a maximum of 12 months for each patient after his/her last dose of study medication to monitor survival status. Day 1 (baseline) of the study will be defined as the first day a patient receives vemurafenib. Recruitment period will be approximately 18 months. Enrolled patients will receive continuous oral dosing of vemurafenib at 960 mg b.i.d. until the development of progressive disease (as per Investigator assessment), unacceptable toxicity, withdrawal of consent, protocol violations endangering patient's safety, death or reasons deemed critical by the treating physician, or study termination by the Sponsor. Patients who develop disease progression but, in the opinion of the Investigator, would still benefit from continuing vemurafenib may continue treatment with vemurafenib after discussion with the Sponsor. Patients who discontinue vemurafenib for any reason (e.g., disease progression, an adverse event [AE], etc.) other than withdrawal of consent will continue to be followed for survival and new anti-cancer therapy every 3 months after last dose until

	death, for a maximum of 12 months for each patient after his/her last dose of study medication, withdrawal of consent, or loss to follow-up.
END OF STUDY	The end of study will occur when all patients have been followed for survival for a maximum period of 12 months from the last dose of study medication, have died, withdrawn consent or are lost to follow up, whichever occurs first.
INVESTIGATIONAL MEDICAL PRODUCT(S) DOSE/ ROUTE/ REGIMEN	Patients will receive continuous oral doses of vemurafenib 960 mg b.i.d. starting on Day 1 of the study Treatment Phase until the development of progressive disease (as per Investigator assessment), unacceptable toxicity, consent withdrawal, protocol violation endangering patient's safety, death, reasons deemed critical by the treating physician or study termination by the Sponsor. Patients who develop disease progression but, in the opinion of the Investigator, would still benefit from continuing vemurafenib may continue treatment with vemurafenib after discussion with the Sponsor.

NON-INVESTIGATIONAL MEDICAL PRODUCT(S)	N/A
COMPARATOR "DRUG" (or STANDARD OF CARE) DOSE/ ROUTE/ REGIMEN	N/A
CENTERS	This is a multinational, multicenter study with approximately 15 centers.
- EFFICACY	Efficacy of vemurafenib will be captured by Response Rate (RR), clinical benefit ([CR or sCR, PR or VGPR and stable disease (SD)], and time-dependent endpoints (DOR, overall response rate assessed via best overall response (BOR), time to response, time to tumor progression, PFS and OS). The primary endpoint will be RR at Week 8 in each indication. For solid tumors to be assigned a status of partial response (PR) or complete response (CR) (i.e., a responder), changes in tumor measurements must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met, i.e., patients need to have two consecutive assessments of PR or CR to be responders. For patients with solid tumors, response will be assessed according to RECIST, v1.1, criteria (Eisenhauer EA et al. Eur J Cancer 2009;45(2):228-47). Assessments will be performed by the Investigator using computed tomography (CT) or magnetic resonance imaging (MRI) scan every 8 weeks. For patients with MM, response will be assessed according to International Myeloma Working Group [IMWG] uniform response criteria (Durie BGM et al. Leukemia 2006;20:1467-73.), e.g., patients need to have two consecutive assessments of CR, sCR, VGPR or PR to be responders. Assessments will be performed by the Investigator 8 weeks after starting vemurafenib and every 28 days thereafter. Bone marrows assessments will be performed only once to confirm CR or sCR. Secondary endpoints for solid tumors and MM will include duration of response (DOR), time to response, time to progression (TTP),overall response rate (ORR), clinical benefit rate [CR or sCR, PR or VGPR and stable disease (SD)], time to tumor progression, PFS and overall survival (OS).
- SAFETY	The NCI-CTCAE, v4.0, will be used to quantify the intensity of AEs occurring during treatment in this study. Patients will be assessed for AEs at each clinical visit and as necessary throughout the study. Incidence, type, and severity of AEs, serious adverse events (SAEs), incidence of AEs and SAEs leading to vemurafenib interruption or discontinuation, and cause of death will be reported All other safety monitoring will occur by the reporting of AEs, by the assessment of routine laboratory values (blood counts and differential and serum chemistries), vital signs,

electrocardiograms (ECGs), dermatology, and head & neck evaluations for cutaneous squamous cell carcinoma (SCC) and non-cutaneous SCC, respectively, chest CT scans for non-cutaneous SCC surveillance and findings on physical examinations.

Performance Status (PS) will be measured using the ECOG PS Scale at each clinical visit.
As part of the physical exam, a medical history will be collected, including demographics, relevant medical history, previous and current diseases, prior therapies including surgeries and relative responses, prior skin cancer history, therapies and procedures, all medications started within 14 days prior to screening visit, and measurements for weight (kg) and height (cm, screening visit only).

The initial (screening/baseline) complete physical examination should include the evaluation of the head, eyes, ears, nose, and throat (HEENT) and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, neurological systems. Subsequent physical examinations during the study for safety assessment may be restricted to evaluation of specific systems or areas of interest, including those with previously abnormal findings or associated with symptomatic or laboratory evidence of toxicity. A skin examination by the treating physician should, however, be performed at each visit.

Vital signs will be recorded for all patients and will include: blood pressure (BP), temperature (degrees Celsius, °C), heart rate, and respiratory rate.

ECG monitoring will occur at Screening and throughout the study treatment.

Guidelines for dose modification and discontinuation are reported in protocol section 6.1.1

Special Safety Considerations

Cutaneous squamous cell carcinoma (cSCC)
Cutaneous SCC is defined as an event requiring close monitoring. These events must always be designated as SAEs in order to ensure their reporting to the Health Authorities in an appropriate and timely manner. Patients are required to have full skin examination by a dermatologist to screen and monitor for SCC, basal cell carcinoma (BCC), actinic keratosis and keratoacanthoma (KA). Dermatology evaluation will be performed at screening/baseline (anytime up to 28 days prior to Day 1), approximately day 28 of therapy, every 12 weeks thereafter while patient is on study, when patient discontinues vemurafenib unless done within the prior 12 weeks and at the end of study safety follow-up visit, 28 days after discontinuing vemurafenib. Patients should report to their physician any new skin lesion or change, including rash and photosensitivity, while on study treatment and any suspicious lesions should be referred to a dermatologist for further evaluation as required.

		The initial examination by the dermatologist should include a complete dermatological history of prior medications and cutaneous SCC risk factors (i.e., radiation therapy, sun exposure, immunosuppression, prior SCC, use of tanning beds, precursor lesions, and photochemotherapy for psoriasis). Any lesion suspected of representing a new SCC, BCC, actinic keratosis, or keratoacanthoma identified by the dermatologist should be treated as per local standard of care. Skin biopsies of any suspicious lesions identified at baseline and during the study must be biopsied/excised and sent for pathological examination. Available blocks/sections should also be sent to a designated central pathology laboratory for confirmation of diagnosis. Patients who develop cSCC or any skin lesions during the trial may choose to continue or discontinue from the trial after consultation with the Investigator. If the patient elects to continue in the trial, definitive treatment (i.e., surgical excision) of any SCC is required. *Non-cutaneous squamous cell carcinoma (Treating Physician or Other Qualified Physician):* A head and neck examination must be performed by the treating physician at baseline and during the study for all enrolled patients. The head and neck examination will consist of at least a visual inspection of the oral mucosa and lymph node palpation. This will be done at screening/baseline (anytime up to 28 days prior to Day 1), every 12 weeks while the patient is on study, when the patient discontinues vemurafenib unless done within the prior 12 weeks and at the end of study Safety Follow-Up visit 28 days after discontinuing vemurafenib. Any suspicious findings will be referred to an appropriate specialist. For all patients (with solid tumours and MM) a CT scan of the chest is required for non-cutaneous SCC screening and surveillance. As radiologic assessments for tumor burden are a standard requirement for solid tumour patients, it is not necessary to perform a separate chest CT. Instead, the same (routine tumor assessment CT) should suffice for monitoring of non-cutaneous SCC for patients with solid tumours. However, chest CTs for the evaluation of SCC are required at a minimum of every 6 months for each patient. *Photosensitivity* Photosensitivity has been reported in patients treated with vemurafenib in clinical trials. The majority of cases were mild or moderate in severity. All patients should be advised to avoid sun exposure and wear protective clothing and use sun block and lip balm (minimum of SPF 30, re-applied every 2 to 3 hours) during vemurafenib treatment and for at least 5 to 10 days after study drug discontinuation.
-	PHARMACOKINETICS/ PHARMACODYNAMICS	N/A
-	QUALITY OF LIFE AND	N/A

	PHYSICAL SYMPTOMS	
-	EXPLORATORY - BIOMARKERS	N/A

PROCEDURES (SUMMARY):

Patients with BRAF V600 mutation-positive cancers will be identified through mutation analysis assays as routinely preformed at each participating site (the BRAF V600 mutation and test used for the detection of BRAF mutation assay will be recorded in the eCRFs). All efforts should be made to collect a tumor sample for retrospective confirmation of the BRAF mutation using the cobas 4800 V600 mutation kit. This tumor sample should preferably be from the original specimen used to detect the BRAF mutation.

Patients will be assessed for tumor response or progression using the RECIST criteria (current version 1.1) or IMWG response criteria and monitored for AEs according to the study procedures.

STUDY ASSESSMENTS:

Screening Period

The following assessments should be performed within 28 days before the first administration of vemurafenib on Day 1 (unless they have already been conducted during this time period as part of the patient's routine clinical care):

- Signed written informed consent approved by the relevant Independent Ethics Committee (IEC) / Institutional Review Board (IRB) must be obtained prior to performing any study-related procedures
- Documentation of BRAF V600 mutation and test used for the identification of the mutation.
- All efforts should be made to collect a tumor sample for retrospective confirmation of the BRAF mutation using the cobas 4800 V600 mutation kit. This tumor sample should preferably be from the original specimen used to detect the BRAF mutation. The original tumour block will be returned back to the site.
- Medical history (including demographics)
- Physical examination, including the evaluation of the head, eyes, ears, nose, and throat (HEENT); cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and a neurological systems examination; height and weight (height will only be measured during screening)
- Vital signs (blood pressure, heart rate, temperature, respiratory rate)
- 12-lead ECG, including heart rate, PR interval, QRS duration, QT and QTc intervals and ECG findings
- ECOG Performance Status
- Hematology, including hemoglobin, hematocrit, platelet count, white blood cell count (WBC) and absolute neutrophil count (ANC)
- Biochemistry (including glucose, blood urea nitrogen ([BUN]], creatinine or creatinine clearance, sodium, potassium, calcium, magnesium, bicarbonate ([if routinely performed on venous blood samples]), total bilirubin with fractionation into direct and indirect (if total bilirubin elevated during the study), alkaline phosphatase, AST ([SGOT]], ALT [(SGPT)].
- Serum pregnancy test within 7 days prior to commencement of dosing for women of child-bearing potential. Women surgically sterile or postmenopausal for ≥ 1 year are not to be considered for a pregnancy test.
- Tumor assessments for patients with solid tumors (CT/MRI of the chest, abdomen and pelvis [C/A/P]). CT/MRI of the brain may also be performed as per standard of care
- Assessments for mutliple myeloma (Skeletal survey, Serum protein electrophoresis (SPEP) with quantitation of M-protein by immunofixation, Urine protein electrophoresis (UPEP) using 24 hours urine protein electrophoresis, Serum free light chains, Bone marrow for histology, cytogenetics and FISH, and flow cytometery with or without biopsy, Beta 2 microglobulin albumin and lactate dehydrogenase (LDH)

- Dermatology evaluation by a dermatologist.
- Head and neck examination (as part of the evaluation for SCC) performed by the treating physician
- CT of chest for evaluation of noncutaneous SCC (for all patients, solid tumors and MM. For solid tumors, the routinely performed chest CT for tumor assessment may be used as chest CT for the evaluation of non cutaneous SCC while the patient is taking vemurafenib).
- Concomitant medications
- AEs (including SAEs) related to study-mandated procedures from time ICF is signed

Treatment Period

Visits during the treatment period are to be completed on Day 1, Day 15, Day 29, and every 28 days thereafter. A window of 4 days prior to the scheduled visit date and one day after the scheduled visit date (– 4 days / + 1 day) is allowed for each visit from Cycle 2 onwards (28-day cycle). The following assessments should be performed during the Treatment Period:

- Physical examination (as described previously) on Day 1, Day 15, Day 29 and every 28 days for the first 8 cycles and then every 8 weeks thereafter until study drug discontinuation
- Vital signs (as described previously) on Day 1, Day 15, Day 29 and every 28 days for the first 8 cycles and then every 8 weeks until study drug discontinuation
- 12-lead ECG (as described previously) on day 29, every 28 days for the following 3 months and every 12 weeks thereafter until study drug discontinuation
- ECOG performance status on Day 1, Day 15, Day 29 and every 28 days for the first 8 cycles and then every 8 weeks thereafter until study drug discontinuation
- Hematology (as described previously) on Day 1, Day 15, Day 29 and every 28 days thereafter until study drug discontinuation
    - Hematology assessments do not need to be repeated on Day 1 if performed within 7 days prior to the first vemurafenib administration
- Biochemistry (as described previously) on Day 1, Day 15, Day 29 and every 28 days thereafter until study drug discontinuation
    - Biochemistry assessments do not need to be repeated on Day 1 if performed within 7 days prior to the first vemurafenib administration
- The following tumor assessments are to be performed for patients with solid tumors;
    - CT/MRI of the chest/abdomen/pelvis (C/A/P) every 8 weeks after starting vemurafenib. The same imaging technique (CT or MRI) should be used for each patient throughout the study
    - CT/MRI of the brain as per standard care
- The following asssements are to be performed for patients with MM 8 weeks after starting vemurafenib and every 4 weeks thereafter;
    - Serum protein electrophoresis (SPEP) with quantitation of M-protein level by immunofixation, urine protein electrophoresis (UPEP) using 24-hour urine protein electrophoresis, Serum free light chains , LDH, and beta 2 microglobulin. Bone marrow analsyis only to be done only to confirm complete remission after two consecutaive immunofixation analyses are negative.
- Dermatology evaluation by a dermatologist 28 days after starting vermurafenib and every 12 weeks thereafter until study drug discontinuation
- Head and neck examination (as part of the evaluation for SCC) performed by the treating physician every 12 weeks after starting vemurafenib

- Chest CT for evaluation of SCC every 6 months after starting vemurafenib (for all patients with solid tumors and MM)
- Drug dispensation on Day 1 and every 28 days thereafter until study drug discontinuation
- Drug accountability every 28 days after starting vemurafenib until study drug discontinuation
- Review of the Drug Dosing Exception Diary every 28 days after starting vemurafenib until study drug discontinuation
- Concomitant medications throughout the Treatment Period
- AEs (including SAEs) throughout the Treatment Period
- Vemurafenib administration throughout the Treatment Period

End-of-Treatment Visit

The End-of-Treatment Visit will occur when the patient discontinues vemurafenib for any reason, unless the patient withdraws consent or is lost to follow up. The following assessments will be conducted at the End-of-Treatment Visit:

- Physical examination (as described previously)
- Vital signs (as described previously)
- 12-lead ECG (as described previously)
- ECOG Performance Status
- Hematology (as described previously)
- Biochemistry (as described previously)
- Tumor assessments (as described previously) if not done within the last 8 weeks
- Response assessments for multiple myeloma if not done within the last 28 days
- Dermatology evaluation by a dermatologist if not done within the previous 12 weeks
- Head and neck examination (as part of the evaluation for SCC) performed by the treating physician if not done within the previous 12 weeks
- Drug accountability
- Review of the Drug Dosing Exception Diary
- Concomitant medications
- AEs (including SAEs)

Safety Follow-Up Visit

The Safety-Follow-Up Visit(s) will occur after 28 (± 5) days from discontinuation of vemurafenib. The following assessments will be conducted at the Follow-Up Visit

- 12-lead ECG (as previously described)
- Dermatology evaluation by a dermatologist
- Head and neck examination (as part of the evaluation for SCC) performed by the treating physician

- CT of the chest for evaluation of SCC must be performed 6 months following study drug discontinuation or until initiation of another anti-neoplastic therapy
- Concomitant therapy
- AEs (including SAEs)
- Follow up for disease progression for those patients who have discontinued study drug for any reason (AEs, etc.) other than disease progression
- Survival status

Survival Follow-Up Period

The following assessments will be conducted during the Survival Follow-Up Period

- Survival status every 3 months after the last dose until death or for a maximum of 12 months for each patient after their last dose of study medication, withdrawal of consent or loss to follow-up (whichever occurs first)
- Record of next anti-cancer therapy

STATISTICAL CONSIDERATIONS AND ANALYTIC PLAN

Primary Variable

The primary endpoint is RR at Week 8 for each cohort, as assessed by the Investigator using RECIST, v1.1 for patients with solid tumors or IMWG uniform response criteria for patients with MM.
For patients with solid tumors, responders at Week 8 will be defined based on tumor assessment status of PR or CR at Week 8.
For MM patients to be assigned the status of a responder, patients need to have CR, sCR, VGPR, or PR. Bone marrows will be performed only to confirm CR or sCR. Patients without a post-baseline tumor assessment will be considered to be non-responders.

Secondary Efficacy Variables

The secondary efficacy endpoints for each cohort will include: BOR, clinical benefit (CR (or sCR) plus PR (or VGPR) plus SD), duration of response (DOR), time to response, time to tumor progression, PFS, and OS.

Safety Variables

Adverse events (AEs), all AEs, AEs grade 3 or 4, AEs leading to treatment interruption and discontinuation, serious adverse events (SAEs), premature discontinuation from study and treatment, hematology and biochemistry parameters, exposure to study medication and skin evaluation, head/neck evaluations, chest CT scan will be the primary safety variables for each cohort. Vital signs, electrocardiogram, ECOG performance status, concomitant medications and physical examination will be the secondary safety variables.

Study Populations

The main analysis population for the efficacy analysis will be the intent-to-treat (ITT) population, which will include all patients enrolled in the study irrespective of whether they have received study medication or not. ITT1 to ITT8 will correspond to the ITT population for each cohort (Cohort 1 to Cohort 8, respectively).

The per-protocol (PP) population will not be defined due to the small number of patients per cohort, but protocol deviations will be listed.

The safety populations SP1 to SP8 will correspond to the the safety populations for Cohort 1 to Cohort 8, respectively, and will include, for each cohort, all patients who have received at least one dose of study medication.

Statistical Model

Primary Efficacy Variable

The main analysis for the RR will be based on Adaptive design based on Simon's two stage design for a single proportion (*Ref: Lin and Shih (2004). Adaptive Two-stage design for Single-Arm Phase II A Cancer Clinical TrialsLin and Biometrics 60, 482-490*).

Stage I will be defined as when a pre-specified number of patients (as determined in the Sample Size section 8.3) will have a minimum of 8 weeks of treatment, develop progressive disease, prematurely withdraw from study, or die, whichever occurs first.

If a pre-specified minimal response rate will not be achieved in certain cohorts in the first stage of the study, this cohort will be closed and no further enrollment of patients will be performed for that cohort. Otherwise, enrollment continues into Stage II until a pre-determined number of additional patients has been reached (as explained in the Sample Size section). At the conclusion of this study, the study treatment will be declared effective or ineffective for each indication (Cohort) based on rules for Stage II.

The analysis at Stage II (for lower or higher desirable confirmed response) for each Cohort will be performed when all patients enrolled in the study, as estimated in the Sample Size section, will have a minimum of 8 weeks of treatment, develop progressive disease, withdraw, or are lost to follow-up, whichever occurs first.

The final analysis for the RR for each Cohort will be at the end of Stage II.

Secondary efficacy variables (final analysis for OS)

The final analysis for OS for each cohort will take place when all patients in that cohort have been followed for survival for a maximum of 12 months for each patient after their last dose of study medication, have died, have withdrawn consent, or are lost to follow up, whichever occurs first. More details are in Efficacy Analysis Data section (8.3.2).

Hypothesis Testing

The adaptive two-stage design allows the original estimation of the Stage II response rate to be reassessed, based on information at Stage I, in the event that it was too optimistic or too sceptical to be the true response rate.

For example, for patients in each cohort, we assume that RR of 15% would be a very low RR and vemurafenib will be "under-performing" for this cohort. A RR of 45% would be a high desirable RR, while a RR of 35% woud be a low desirable RR, for Stage II.

The hypotheses for all cohorts for Stage I are:

H_0: $\pi_{N1} < \pi_0$ where $\pi_0 = 15\%$
H_1: $\pi_{N1} \geq \pi_0$ where $\pi_0 = 15\%$

where N1 is a number of patients in Stage 1 and $\pi 0$ is a very low, undesirable RR.

If H0 is rejected (and H1 is accepted at Stage I), further patients will be enrolled based on the number of responders in Stage I and their data will be collected in the second stage.

The hypotheses for all cohorts at the end of Stage II for a low desirable response, π1L, are:

H_0: $\pi_N \leq \pi_{1L}$ where $\pi_{1L} = 35\%$
H_1: $\pi_N > \pi_{1L}$ where $\pi_{1L} = 35\%$

The N notifies the total number of patients for each cohort.

The hypotheses for all cohorts at the end of Stage II for a high desirable response, π1H, are:

H_0: $\pi_N \leq \pi_{1H}$ where $\pi_{1H} = 45\%$
H_1: $\pi_N > \pi_{1H}$ where $\pi_{1H} = 45\%$

Stopping rules for enrollment and screening

If no patients are enrolled within any cohort after one year from the start of the study, as described above, then that particular cohort will be closed and enrollment for that cohort will be stopped.

Stopping rules for each cohort:

Rules for Stage 1:
Stage I will be stopped if the number of responders is less than the pre-specified number assessed in the Sample Size estimation section (e.g. if there is none or only one responder out of first seven patients). However if a clear clinical benefit has been observed for patients in the cohort, e.g. the majority of patients recorded SD at Week 8 and no CR or PR is recorded, then enrolment into Stage II might be allowed for this cohort.

If there is the required response during Stage I or a good clinical benefit is observed for particular cohort as mentioned above, then additional patients will be enrolled in the second stage of the corresponding cohort, in order to achieve total number of patients as specified in the Tables 1 and 2 below.

Cohort 8 will be closed to enrollment when all other cohorts are closed regardless of the number of patients recruited at that time. This cohort is quite heterogeneous and will be examined primarily to seek efficacy signals in the relatively rare BRAF V600 mutation-positive tumors.

Rules for Stage 2:
A study treatment will be considered to be non-efficacious in a cohort in Stage 2 if the number of responders is lower than specified in the sample size calculations, as presented in the Table below or
- unacceptable toxicity occurs or
- best overall response, BOR (confirmed) is lower than 15%.

Efficacy Data Analyses

The primary efficacy endpoint is RR at Week 8 in each cohort, as assessed by the Investigator using RECIST, v1.1 or IMWG response criteria. This is an early phase II study and cohorts are independent, hence there will be no adjustment for multiplicity. Number and percentage of responders with corresponding Clopper-Pearson 95% confidence intervals will be provided for each Cohort. The overall response rate will be assessed via BOR. The clinical benefit and BOR will be analyzed in a similar way to RR.

Duration and time of response in each indication will be summarized only for responders, i.e., for the patients whose confirmed response is CR or PR for patients with solid tumors and CR, sCR, VGPR or PR for patients with MM.

Estimates for the survivor function for the time-to-event variables, such as time to progression (TTP), PFS, OS, duration of response, and time to response, will be obtained by using the Kaplan-Meier (KM) approach together with associated 95% CI.

Interim Analysis:

There will be no interim efficacy analysis except an efficacy analysis of response rate at Stage I

Other analyses

Demographics and medical history will be summarized for each cohort.

Safety Data Analyses

Safety Data Analysis

The safety variables will be summarized for the safety population where the safety population is SP1 to SP8. All safety variables will be summarized for each cohort.

All AEs will be assessed according to the NCI CTCAE, v4.0, grading system. The analysis of AEs will focus on treatment-emergent AEs, i.e., AEs occurring on the day of or after first administration of study drug (vemurafenib). Non-treatment emergent AEs (i.e., those occurring before commencement of study medication) will only be listed.

The incidence, type, and severity of AEs will be summarized according to the primary system-organ class (SOC) and within each SOC, by MedDRA preferred term. Summary tables will be presented for time to first onset of the AE of special interest, e.g. SCC.

AEs leading to treatment interruption and discontinuation as well as SAEs will be analyzed in a similar way to all AEs. Cause of death will also be summarized and listed.

Results from skin evaluation, head and neck evaluations, chest CT scan (e.g., number of lesions, SCC - keratoacanthoma type, etc.) will be summarized using frequencies and percentages. Premature discontinuation of treatments with corresponding reason for discontinuation will be summarized by frequency tables and listed. The discontinuation from study will be also summarized and listed.

Descriptive statistics will be presented for cumulative vemurafenib doses and duration of exposure.

Laboratory parameters, hematology, and serum biochemistry will be presented in shift tables of NCI-CTCAE grade at baseline versus worst grade during the Treatment Period. The summary of laboratory parameters presented by means, standard deviation, minimum, and maximum will be also presented.

Vital signs (blood pressure, temperature, heart rate, and respiratory rate) and ECG (heart rate, PR interval, QRS duration, QT interval and QTc interval) will be summarized over time by means of mean, median, and range (mean and maximum). The ECG findings will be also presented by frequency tables over time. The ECOG PS will be summarized by frequency tables over time and percentage of patients in different categories will be presented by bar charts at different time points. Physical examination variables collected only at baseline (e.g., height) will be summarized for baseline only while other physical examination variables will be summarized over time by visits and reported in patients' listings. Concomitant therapy will be summarized by frequency tables and percentages.

Sample Size Estimation

The sample size estimation is based on Lin and Shih's paper and corresponding SAS program.

There will be 8 cohorts. The estimated number of patients required for this study will be in range of 104 to 152 patients (depending on response in Stage I).

Cohorts will have a minimum of 13 and a maximum of 19 patients (depending on results in Stage I).

A proportion of 15% is chosen for a low response, based on Section 8.3.1.1 in the protocol and on our present knowledge.

However, if the number of responders are 2, 3, or 4 out of 7 patients in Stage I, then the study medication is possibly efficacious for that cohort and further data will be collected based on "low desirable response at Stage II" Sample Size estimation, i.e., an additional 12 patients will be enrolled in order to have a total of 19 patients for that cohort.

If there are 5 or more responders out of 7 patients, then further data will be collected based on "high desirable response at Stage II" Sample Size estimation, i.e., an additional 6 patients will be enrolled in order to have a total of 13 patients for that cohort.

Assuming, RRs as specified in the prior hypothesis testing, a power of 80% for high desirable response and 70% for low desirable response and two-sided alpha of 0.1, the following number of patients is required for each Cohort.

Table 1.
Sample Size for Each Cohort

	At the end of Stage Two	
	Low desirable response	**High desirable response**
NSCLC	19	13
Ovarian cancer	19	13
Colorectal cancer	19	13
Cholangiocarcinoma/cancer of biliary tract	19	13
Breast Cancer	19	13
Prostate cancer	19	13
Multiple Myeloma	19	13
Other tumors	19	13
Total number of patients	**152**	**104**

Details regarding Stage I and number of responders are presented in **Table 2**.

Table 2.
Sample Size for Each Cohort and Each Stage

	Stage (Two-Stage Design)		**Total Number of Patients in Each Cohort**	**Two-Sided Alpha Level / Power**
	Stage I	**Stage II ****		
All Cohorts				
Low response at the end of Stage I				
Number of patients	7	19	19	10% / 70%
Number of responders *	≥ 2 and ≤ 4	≥ 5		
High response at the end of Stage I				
Number of patients	7	13	13	10% / 80%
Number of responders *	≥ 5	≥ 6		

The sample size was estimated using the method of Lin and Shih's paper (Biometrics. 2004;60:482-490) and corresponding SAS program.

** Number of patients needed to respond in order to continue into Stage II or have a positive result at the end of trial.*

***This columns display a maximum number of patients required for each cohort and number of responders that should be present at end of Stage II in order to declare efficacious treatment.*

Table 3.
Schedule of Assessments

	Screening Period[1]	Treatment Period [2] (Allowed visit window: –4 days / +1 day from cycle 2 onwards)										End of Treatment Visit [3]	Safety-Follow-Up Visit[4]	Survival Follow-Up[5]
Cycle		1		2	3	4	5	6	7	8	9 onwards			
Day	–28 to –1	1	15	29	57	85	113	141	169	197	Every 28 Days			
Informed consent[6]	X													
Documentation of BRAF V600 mutation and test performed	X													
Medical history and demographics	X													
Physical examination[7]	X	X	X	X	X	X	X	X	X	X	X (every 8 weeks)	X		
Vital signs[8]	X	X	X	X	X	X	X	X	X	X	X (every 8 weeks)	X		
12-lead ECG[9]	X			X	X	X	X			X	X (every 12 weeks)	X	X	
ECOG performance status	X	X	X	X	X	X	X	X	X	X	X (every 8 weeks) X	X		
Hematology[10]	X	X[11]	X	X	X	X	X	X	X	X	X	X		
Biochemistry[12]	X	X[11]	X	X	X	X	X	X	X	X	X	X		
Serum pregnancy test[13]	X													
Solid tumor assessments	X				X		X		X		X (every 8 weeks)	X		

	Screening Period[1]	Treatment Period [2] (Allowed visit window: –4 days / +1 day from cycle 2 onwards)										End of Treatment Visit [3]	Safety-Follow-Up Visit[4]	Survival Follow-Up[5]
Cycle		1		2	3	4	5	6	7	8	9 onwards			
Day	–28 to –1	1	15	29	57	85	113	141	169	197	Every 28 Days			
(CT/MRI)[14]														
Assesments for Multiple Myeloma[15]	X				X[16]	X[16]	X[16]	X[16]	X[16]	X[16]	X[16]	X[16]		
Dermatology evaluation[17]	X			X			X			X	X (every 12 weeks)	X	X	
Head and neck assessment for SCC[18]	X					X			X		X (every 12 weeks)	X	X	
Chest CT for evaluation of SCC[19]	X								X		X (every 6 months)		X[20]	
Drug dispensation		X		X	X	X	X	X	X	X	X			
Drug accountability				X	X	X	X	X	X	X	X	X		
Drug Dosing Exception Diary[21]				X	X	X	X	X	X	X	X	X		
Concomitant medications[22]	X	X										X	X	
AEs / SAEs[23]	X	X										X	X	
Vemurafenib administration		X												
Follow-up for disease progression													X	
Survival status[5)]													X	X
Next anticancer therapy														X

	Screening Period[1]	Treatment Period [2] (Allowed visit window: –4 days / +1 day from cycle 2 onwards)										End of Treatment Visit [3]	Safety-Follow-Up Visit[4]	Survival Follow-Up[5]
Cycle		1		2	3	4	5	6	7	8	9 onwards			
Day	–28 to –1	1	15	29	57	85	113	141	169	197	Every 28 Days			

Notes Day 1 = first dose of study drug (vemurafenib)

1. Apart from obtaining written informed consent, no screening procedure may be performed before the patient has been confirmed to be positive for the BRAF V600 mutation. All efforts should be made to collect a tumor sample (formalin-fixed paraffin-embedded tumor tissue [FFPET] or 3-5 serially cut unstained 5-µm sections from one FFPET block) for retrospective confirmation of the BRAF mutation using the cobas 4800 V600 mutation kit. This tumor sample should preferably be from the original specimen used to detect the BRAF mutation. The original tumour block will be returned to the site.
2. Visits during the Treatment Period are to be completed on Day 1, Day 15, Day 29 and every 28 days thereafter until study drug discontinuation. A window of 4 days prior to the scheduled visit date and one day after the scheduled visit date (–4 days / + 1 day) is allowed for each visit from Cycle 2 onwards.
3. The End of Treatment Visit will be performed when the patient discontinues vemurafenib regardless of when it occurs.
4. The Safety Follow-Up Visit will be performed after 28 (±5) days from discontinuation of vemurafenib for any reason other than disease progression (such as AE).
5. The Survival Follow-Up period will extend from the last dose until death or for a maximum of 12 months for each patient after his/her last dose of study medication, withdrawal of consent or loss to follow-up (whichever occurs first).
6. Informed consent must be obtained prior to performing any study procedure including Screening assessments.
7. Includes the evaluation of the head, eyes, ears, nose, and throat (HEENT); cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal and neurological systems examination; and height (cm) and weight (kg). Height will only be measured during screening.
8. Includes blood pressure, heart rate, temperature and respiratory rate.
9. Includes heart rate, PR interval, QRS duration, QT and QTc intervals and ECG findings.
10. Includes hemoglobin, hematocrit, platelet count, white blood cell count (WBC) and absolute neutrophil count (ANC)
11. Hematology and biochemistry assessments do not need to be repeated on Day 1 if performed within 7 days of first vemurafenib administration. NB: if it is necessary to repeat these blood tests, the results must be known before the patient receives first dose of vemurafenib to ensure that the inclusion and exclusion criteria related to these tests are met.
12. Includes glucose, blood urea nitrogen [BUN], creatinine or creatinine clearance, sodium, potassium, calcium, magnesium, bicarbonate ([if routinely performed on venous blood samples],), total bilirubin with fractionation into direct and indirect (if total bilirubin elevated during the study), alkaline phosphatase, AST ([SGOT]], ALT ([SGPT]],

	Screening Period[1]	Treatment Period [2] (Allowed visit window: –4 days / +1 day from cycle 2 onwards)										End of Treatment Visit [3]	Safety-Follow-Up Visit[4]	Survival Follow-Up[5]
Cycle		1		2	3	4	5	6	7	8	9 onwards			
Day	–28 to –1	1	15	29	57	85	113	141	169	197	Every 28 Days			
	13. Serum pregnancy test to be performed within 7 days prior to first vemurafenib administration for women with childbearing potential. 14. Includes for solid tumour patients only: CT/MRI of the chest, abdomen and pelvis [C/A/P]). The same imaging technique (CT or MRI) should be used for these patients throughout the study. CT/MRI of the brain may also be performed as per standard of care. 15. Skeletal survey, Serum protein electrophoresis (SPEP), Urine protein electrophoresis (UPEP), Serum free light chains, 24 hour urine proteins, Bone marrow for histology, cytogenetics and FISH, and flow cytometery with or without biopsy, Beta 2 microglobulin, albumin and lactate dehydrogenase (LDH) 16. Bone marrow assessment only to be done to confirm complete remission after two consecutaive immunofluorescence analyses are negative. 17. Performed by a dermatologist. For patients who develop any suspicious new skin lesion during treatment with vemurafenib. Further confirmation by a designated central pathology laboratory. 18. Performed by the treating physician as part of the evaluation for SCC. 19. CT of the chest for the evaluation of noncutaneous SCC (for all patients, solid tumors and MM). For patients with solid tumours, the routinely scheduled radiographic assessment for tumor burden may be used (if available) as the chest CT for the evaluation of noncutaneous SCC while the patient is taking vemurafenib. 20. Must be performed 6 months following study drug discontinuation or until initiation of another anti-neoplastic therapy. 21. Patients will keep a diary to record ONLY those occasions when a vemurafenib dose was missed (morning or evening, each day of treatment). The patient will bring this diary with him/her to each study visit to allow missed doses to be recorded by the Investigator. 22. All concomitant medications during the study started within 14 days prior to the screening visit and up to the end of study visit must be recorded. 23. During screening AEs are not recorded in the eCRF unless they are SAEs which are related to protocol-mandated procedures. ALL AEs (including SAEs) must be recorded from the time of first vemurafenib administration. After the last dose of vemurafenib any new, non-serious AEs which the Investigator considers may be related to vemurafenib should be reported up to 28 days after last dose. Any SAEs reported after last dose which the Investigator considers related to vemurafenib must be reported indefinitely.													

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TABLES

FIGURE

APPENDICES

GLOSSARY OF ABBREVIATIONS

ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALP	alkaline phosphatase
ALT (SGPT)	alanine aminotransferase
ANC	absolute neutrophil count
AST (SGOT)	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
b.i.d.	twice daily
BCC	basal cell carcinoma
BOR	best overall response
BRAF	v-raf murine sarcoma viral oncogene homolog B1
cSCC	cutaneous squamous cell carcinoma
°C	degrees Celcius
CHF	congestive heart failure
CI	confidence interval
C_{max}	maximum plasma concentration
CR	complete response(s)
CRC	colorectal cancer
cRcL	Creatinine Clearance
CRF	Case Report Form(s)
CT	computer tomography
Cm	Centimeters
CNS	central nervous system
COSMIC	Catalog of Somatic Mutations in Cancer
dL	deciliter
DLT	dose-limiting toxicity
DOR	duration of response

ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
EGFR	epidermal growth factor receptor
ERK	extracellular signal-regulated kinase
EMA	European Medicines Agency
ER	estrogen receptor
ESF	eligibility screening form
EU	European Union
FDA	United States Food and Drug Administration
FLX	Free Light Chain
g	gram
GCP	Good Clinical Practice
GDP	guanosine diphosphate
GGT	γ-glutamyltransferase
GMP	Good Manufacturing Practice
GTP	guanosine triphosphate
H_0	null hypothesis
H_1	alternative hypothesis
HEENT	head, eyes, ears, nose and throat
hERG	human ether-à-go-go related gene
HR	heart rate
IC_{50}	50% inhibitory concentration
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB/IEC	Institutional Review Board/Independent Ethics Committee

IRC	Independent Review Committee
ITT	intent to treat
IV	intravenous
IxRS	Interactive Voice/Web Response System
KA	Keratoacanthoma
L	Liter
LFT	liver function test
MAP	mitogen-activated protein
MBP	micro-precipitated bulk powder
MedDRA	Medical Dictionary for Regulatory Activities
MEK1	mitogen-activated protein kinase kinase 1
mg	milligram
ml	milliliter
MGUS	monoclonal gammopathy of undetermined significance
MM	multiple myeloma
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NCI-CTC	National Cancer Institute-Common Toxicity Criteria
NCI-CTCAE	National Cancer Institute-Common Toxicity Criteria for Adverse Events
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
OR	objective response(s)
ORR	objective response rate
OS	overall survival
PD	progressive disease, also: Pharmacodynamic
PFS	progression-free survival
PS	Performance Status
PK	pharmacokinetic

p.o.	*per* os (oral administration)
PP	per protocol
PR	partial response(s)
RNA	Ribonucleic acid
RR	response rate
QTc	corrected QT interval
RAS	RAt Sarcoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SCC	squamous cell carcinoma
sCR	stringent complete response
SD	stable disease or standard deviation
SOC	Systgems Organ Class
SP	safety population
SPF	Sun Protection Factor
siRNA	silencing RNA
SPEP	serum protein electrophoresis
$T_{1/2}$	half-life
T_{MAX}	time to maximum plasma concentration
TTP	time to tumor progression
UCI	upper confidence interval
ULN	upper limit of normal
UPEP	urine protein electrophoresis
US	United States
VGPR	very good partial response
WBC	white blood cell

PART I: STUDY DESIGN AND CONDUCT

1. BACKGROUND AND RATIONALE

1.1 The Ras-MAP-Kinase Signaling Pathway

The RAS-MAP-kinase signaling pathway is a highly conserved enzymatic pathway that transduces extracellular signals into long-term changes in intracellular biochemistry and gene expression (1). Because the pathway, in its different forms, is critically involved in cell-cycle control and development, mutations in genes that affect the system—in particular, in genes that encode the RAS-MAP-kinase signaling proteins themselves, their intracellular regulators, or their cognate membrane receptors—are among the most common mutations found in cancer cells (see below). Consequently, the RAS-MAP-kinase pathway has been the subject of intense pharmacologic analysis, as any agent that specifically targets this pathway could have important clinical utility in a variety of cancers.

The core of the RAS-MAP-kinase signal transduction system consists of a membrane-associated RAS protein and 3 serine/threonine protein kinases.

1.1.1 RAS

The RAS proteins belong to the large RAS superfamily of monomeric GTPases (1). Like other GTP-binding proteins, RAS functions as a switch, cycling between two distinct conformational states:active when GTP is bound and inactive when GDP is bound. Two classes of signaling proteins regulate RAS activity by influencing its transition between active and inactive states. Guanine nucleotide exchange factors (GEFs) promote the exchange of bound nucleotide by stimulating the dissociation of GDP and the subsequent uptake of GTP from the cytosol, thereby activating RAS. GTPase-activating proteins (GAPs) increase the rate of hydrolysis of bound GTP by RAS, thereby inactivating RAS.

Three RAS proteins (H-RAS, K-RAS and N-RAS) are implicated in human cancer. Mutations in genes encoding these three proteins can produce hyperactive variants that are resistant to GAP-mediated GTPase stimulation. These mutational alterations lock the proteins permanently into their GTP-bound active states, which may ultimately promote dysregulated growth and cancer. Activated RAS mutations are particularly common in cancer. Mutations in K-RAS, for instance, have been identified in 58% of pancreatic, 34% of large intestine, 29% of biliary tract, 20% of small intestine, 17% of lung, 15% of endometrial, and 14% of ovarian cancer samples sequenced to date (2, 3).

1.1.2 MAP-Kinase

Once activated (either by binding GTP in normal cells or as a result of mutational alterations in cancer cells), RAS activates a downstream serine/threonine phosphorylation cascade composed of 3 mitogen-activated protein (MAP) kinases (1). The pathway activated by RAS begins with a MAP-kinase-kinase-kinase called RAF, which activates the MAP-kinase-kinase MEK. MEK, in turn, activates a MAP-kinase called ERK.

The MAP-kinase ERK then relays the signal further downstream by phosphorylating various proteins in the cell, including gene regulatory proteins and other protein kinases.

Among the genes activated by this pathway are those required for cell proliferation, such as the genes encoding G1 cyclins. Consequently, constitutive activation of the phosphorylation cascade can result in inappropriate mitotic drive, resulting in the unregulated growth that characterizes cancer cells.

1.2 Oncogenic BRAF Kinase Mutations in Various Cancers

The MAP-kinase-kinase-kinase RAF acts at the intersection between the initial part of the signaling pathway, comprised of a receptor tyrosine kinase and RAS, and the subsequent phosphorylation cascade that transduces the extracellular signal to the nucleus. To date, mutations in three different RAF proteins (ARAF, BRAF, and CRAF) have been implicated in human cancer (2, 3). Among these, mutations in BRAF are the most common, particularly in melanoma, where BRAF mutations have been identified in 67% of primary melanoma tumors and 80% of melanoma short-term cultures (4). BRAF mutations have also been identified in 38% of thyroid, 12% of large intestine, 12% of genital tract, 11% of ovarian, 11% of eye, and 10% of biliary tract cancer cell line isolates sequenced to date and described in the Catalog of Somatic Mutations in Cancer (COSMIC) database (2, 3).

1.2.1 Melanoma

Activating mutations in BRAF have been identified at high frequency in melanoma primary tumors, occurring in up to 67% of sequenced melanoma samples (4). These mutations typically fall within the kinase domain of the protein, with a single substitution (V600E) accounting for 90% of the sequenced mutants. Mutated BRAF proteins isolated from these tumors have elevated kinase activity and have the capacity on their own to transform NIH3T3 cells. Moreover, depletion of mRNA for oncogenic BRAF via silencing RNAs has been shown to induce a variety of phenotypic changes in cultured melanoma cells, including lower proliferation rates, reduced anchorage-independent growth, and apoptosis (5, 6). Other uncommon BRAF variants, including V600K, V600R and V600D, have been observed, and nonclinical data indicate that these variant mutations also result in constitutive activation of the BRAF kinase (7).

Recently, it has been demonstrated that therapeutic inhibition of the activating BRAF V600E mutation with vemurafenib, a new selective BRAF kinase inhibitor, has significant anticancer activity in melanoma patients. These results will be described in more detail below (Section 1.3, Vemurafenib).

1.2.2 Colorectal Cancer

Colorectal cancer (CRC) develops slowly over several years and progresses through cytologically distinct benign and malignant stages of growth, ranging from single crypt lesions through adenoma to, finally, malignant carcinoma with the potential for invasion and metastasis (8-10). This progression occurs in parallel with widespread genomic instability that leads to successive accumulation of mutations in genes controlling epithelial cell growth and differentiation (11).

Among these multiple genomic alterations, activating mutations in BRAF were found in published studies to occur in 5% to 15% of CRC cases, 80% of which induced a V600E transition in the kinase domain (12-14). In the COSMIC database, BRAF mutations were

observed in 13% (1357 of 10,828 unique samples) of cancers originating in the colon and rectum, 99% of which were the V600E transition (2, 3). The most common mutations in CRC occur in three proteins, the p53 tumor suppressor (52% of sequenced samples), K-Ras (34%), and APC (29%).

An increasing number of studies have shown that the presence of activating BRAF mutations in CRC tumors is associated with significantly shorter OS (15-21). Thus, in one recent study (16), the median OS was 8.6 months among CRC patients with mutated BRAF tumors compared with 20.8 months among those with wild type BRAF tumors ($P<0.0010$). The impact of BRAF mutations on PFS, however, appears to be more complex, with half of the studies showing a significant decrease in PFS (19-21), and half showing no effect (16-18).

In addition to the effects on OS and, possibly, PFS, another clinically important feature of BRAF mutations is that patients whose tumors bear activating BRAF mutations do not experience significant benefit from either cetuximab or panitumumab treatment, therapeutic antibodies directed against EGFR that are used in CRC therapy (22). This is consistent with the fact that BRAF activity functions downstream of the receptor and, hence, activated BRAF mutations can suppress the growth inhibition normally induced by the therapeutic antibody.

One small phase I study assessed the efficacy and safety of the selective BRAF kinase inhibitor vemurafenib in 21 CRC patients harboring BRAF V600E mutations (23). Among 19 patients who were evaluable for response, 1 had a confirmed PR and 4 had minor responses (≥ 10% shrinkage). Five patients showed a mixed response pattern (i.e., with both regressing and progressing lesions). Although the observed activity in this small CRC study was less than in melanoma, it is important to note that all of the patients in the trial had received at least 3 lines of prior therapy and the pharmacokinetic distribution of study drug appeared to be 20% lower than expected. Despite these caveats, though, anticancer activity in CRC was observed. This further encourages exploration of the efficacy of vemurafenib in CRC tumors harboring activated BRAF V600 mutations.

1.2.3 NSCLC

BRAF mutations have been detected in patients with non–small-cell lung cancer (NSCLC), although at a significantly lower frequency than in melanoma patients (4, 24). In the COSMIC database, for instance, BRAF mutations were observed in 1% of NSCLCs (7 of 1372 unique samples) (2, 3). By comparison, mutations in p53, epidermal growth factor receptor, K-Ras kinase, and cyclin-dependent kinase inhibitor 2A occurred at frequencies of 26%, 22%, 15%, and 14%, respectively. Intriguingly, of the 7 BRAF mutations identified in NSCLCs, only one occurred in amino acid 600 (V600E transition); the remaining 6 occurred in amino acids 466 (n=2), 469 (n=2), and 597 (n=2). The mutations at 466 and 469 are thought to alter residues important in AKT-mediated BRAF phosphorylation, which has led to the speculation that BRAF mutations may be qualitatively different in NSCLCs and melanomas, specifically in that they may affect AKT, rather than RAS, signalling in the former (24).

However, a more recent study, which does not appear to have been included in the COSMIC database yet, suggests that the V600E mutation may occur more frequently and may have important clinical relevance (25). In this study, 1046 surgically resected NSCLCs, comprising 739 adenocarcinomas and 307 squamous cell carcinomas (SCCs), were subjected to sequencing analysis. BRAF mutations were found to be present in 36 adenocarcinomas (4.9%) and one SCC (0.3%). Twenty-one of the mutations (56.8%) were V600E, and 16 (43.2%) were non-V600E. Importantly, V600E-mutated tumors showed an aggressive histotype characterized by micropapillary features in 80% of patients and were significantly associated with shorter disease-free survival (15.2 vs. 52.1 months; $p<0.001$) and OS (29.3 vs. 72.4 months; $p<0.001$). By contrast, all non-V600E mutations were associated with neither clinicopathologic parameters nor prognosis. Thus, BRAF V600E mutations in human lung cancers may identify a subset of tumors sensitive to targeted therapy.

1.2.4 Breast Cancer

According to the COSMIC database (2, 3), the most common mutations identified to date in breast cancer cells occur in three proteins: the catalytic subunit of phosphoinositide-3-kinase (26% of sequenced samples), the p53 tumor suppressor (23%), and cadherin-1 (16%).

In the same database, mutations in BRAF were found in 2% of breast cancer cell lines (14 of 599 unique samples), of which 10 contained the BRAF V600E mutation. These values are similar to those observed in other published studies, although BRAF mutations were observed to occur at a frequency as high as 10% in some series. In one study on 31 breast cancer cell lines, for instance, 3 carried mutations in BRAF (26). A second study found BRAF mutations in 4 of 36 breast cancer cell lines (2 of the 4 carried V600E mutations) (27). A third study that used high-resolution DNA melting to identify somatic mutations identified one mutation in exon 15 of the BRAF gene out of 60 samples (28), whereas another study found no BRAF mutations in 12 sequenced breast cancer cell lines (29). Whether BRAF mutations (and mutations in other RAS-MAP kinase pathway genes) may be found in combination with phosphoinositide-3-kinase pathway mutations remains controversial (27, 30)

Intriguingly, recent evidence suggests that BRAF mutations may be associated with distinct clinical breast cancer pathologies. In an extensive molecular characterization of 41 human breast cancer cell lines (31), 146 oncogenic mutations were identified among 27 well-known cancer genes (3.6 mutations per cell line). Mutations in genes from the p53, RB and PI3K tumor suppressor pathways were widespread among all breast cancer cell lines. However, two gene mutation profiles specifically associated with luminal-type and basal-type breast cancer cell lines. The luminal mutation profile involved E-cadherin and MAP2K4 gene mutations and amplifications of Cyclin D1, ERBB2 and HDM2. The basal mutation profile involved BRCA1, RB1, RAS and BRAF gene mutations and deletions of p16 and p14ARF. The authors suggested that these subtype-specific gene mutation profiles may constitute a genetic basis for the heterogeneity observed among human breast cancers. To date, though, the effect of activated BRAF alleles on outcomes and patient management in breast cancer patients has not been examined.

1.2.5 Ovarian Cancer

Ovarian carcinomas are a heterogeneous group of neoplasms, but are usually classified into 4 major histopathologic subtypes: serous, endometrioid, mucinous, or clear cell (32). Each of the 4 types appears to be characterized by distinct genetic abnormalities. Of these, the low-grade serous carcinomas characteristically have mutations in KRAS or BRAF, which are critical to tumor growth (33, 34). In the COSMIC database (2, 3), 17 (39%) of 44 unique samples of serous micropapillary carcinoma had BRAF mutations, all of which were the V600E allele. BRAF mutations are much rarer in high-grade serous carcinomas (35, 36) and in other histopathological subtypes of ovarian cancer (32).

These preceding data have led to the hypothesis that two separate and distinct pathways lead to low-grade vs. high-grade serous carcinomas in ovarian cancer. Low-grade carcinomas are thought to develop from serous borderline tumors and progress in a stepwise fashion. They are slow-growing, indolent tumors that have a relatively good prognosis compared with high-grade carcinomas. Molecular genetic analysis has shown that serous borderline tumors and low-grade serous carcinomas typically display sequence mutations in KRAS or BRAF, but with infrequent mutations in TP53 (35, 36). By contrast, high-grade serous carcinomas often present in advanced stages (stages III and IV) and rarely harbor mutations in KRAS or BRAF. Instead, > 75% of these high-grade tumors, which grow rapidly and are highly aggressive, harbor TP53 mutations (37-41).

From the preceding considerations, ovarian cancer patients with low-grade serous carcinomas may be particularly attractive candidates for treatment with the specific activated BRAF kinase inhibitor vemurafenib. However, despite the fact that activated BRAF mutations appear to be found primarily in low-grade serous carcinoma (35, 36), BRAF mutations have been found at a frequency of 4% in higher grade serous carcinomas, where their presence can augment the activity of the MEK inhibitor Cl-1040 (33). Furthermore, poor survival has been shown to associate with a specific single-nucleotide polymorphism in BRAF in patients with invasive epithelial ovarian cancer (42), suggesting a potential role for BRAF kinase in higher grade disease. Finally, borderline evidence of an association between single-nucleotide polymorphisms in BRAF and susceptibility to mucionous ovarian cancer has also been observed (43). To date, however, the effect of activated BRAF alleles on clinicopathologic feature, outcomes, and patient management in ovarian cancer patients has yet to be fully examined.

1.2.6 Prostate Cancer

Studies have shown that genes involved in androgen (testostersone) action, carcinogen defenses, and growth-factor–signaling pathways are critical determinants in prostate cancer pathogenesis (44). The key signal transduction pathway affected in prostate cancer cells appears to be the phosphoinositide-3 kinase pathway. Consistent with this observation, several studies have found that BRAF mutations are rare in prostate cancers (45-47).

Nonetheless, other results suggest that activating BRAF mutations may play an important role in some prostate cancers. First, though relatively rare, the BRAF V600E allele does occur in some prostate cancer patients. In one study, mutations in codon 600

were found in 21 (10.2%) of 206 prostate adenocarcinomas (48), whereas BRAF mutations were found in 42 (4%) of 1,188 unique prostate cancer samples in the COSMIC database (2, 3) (of the latter, 22 contained V600E, 4 contained V600E, and 16 contained V600M mutations). Second, after screening a large cohort of prostate cancer patients, gene rearrangements in the RAF family were observed to recur in advanced prostate cancer (49). Third, MAP kinase activation has been shown to correlate with disease progression in human prostate cancer specimens (50), although this may not be strictly attributable to BRAF kinase (46). Finally, RAF kinase protein expression was found to be elevated and BRAF inhibitor reduced in human prostate tumors (48).

The observation that MAP kinase activation correlates with disease progression suggests that the Ras-MAP kinase pathway may promote the development of more advanced androgen-independent forms of the disease. Indeed, in a genetically engineered mouse model system, the BRAF V600E allele was found to initiate, but not maintain, invasive prostate adenocarcinoma (51). However, the effect of activated BRAF alleles on clinicopathologic feature, outcomes, and patient management in prostate cancer patients has yet to be fully explored.

1.2.7 Multiple Myeloma

Multiple myeloma (MM) is a clonal late B-cell disorder in which malignant plasma cells expand and accumulate in the bone marrow, leading to cytopenias, bone resorption, and the production of the monoclonal protein (52). The disease appears to evolve hereogeneously in different patients. In some with new diagnosis MM, the disease may exhibit a slow progressive evolution from monoclonal gammopathy of undetermined significance (MGUS) (for example, evolving anemia over several months), whereas in others it may be associated with features of high clonal aggressiveness (for example, plasma cell leukemia or extramedullary plasmacytomas) (53, 54).

Consistent with the primary function of plasma cells, i.e., immunoglobulin gene rearrangements, many of the causative genetic changes in MM arise as a result of aberrant chromosomal translocations, deletions, and other abnormalities (53, 54). Nonetheless, point mutations in RAS mutations are also observed, consistent with an important role for the RAS-MAP-kinase pathway, as well. The prevalence of activating N- or K-RAS mutations is about 30 to 40% in newly diagnosed MM tumors, with only a small increase occurring during tumor progression (55, 56). Activating BRAF mutations also occur in MM, but at apparently lower frequency (57). In the COSMIC database, 4 (2%) of 180 unique MM samples contained BRAF mutations, of which 3 contained the V600E allele (2, 3). Similarly, among 38 tumor genomes subjected to massive parallel sequencing, 4% contained activating BRAF mutations (58).

Although no studies have been published on BRAF inhibition in MM patients, it is intriguing to note that MEK inhibition was cytotoxic for the majority of tumor cells tested from patients with relapsed and refractory MM (84%), regardless of mutational status of RAS or BRAF genes (59). However, the effect of activated BRAF alleles on clinicopathologic feature, outcomes, and patient management in MM remains unknown.

1.2.8 Cholangiocarcinoma / Cancers of the Biliary Tract

Biliary tract cancers include a spectrum of invasive adenocarcinomas encompassing both cholangiocarcinoma, i.e., cancers arising in the intrahepatic, perihilar, or distal biliary tree, and carcinoma arising from the gallbladder. The role of BRAF mutations in this genetically diverse collection of cancers remains enigmatic (60, 61). Two European collections of biliary tract cancers, including both gall bladder carcinomas and intrahepatic cholangiocarcinomas, were found to contain BRAF mutations at a frequency of approximately 20% (62-64). However, no mutations were identified in a similar collection from North America and Chile, despite the use of three methods to detect mutations (65).

Not surprisingly, given the rarity of this group of cancers, very little is also known about the association between activating BRAF mutations and the clinicopathology, patient management, and outcomes of cholangiocarcinoma and other cancers of the biliary tract. One study on the European collection did show that activating BRAF mutations were significantly more likely in cholangiocarcinomas than hepatocellular carcinomas (64), suggesting a potential specificity for the former tumor type. However, further research in this area is required.

1.3 Vemurafenib

1.3.1 Vemurafenib Background

Vemurafenib (also known as RO5185426, PLX4032, or RG7204) is a low molecular weight, orally available inhibitor of the activated form of the BRAF serine-threonine kinase enzyme, which is commonly found in melanoma. Vemurafenib selectively inhibits oncogenic BRAF kinase. The rationale for identifying such a compound was first provided in 2002, when the high prevalence of activating mutations in the BRAF gene was identified in a variety of cancers, including melanoma (66). The high level of selectivity of vemurafenib has been demonstrated in biochemical, cell-based, and *in vivo* assays.

In vitro biochemical and cell-based assays have confirmed a high degree of selectivity of vemurafenib for the oncogenic BRAF V600E kinase (67). The 50% inhibitory concentration (IC_{50}) of vemurafenib for V600E BRAF is 44 nM. It is equipotent against CRAF (44 nM) and 3-fold less potent against BRAF wild type (110 nM). In a panel of 58 kinases, vemurafenib had an IC_{50} <1 μM for only 1 kinase (BRK kinase) outside the BRAF family. Vemurafenib was also screened against 63 receptors in 8 different families. At 10 μM, vemurafenib showed marginal activity (20–24% inhibition) against 4 receptors and was inactive against the other 59 targets.

In several mouse xenograft models of BRAF V600E-expressing melanoma, vemurafenib treatment caused partial or complete tumor regression and improved animal survival in a dose-dependent manner (68).

In preclinical models, vemurafenib exhibited potent kinase inhibitory activity against BRAF V600K, BRAF V600D, and BRAF V600R, with IC_{50} ranging from 3 nM to 110 nM. Vemurafenib also exhibited potent inhibitory effects on the RAF/MEK signaling pathway, i.e., MEK and ERK phosphorylation and cellular proliferation (7, 68). In

melanoma cell lines that expressed other BRAF mutations than V600E, such as BRAF V600K, BRAF V600D, and BRAF V600R, inhibitory activity for vemurafenib was also observed (7, 68).

Please refer to the Investigator's Brochure for further details on the *in vitro* and *in vivo* pharmacology.

1.3.2 Vemurafenib Clinical Development Program

Following are key clinical trials in the vemurafenib clinical development program for melanoma:

1.3.2.1 Phase I dose-finding study (PLX 06-02)

The dose of vemurafenib was established in a multicenter, phase I, dose-escalation study with a total of 55 patients, 49 of whom had a diagnosis of melanoma.

1.3.2.2 Two phase I extension cohorts

Once the recommended phase II dose of 960 mg per os (p.o.) twice daily (b.i.d.) had been identified, a cohort of 32 additional patients with metastatic melanoma and prospectively identified BRAF V600 mutations were enrolled in the extension phase of this study (69). A different cohort of 21 patients with metastatic colorectal cancer and identified BRAF V600 mutations were treated in the extension phase with the established dose of 960 mg b.i.d. (69). The primary objective of these extension cohorts was to determine clinical response rate (RR). Secondary objectives were safety and additional pharmacokinetic and pharmacodynamic evaluations.

1.3.2.3 Phase II single-arm study (NP22657/BRIM-2)

Study NP22657 (BRIM 2) was an open label, single-arm, multicenter phase II study in previously treated patients with metastatic melanoma harboring the BRAF V600 mutation. In this study 132 patients were enrolled and treated with oral vemurafenib 960 mg b.i.d. The tumor BRAF mutation status was assessed by the cobas® 4800 BRAF V600 Mutation Test. The primary objective of this study was to evaluate the efficacy of vemurafenib using best overall response rate (BORR) as assessed by an independent review committee (RECIST, version 1.1). Secondary objectives included BORR assessed by the Investigator, duration of response, PFS, OS, safety/toxicity, effect on QT interval, quality of life using FACT-M (Version 4), validation of the cobas® 4800 BRAF V600 Mutation Test, and pharmacodynamic (PD) parameters.

1.3.2.4 Phase III randomized controlled study (NO25026/BRIM-3)

This randomized, open-label, multicenter, phase III study examined patients with treatment-naïve metastatic melanoma confirmed by histopathology (unresectable stage IIIC or stage IV) and with a BRAF V600 mutation by the cobas® 4800 BRAF V600 Mutation Test (70). Patients were randomly assigned to be treated with either vemurafenib 960 mg p.o. b.i.d. every day or intravenous dacarbazine 1000 mg/m^2 on day 1 every 3 weeks. Within this trial, OS and PFS were defined as co-primary endpoints (NO25026 protocol version C). Major secondary study objectives included comparisons of BORR, time to response, DOR, time to treatment failure, and tolerability/safety. Further assessments of the pharmacokinetic profile of vemurafenib, validation of the

cobas® 4800 BRAF V600 Mutation Test, evaluation of QoL, and additional pharmacodynamic analyses were planned. The final analysis was planned to occur after 196 deaths, and an interim analysis was planned after 50% of the projected deaths (n=98). The final analysis of PFS was to occur at the interim analysis of OS.

1.3.3 Phase I Dose-Finding and Pharmacokinetics

A total of 55 patients were enrolled in the dose escalation phase of study PLX06-02, including patients with metastatic melanoma (n=50), thyroid cancer (n=3), rectal carcinoma (n=1) and ovarian cancer (n=1). Several different capsule strengths and formulations were evaluated in this part of the study. Twenty-six patients received doses of vemurafenib ranging from 160 mg to 1120 mg b.i.d using the optimized drug formulation (referred to as micro-precipitated bulk powder [MBP] formulation) with greater bioavailability. With this optimized formulation, minimum efficacious exposures above the exposure identified in the preclinical models (≥400μM·h) were achieved at 240 mg b.i.d. Vemurafenib MBP formulation has shown dose proportional increases in exposure across all cohorts, particularly from 240 to 960 mg b.i.d. Mean steady state exposure levels of vemurafenib (area under the plasma concentration-time curve, AUC_{0-24h}) in these dose cohorts ranged from 467.1 μM·h to 1324.6 μM·h. The 960 mg b.i.d dose of vemurafenib achieved mean steady state exposure levels of 69.6 μM and 1324.6 μM·h, for maximum plasma concentration (C_{max}) and AUC_{0-24h}, respectively.

An apparent mean half-life of ~90 hours (range, 30 to 145 hours) following multiple doses in patients receiving 960 mg bid in the melanoma extension cohort was determined based on the mean accumulation ratio of vemurafenib exposure between Day 1 and Day 15. With the twice-daily dosing regimen, all patients were exposed to relatively constant daily levels of the drug at steady state.

Dose-limiting toxic effects were not observed until a dose of 720 mg b.i.d. At the next highest dose given to one group of patients, 1120 mg b.i.d, four of six patients developed non-life threatening dose-limiting toxicity (DLT): three patients with grade 3 rash (two of whom also had grade 3 fatigue) and one patient with grade 3 arthralgia. All events resolved with temporary drug interruption. In all cases, patients resumed treatment at lower doses of 720 mg b.i.d. One DLT, Grade 4 pancytopenia, was observed at 720 mg b.i.d. Upon resolution of the pancytopenia after 9 days of study drug interruption, the patient was rechallenged with vemurafenib at a lower dose of 360 mg b.i.d without recurrence of the pancytopenia. No new occurrence of pancytopenia was observed in the 1120 mg b.i.d dose cohort or since in the extension cohort.

The dose of 960 mg b.i.d orally was determined to be tolerated in the first six patients given the dose. This dose level of 960 mg b.i.d was established as the recommended phase II dose for the extension cohort (these 6 patients were included as the first six patients in the extension cohort) and for future phase II and III studies.

1.3.4 Clinical Efficacy in Melanoma

Note: Efficacy and safety data on vemurafenib, which are summarized in this and the following section (Section 1.3.5), have been obtained primarily from studies on patients with metastatic melanoma. Examining the reproducibility of these data in other indications is a primary goal of the present study.

1.3.4.1 PLX06-02

Of the patients enrolled in the dose-escalation portion of the melanoma study PLX 06-02 who received doses of 240 mg b.i.d. or more, 16 presented with tumors that harbored the V600 BRAF mutation. Among these 16 patients, a PR or CR was seen in one patient receiving 240 mg b.i.d., two of the four patients receiving 320 or 360 mg b.i.d., four of the six patients receiving 720 mg b.i.d., and four of the five patients receiving 1120 mg b.i.d. The overall RR (including either confirmed or unconfirmed responses) was 69% (11 of 16 patients), with 10 PR and one CR. Responses were seen at all sites of metastatic disease, including liver, small bowel, and bone. The DOR ranged from two to more than 18 months.

Five patients with metastatic melanoma without BRAF mutation received vemurafenib doses of at least 240 mg b.i.d. None had evidence of tumor regression during the study. Four developed progressive disease (PD) within the first two months of treatment (69).

All 32 patients enrolled in the extension cohort of study PLX 06-02 had metastatic melanoma with BRAF V600E mutation. All were treated with vemurafenib at the recommended phase II dose of 960 mg p.o. b.i.d. Thirteen patients (41%) required a dose reduction during therapy (to 720 mg b.i.d. in 10 patients, to 600 mg b.i.d. in one patient, and to 480 mg b.i.d. in two patients). Among the 32 evaluable patients in the melanoma extension cohort, the unconfirmed response rate was 81.3%; 3 patients had a CR and 24 patients had a PR. The confirmed response rate (CR + PR) was 56.3%.

Responses were observed in visceral organs and bone metastases, as well as lungs and lymph nodes. Responses were also observed in patients with increased concentrations of serum lactate dehydrogenase (10 PR among the 13 patients). Responses were observed in patients who had received no previous therapy (six of seven patients responded with vemurafenib in first-line treatment) and in patients who received one or more prior systemic therapies (nine of nine patients in second-line, four of four patients in third-line and seven of 12 patients in > third-line). The median OS is 16 months with a 2-yr survival rate of 44% (79).

1.3.4.2 NP22657/BRIM-2

A total of 132 patients were enrolled into study NP22657/BRIM-2 between October 2009 and March 2010 (71, 72). Of these, 122 (92.5%) harbored the BRAF V600E mutation and 10 (7.5%) the BRAF V600K mutation. As of the data cut-off date of 31 January 2011, 35 patients (27%) were still receiving treatment and 97 (73%) had discontinued (disease progression [n=89], AE [4], death [1], consent withdrawal [1], other [2]). Median follow-up was 10 months (range, 0.6–14.7 months).

In total, 7 CR, 63 PR, 38 SD, and 18 PD have been confirmed by an Independent Review Committee (IRC), resulting in an IRC-assessed ORR of 53% (primary endpoint). Investigator-assessed ORR and RR (the latter includes unconfirmed responses) were 57% and 69%, respectively. Median duration of response was 6.7 months (95% CI, 5.6–9.8 months; range 1.3–12.7 months). Median PFS was 6.7 months (95% CI, 5.5–7.8 months), with a six-month PFS rate of 54% (95% CI, 45%–63%). The median OS had not been reached (77% alive at 6 months and 58% at 12 months).

Of note, of the 10 patients harboring the V600K allele, 4 exhibited PRs. .

1.3.4.3 NO25026/BRIM-3

A total of 675 patients with previously untreated, metastatic melanoma harboring the BRAF V600E mutation were randomly assigned to receive either vermurafenib or dacarbazine in the global, randomized phase III study NO25026/BRIM-3 between January 2010 and December 2010 (70). In the interim analysis for OS and final analysis for PFS (see Section 1.3.2.4), vemurafenib was associated with a relative reduction of 63% in the risk of death and of 74% in the risk of either death or disease progression, as compared with dacarbazine (P<0.001 for both comparisons). The survival benefit in the vemurafenib group was observed in each prespecified subgroup, according to age, sex, ECOG performance status, tumor stage, lactate dehydrogenase level, and geographic region. After review of the interim analysis by an independent data and safety monitoring board, crossover from dacarbazine to vemurafenib was recommended.

In the vemurafenib group, most patients had a detectable decrease in tumor size and 106 of 219 patients (48%; 95% CI, 42%–55%) had a confirmed objective response (including 2 patients with a CR and 104 with a PR). Median time to response was 1.45 months. Ten patients in the vemurafenib group were later found to have BRAF V600K mutations; of these, 4 had a PR (40%). In the dacarbazine group, a minority of patients had a detectable decrease in tumor size and only 12 of 220 patients (5%; 95% CI, 3%–9%) met the criteria for a confirmed response (all partial responses). Median time to response of 2.7 months. The difference in confirmed RR between the two study groups (48% vs. 5%) was highly significant (P<0.001).

1.3.5 Clinical Safety in Melanoma

Safety data from the clinical trials with vemurafenib include arthralgia, fatigue, rash, photosensitivity reaction, nausea, alopecia and pruritus Vemurafenib also has been associated with reports of cutaneous SCC, most of which are keratoacanthoma (KA) sub-type, or with some features of KA (incompletely expressed or with some features unusual in KA). AEs with vemurafenib have been predominantly mild in severity and transient, even with continuous dosing (over 15 months of treatment in 1 patient). At the recommended phase II and phase III dose of 960 mg b.i.d., AEs have been consistent with the safety profile observed in the phase I setting. Treatment-related Grade 3 AEs and DLTs have been successfully managed by a temporary discontinuation of study drug and/or a reduction in dose. Further details of cSCC findings across all vemurafenib melanoma clinical trials can be found in the latest Investigator's Brochure (current version 7). New primary malignant melanomas have been reported in clinical trials in patients with metastatic melanoma. These lesions were managed with excision, and patients continued treatment without dose adjustment.

1.3.5.1 PLX 06-02

Among patients enrolled in the phase I study PLX 06-02, the most common vemurafenib-related Grade 2 or 3 toxicities observed were arthralgia, rash, nausea, photosensitivity, fatigue, cutaneous SCC, pruritus, and palmar-plantar dysesthesia (**Table 4**). In total, 89% of the toxicities were Grade 1 or 2. Rashes were evenly distributed among face/neck, trunk, and extremities. Four patients had a Grade 4 AE: two had elevated γ-

glutamyltransferase (GGT) levels; one had fatigue; and one had reversible pancytopenia of uncertain attribution. Thirteen patients out of 32 total (41%) in the extension cohort required a dose reduction (10 patients to 720 mg b.i.d., one patient to 600 mg b.i.d., and two patients to 480 mg b.i.d.) (69).

Table 4.

PLX 06-02: Vemurafenib-Related Adverse Events ≥ Grade 2 in > 5% of Patients

	< 240 mg (N=30)[b]	240 mg (N=4) [a]	320/360 mg (N=8)	720 mg (N=7)	960 mg (N=32)	1120 mg (N=6)	Overall (N=87)
Arthralgia							
Grade 2	0	1 (25%)	2 (25%)	0	10 (31%)	1 (17%)	14 (16%)
Grade 3	0	0	0	0	1 (3%)	1 (17%)	2 (2%)
Rash							
Grade 2	1 (3%)	0	0	1 (14%)	7 (22%)	1 (17%)	10 (12%)
Grade 3	0	0	0	0	1 (3%)	2 (33%)	3 (3%)
Cutaneous squamous cell carcinoma							
Grade 2	0	0	0	0	0	0	0
Grade 3	1 (3%)	2 (50%)	3 (38%)	0	10 (31%)	2 (33%)	18 (21%)
Nausea							
Grade 2	1 (3%)	0	1 (13%)	1 (14%)	4 (13%)	1 (17%)	8 (9%)
Grade 3	0	0	0	0	1 (3%)	0	1 (1%)
Fatigue							
Grade 2	0	0	0	0	2 (6%)	1 (17%)	3 (3%)
Grade 3	0	0	0	0	2 (6%)	2 (33%)	4 (5%)
Photosensitivity reaction							
Grade 2	0	0	0	1 (14%)	4 (13%)	1 (17%)	6 (7%)
Grade 3	0	0	0	0	1 (3%)	0	1 (1%)
Palmar-plantar dysesthesia							
Grade 2	0	0	0	0	2 (6%)	1 (17%)	3 (3%)
Grade 3	0	0	0	0	2 (6%)	0	2 (2.3%)
Pruritus							
Grade 2	0	0	0	0	4 (13%)	0	4(5%)
Grade 3	0	0	0	0	0	1 (17%)	1 (1%)
Lymphopenia							
Grade 2	0	0	2 (25%)	0	2 (6%)	0	4 (5%)
Grade 3	0	0	0	0	0	1 (17%)	1 (1%)

[a] Initial dose escalation utilized a crystalline formulation with inadequate bioavailability; the MBP formulation was used for doses > 320 mg/day.

1.3.5.2 NP22657/BRIM-2

Treatment-related AEs reported in more than 5% of patients in BRIM-2 are shown in **Table 5**.

Table 5.

BRIM-2: Treatment-Related Adverse Events ≥ Grade 2 in ≥ 20 Patients

	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Overall	130 (99)	79 (60)	5 (4) [a]
Arthralgia	78 (59)	8 (6)	0 (0)
Rash	69 (52)	9 (7)	0 (0)
Photosensitivity reaction	69 (52)	4 (3)	0 (0)
Fatigue	56 (42)	2 (2)	0 (0)
Alopecia	48 (36)	0 (0)	0 (0)
Pruritus	38 (29)	3 (2)	0 (0)
Skin papilloma	38 (29)	0 (0)	0 (0)
Cutaneous SCC / KA [b]	34 (26)	34 (26)	0 (0)
Nausea	30 (23)	2 (2)	0 (0)
Elevated liver enzymes	23 (17)	8 (6) [c]	4 (3) [d]

SCC, squamous cell carcinoma; KA, keratoacanthoma.

[a] One patient had 2 grade 4 AEs.

[b] Cases of cutaneous SCC / KA were generally managed with simple excision and did not generally require dose modification.

[c] Managed with dose reduction; one removed from study.

[d] Led to discontinuation of therapy.

The median average daily dose of vemurafenib was 1740 mg per day. A total of 59 patients (45%) had their vemurafenib doses reduced: 37 (28%) to 720 mg b.i.d.; 21 (16%) to 480 mg b.i.d.; and 1 to less than 480 mg b.i.d. Eighty-five patients (64%) had their dosing interrupted during the course of the trial. Common AEs that led to dose reduction and interruptions were rash, arthralgia, liver function test abnormalities (GGT elevation), and photosensitivity. Four patients discontinued vermurafenib due to an AE: retinal vein occlusion (n=1); jaundice, blood bilirubin increased, fatigue, AST, and ALT (1); delirium (1); and cellulitis (1).

Grade 3 cutaneous SCCs / keratoacanthomas occurred in 34 patients (26%). Median time to first occurrence was 8 weeks (range, 2–36 weeks), and the median number per patient was 1 (range, 1–7).

1.3.5.3 NO25026/BRIM-3

A total of 618 patients (92%) underwent at least one assessment as of the clinical cutoff date (December 2010) and were evaluated for toxic effects. AEs of grade 2 or more that were reported in more than 5% of patients in either study group are shown in **Table 6**.

Table 6.

BRIM-3: Adverse Events ≥ Grade 2 in > 5% of Patients in Either Study Group (N=618)

Adverse event, n (%)	Vemurafenib (N=336) [a]	Dacarbazine (N=282)
Arthralgia		
Grade 2	60 (18)	1 (< 1)
Grade 3	11 (3)	2 (< 1)
Rash		
Grade 2	33 (10)	0 (0)
Grade 3	28 (8)	0 (0)
Fatigue		
Grade 2	38 (11)	33 (12)
Grade 3	6 (2)	5 (2)
Cutaneous squamous cell carcinoma [b]		
Grade 3	40 (12)	1 (< 1)
Keratoacanthoma [c]		
Grade 2	7 (2)	0 (0)
Grade 3	20 (6)	0 (0)
Nausea		
Grade 2	25 (7)	32 (11)
Grade 3	4 (1)	5 (2)
Alopecia		
Grade 2	26 (8) [d]	0 (0)
Pruritus		
Grade 2	19 (6)	0 (0)
Grade 3	5 (1)	0 (0)
Hyperkeratosis		
Grade 2	17 (5)	0 (0)
Grade 3	4 (1)	0 (0)
Diarrhea		
Grade 2	16 (5)	4 (1)
Grade 3	2 (< 1)	1 (< 1)
Headache		
Grade 2	15 (4)	5 (2)
Grade 3	2 (< 1)	0 (0)
Vomiting		
Grade 2	9 (3)	14 (5)
Grade 3	4 (1)	3 (1)
Neutropenia		
Grade 2	1 (< 1)	4 (1)
Grade 3	0 (0)	15 (5)
Grade 4	1 (< 1)	8 (3)
Grade 5	0 (0)	1 (< 1)

[a] One patient in the dacarbazine group who was treated with vemurafenib in error was included in the vemurafenib group for the assessment of AEs.

[b] The criteria for the diagnosis of cutaneous SCC were defined in the protocol and were reported as grade 3, according to the NCI-CTCAE, v4.0. These events were evaluated by the Investigators as grade 1 in one patient and as grade 2 in one patient.

[c] Three patients with keratoacanthomas that were assessed by the Investigator as grade 1 are included among the grade 2 keratoacanthomas.

[d] In one patient, alopecia that was scored as grade 3 by the investigator was rescored as grade 2, since the NCI-CTCAE, v4.0 does not include grade 3 alopecia.

The most common AEs in the vemurafenib group were cutaneous events, arthralgia, and fatigue; photosensitivity skin reactions of grade 2 or 3 were seen in 12% of the patients, with grade 3 reactions characterized by blistering that often could be prevented with sunblock. AEs led to dose modification or interruption in 129 of 336 patients (38%) in the vemurafenib group.

In the vemurafenib group, a cutaneous SCC, keratoacanthoma, or both developed in 61 patients (18%). All lesions were treated by simple excision. Pathological analyses of skin-biopsy specimens from these patients are currently being performed by an independent dermatology working group.

1.3.5.4 Cardiac effects in NP2265/BRIM-2

The effects of single and multiple doses of vemurafenib 960 mg bid on ECG measurement, including the QT interval, were evaluated in 132 adult patients with metastatic melanoma in the phase 2 study, NP22657. Centralized measurement of ECG intervals and T/U wave morphology was conducted by the core ECG laboratory on the robust schedule of serial time matched 12-lead ECGs obtained for up to 16 cycles. For each of the time points, the means from the available triplicate assessments were used as a single observation for the numeric ECG parameter. The T-wave and U-wave morphology and the ECG normality were assessed on each ECG from a triplicate.

Vemurafenib treatment at 960 mg bid did not appear to have a clinically meaningful effect on heart rate (HR). The study population-specific correction (QTcP) had eliminated most of the bias from the QT-RR relationship and was therefore used for the primary statistical analyses of variables related to the QTc interval.

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

Two patients (1.5%) developed treatment-emergent absolute QTcP values >500 ms (CTC Grade 3), while 49 (37.1%) and 6 (4.5%) patients exhibited QTcP values >450 ms and >480 ms, respectively. No patients had treatment-emergent QT (uncorrected) values >500 ms. Maximum treatment-emergent individual QTcP changes from baseline of >30 ms were observed in 58 (43.9%) of patients, but only one patient (0.8%) exhibited a QTcP change from baseline of >60 ms.

In the central tendency analysis, the largest mean QTcP prolongation (dQTcP) after the first vemurafenib dose on Day 1 was 3.3 ms with the upper bound of the 1-sided 95% CI (UCI) of 5.0 ms, constituting a small QTc effect below the threshold of clinical interest. However, the mean QTc prolongation increased with repeated vemurafenib dosing towards the expected steady-state on Day 15, which corresponded with vemurafenib accumulation in plasma. The largest dQTcP on Day 15 was 12.8 ms (UCI 14.9 ms), and appeared to remain sustained at a similar level in subsequent cycles.The pattern of increasing vemurafenib concentration from Day 1 to 15 and the constant exposure in the

later cycles appeared to correlate with the increased mean QTcP change from Day 1 to 15 and the subsequent maintenance of this effect. The relationship between vemurafenib exposure and the QTc interval is being pursued further.

AEs in the study that were possibly attributable to QTc prolongation were as follows: one event of intermittent dizziness in a patient with a maximal QTc of 456 msec, and 2 cases of pericardial effusion in patients with maximal QTc values of 469 msec and 456 msec. The maximal QTc values reported in these patients did not necessarily occur at the same time as the AEs in question. Pericardial effusion is not a consequence of electrocardiographic changes and is not known to affect the QT interval.

1.4 Rationale for the Study

As described in Section 1.2 (Oncogenic BRAF Kinase Mutations in Various Cancers), mutations in the BRAF gene, in particular mutations resulting in a V600E mutant kinase, may play significant roles in the pathogenesis of a variety of clinically significant cancers. Moreover, the presence of BRAF mutations is known to attenuate the activity of other anticancer agents, most notably EGFR therapeutic antibodies. Therefore, the identification of new therapies that specifically target BRAF mutations in cancer cells is of significant interest.

Vemurafenib has reproducibly demonstrated high anticancer activity in a number of phase I, II and phase III trials in metastatic melanoma. Based on this prior activity, as well as the evidence that activated BRAF kinase may play a highly conserved role in dysregulated cell growth across multiple cancer types, it is reasonable to posit that this new drug may be effective in non-melanoma cancers harboring BRAF V600 mutations, as well. Indeed, preliminary evidence suggested that vemurafenib may have some activity in CRC (74). This further encourages exploration of the efficacy of vemurafenib in CRC and other non-melanoma tumors harboring activated BRAF V600 mutations.

2. OBJECTIVES

2.1 Primary Objective

The primary objective of this trial is to evaluate the efficacy of vemurafenib in patients with cancers harboring BRAF V600 mutations as response rate (RR) at Week 8 determined by the Investigator using Response Evaluation Criteria In Solid Tumors, Version 1.1 (RECIST, v1.1) or International Myeloma Working Group (IMWG) uniform response criteria and to identify tumor types for further development

2.2 Secondary Objectives

- To evaluate the safety and tolerability of vemurafenib in this patient population.
- To evaluate in solid tumors and multiple myeloma (MM):
    - overall response rate (ORR)
    - clinical benefit rate (CR (or sCR), PR (or VGPR)) and stable disease [SD]),of vemurafenib
    - duration of response (DOR)

- time to response
- time to tumor progression (TTP)
- PFS
- overall survival (OS).

2.3 Exploratory Objective

To evaluate the Roche Companion Diagnostic (CoDx) cobas® 4800 BRAF V600 Test for the detection of BRAF V600 in tumor samples.

3. STUDY DESIGN

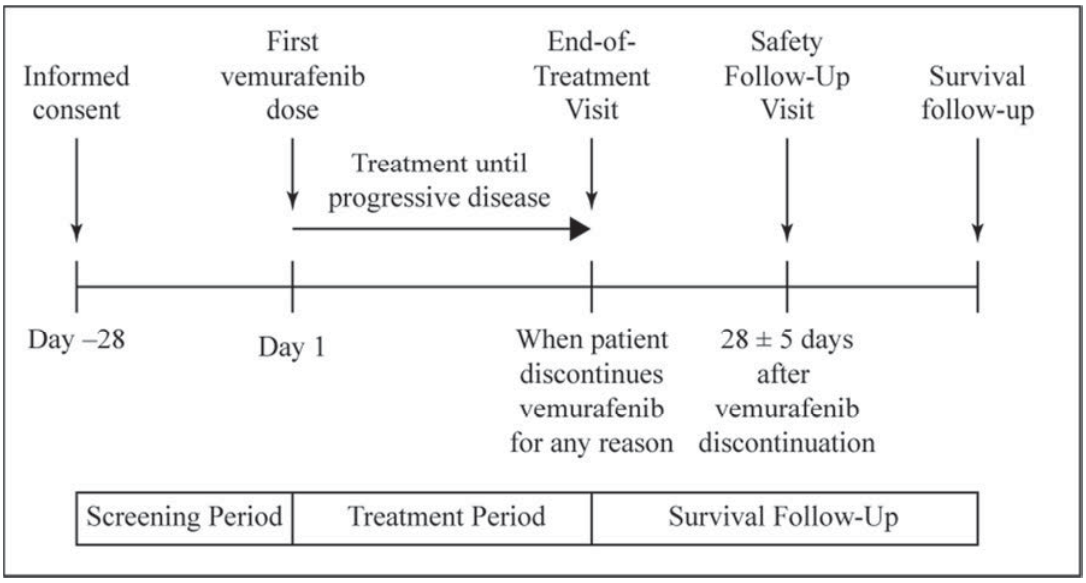
3.1 Overview of Study Design

This is an open-label, multicenter, multinational, phase II study exploring the efficacy and safety of vemurafenib in a diverse population of patients with cancers (excluding melanoma and papillary thyroid cancer) known to harbor BRAF V600 mutations and for whom vemurafenib is deemed the best treatment option in the opinion of the Investigator.

Patients with BRAF V600 mutation-positive cancers will be identified through mutation analysis assays as routinely performed at each participating site according to their local procedure. The BRAF V600 mutation identified at the site, as well as the specific BRAF mutation assay that was performed, will be recorded in the electronic case report form (eCRF). The presence of BRAF V600 mutations will be retrospectively confirmed by the cobas® 4800 BRAF V600 Mutation Test.

The trial will consist of a Screening Period (Day –28 to −1), a Treatment Period, an End-of-Treatment Visit occurring when vemurafenib is discontinued for any reason, a Safety Follow-Up Visit occurring 28 days after the last dose of vemurafenib and a Survival Follow-Up Period lasting for a maximum of 12 months for each patient after their last dose of study drug to monitor survival status (**Figure 1**). Day 1 of the study (baseline) will be defined as the first day a patient receives vemurafenib. One cycle of therapy will be defined as 28 days of treatment. Patients will be asked to attend clinic visits at regular intervals during the study for safety and efficacy assessments.

Figure 1.
Study Design



The study will include 8 cohorts of patients with the following cancers:

Cohort 1. Non-small cell lung cancer (NSCLC)

Cohort 2. Ovarian cancer

Cohort 3. Colorectal cancer

Cohort 4. Cholangiocarcinoma/cancer of the biliary tract

Cohort 5. Breast cancer

Cohort 6. Prostate cancer

Cohort 7. Multiple myeloma (MM)

Cohort 8. Solid tumors other than the above

Recruitment/enrollment in any of the above cohorts may present some difficulties, given the low frequency of BRAF V600 mutations in the specific indications. Therefore, if no patients are enrolled within any cohort after one year from the start of the study, then that particular cohort will be closed and enrollment for that cohort will be stopped. Cohort 8 will be closed to enrollment when all other cohorts are closed, regardless of the number of patients recruited at that time. This latter cohort is expected to be quite heterogeneous and will be examined primarily to seek efficacy signals in the relatively rare BRAF V600 mutation-positive tumors.

Enrolled patients will receive continuous oral dosing of vemurafenib at 960 mg b.i.d. until the development of progressive disease (as per Investigator assessment), unacceptable toxicity, consent withdrawal, protocol violation endangering the patient's safety, death, reasons deemed critical by the treating physician, or study termination by the Sponsor.

Patients who develop disease progression but, in the opinion of the Investigator, would still benefit from continuing vemurafenib may continue treatment with vemurafenib after discussion with the Sponsor.

3.1.1 Rationale for Study Design

The multi-cohort design will allow for the examination of 8 separate cohorts of different cancers with enough statistical power to determine whether further examination may be warranted in the individual indications. The open-label, uncontrolled design is appropriate since the trial will only enroll patients with BRAF V600 mutation positive cancers, who in the opinion of the Investigator, have vemurafenib as their best treatment option, i.e., no other obvious comparator is available.

3.1.2 Rationale for Dose Selection

The dose of vemurafenib at 960 mg b.i.d was identified in the phase I dose-finding study PLX 06-02 and is established as the recommended dosage for phase II and III trials (see Section 1.2.4) for the treatment of melanoma. It is presumed that a similar dosage would be effective in other types of cancers harboring the same BRAF V600 mutations.

3.1.3 End of Study

The end of study will occur when all patients have been followed for survival for a maximum period of 12 months since last dose of study medication, have died, withdrawn consent, or are lost to follow up, whichever occurs first.

3.2 Number of Patients/ Assignment to Treatment Groups

It is estimated that approximately 104–152 patients with solid tumors or MM will be enrolled in this study. Approximately 13–19 patients per indication (cohort) will be included. The number of patients may be less than 104 if a cohort(s) is closed early as a result of stopping rules for that cohort(s).

3.3 Centers

This study is a multinational, multicenter study conducted in approx. 4 countries and approx. 15 sites.

4. STUDY POPULATION

4.1 Overview

The target population will include adult patients with BRAF V600 mutation-positive cancers (excluding melanoma and papillary thyroid cancer). BRAF V600 mutations will be identified by mutation analysis assays as routinely performed at each individual participating site according to their local pocedures. See Sections 4.2 and 4.3 for further Inclusion and Exclusion Criteria.

4.2 Inclusion Criteria

Inclusion Criteria:

For solid tumors only:

1. Histologically confirmed cancers (excluding melanoma and papillary thyroid cancer) harboring a BRAF V600 mutation and are refractory to standard therapy or for which standard or curative therapy does not exist or is not considered appropriate by the Investigator
2. Measurable disease according to RECIST, v1.1
3. Adequate hematologic function, as defined by the following laboratory values performed within 7 days prior to the first dose of vemurafenib:
    a. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
    b. Platelet count $\geq 100 \times 10^9$/L

For multiple myeloma only:

4. Patients with a confirmed diagnosis of MM and harbor a BRAF V600 mutation
5. Patients must have received at least one line of prior systemic therapy for the treatment of MM. A line of treatment is sequential treatment without interruption for response and subsequent progression
6. Patients treated with local radiotherapy (with or without concomitant exposure to steroids for pain control or management of cord/nerve root compression), two weeks must have elapsed since the last date of radiotherapy, which is recommended to be a limited field. Patients who require concurrent radiotherapy should have entry into the Study deferred until the radiotherapy is completed and two weeks have passed since the last date of therapy
7. Patients must have relapsed and/or refractory MM with measurable disease, defined as disease that can be measured either by serum or urinary evaluation of the monoclonal component or by serum assay of free light chain (FLC) based on at least one of the following three measurements:
    a. Serum M-protein > 0.5 g/dL
    b. Urine M-protein > 200 mg per 24 hours
    c. Involved FLC level > 10 mg/dL (> 100 mg/L)provided serum FLC ratio is abnormal
8. Adequate hematologic function, as defined by the following laboratory values performed within 7 days prior to the first dose of vemurafenib:
    a. Absolute neutrophil count (ANC) ≥ 1.0 x 109/L
    b. Platelets count ≥ 50 x 109/L

For all patients (solid tumors and MM):

9. Signed written informed consent approved by the relevant Independent Ethics Committee (IEC) / Institutional Review Board (IRB) must be obtained prior to performing any study-related procedures

10. Male or female ≥ 18 years of age
11. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2
12. Must have recovered from all side effects of their most recent systemic or local treatment
13. Able to swallow pills
14. Adequate hematologic, renal, and liver function, as defined by the following laboratory values performed within 7 days prior to the first dose of vemurafenib:
    a. Hemoglobin ≥ 9 g/dL
    b. Serum creatinine ≤ 1.5 times upper limit of normal (ULN) or creatine clearance (CrCl) > 50 mL/min by Cockroft–Gault formula (Main Protocol Appendix 1)
    c. Aspartate aminotransferase (AST [SGOT]) and alanine aminotransferase (ALT [SGPT]) ≤ 2.5 times ULN (≤ 5 times ULN if considered due to primary or metastatic liver involvement)
    d. Serum bilirubin ≤ 1.5 times ULN
    e. Alkaline phosphatase ≤ 2.5 times ULN (≤ 5 times ULN if considered due to tumor)

15. Negative serum pregnancy test within 7 days prior to commencement of dosing in premenopausal women. Women of non-childbearing potential may be included without serum pregnangy test if they are either surgically sterile or have been postmenopausal for ≥ 1 year
16. Fertile men and women must use an effective method of contraception during treatment and for at least 6 months after completion of treatment as directed by their physician. Effective methods of contraception are defined as those which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly (for example implants, injectables, combined oral contraception, or intra-uterine devices). At the discretion of the Investigator, acceptable methods of contraception may include total abstinence in cases where the lifestyle of the patient ensures compliance. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)
17. Absence of any psychological, familial, sociological, or geographical conditions potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before trial entry

4.3 Exclusion Criteria

1. Melanoma, papillary thyroid cancer, or hematological malignancies (with the exception of multiple myeloma)
2. Uncontrolled concurrent malignancy (early stage or chronic disease is allowed if not requiring active therapy or intervention and is under control)
3. For MM, solitary bone or solitary extramedullary plasmacytoma as the only evidence of plasma cell dyscrasia
4. Active or untreated CNS metastases. Patients with brain metastasis are eligible if asymptomatic, off corticosteroid and without evidence of disease progression in brain for ≥ 2 months
5. History of or known carcinomatous meningitis
6. Concurrent administration of any anti-cancer therapies (e.g., chemotherapy, other targeted therapy, experimental drug, etc.) other than those administered in this study
7. Known hypersensitivity to vemurafenib or another BRAF inhibitor
8. Prior treatment with a BRAF or MEK inhibitor (prior sorafenib is allowed)
9. Pregnant or lactating women
10. Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant bowel resection that would preclude adequate absorption.
11. Any of the following within the 6 months prior to first vemurafenib administration:
    - Myocardial infarction, severe/unstable angina, symptomatic congestive heart failure, cerebrovascular accident, or transient ischemic attack
12. Pulmonary embolism within 30 days prior to first vemurafenib administration
13. Hypertension not adequately controlled by current medications within 30 days prior to first vemurafenib administration
14. History or presence of clinically significant ventricular or atrial dysrhythmias ≥ Grade 2 (National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 [NCI CTCAE, v4.0])
15. Corrected QT (QTc) interval ≥ 450 msec at baseline or history of congenital long QT syndrome
16. Uncontrolled medical illness (such as infection requiring treatment with intravenous [IV] antibiotics)
17. Other severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or vemurafenib administration, or may interfere with the interpretation of study results,

which in the judgment of the Investigator would make the patient inappropriate for entry into this study

18. Unwillingness to practice effective birth control

19. Inability to comply with other requirements of the protocol

4.4 Concomitant Therapy

At study initiation, patients should continue with their concomitant medications, as directed by their physician, with the exception of study precluded medications (see below and Section 4.3 above). All concomitant medication must be fully recorded on the eCRF. Additionally, any diagnostic, therapeutic, or surgical procedure performed during the study period should be recorded including the date, indication, description of the procedure(s) and any clinical findings.

Due to the underlying illness and the frequency of co-existent medical conditions in this patient population, all concomitant medication or treatment required by the patient will be at the discretion of the treating physician.

4.4.1 Excluded Therapy and Potential Interactions With Concomitant Drugs

4.4.1.1 Excluded therapy

The following medications and treatments are not allowed while the patient is on the study:

- other anti-cancer therapies
- concomitant alternative therapies and herbal preparations
- radiotherapy for the treatment of disease during the study; the exception will be limited field radiotherapy for palliative bone pain due to pre-existing bone metastasis if not considered a target lesion for RECIST assessments

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

Appendix 2 includes a non-exhaustive list of typical examples of CYP1A2 and CYP3A4 substrates and CYP3A4 inducers and inhibitors.

4.4.1.2 Potential interactions with concomitant drugs

Overall, < 10% of vemurafenib was observed to be metabolized in melanoma patients in an ADME (absorption, distribution, metabolism, and excretion) study (NP25158).

Preclinical studies suggest that CYP3A4 metabolism and subsequent glucuronidation are responsible for the metabolism of vemurafenib that is observed to occur in patients.

Further details on potential vemurafenib drug-drug interactions mediated via cytochrome P450 enzymes are presented below. Also presented is a brief section on potential interactions between vermuafenib and drugs that may cause QTc interval prolongation and cardiac arrhythmia.

4.4.1.2.1 CYP3A4 substrates

In the CYP450 probe study NP22676, vemurafenib induced CYP3A4 activity in melanoma patients by approximately 2-fold, as evidenced by a parent-to-metabolite AUC ratio of 2.2 for midazolam in the presence vs. the absence of vemurafenib. This interaction was statistically significantly outside the customary no-effect boundary (0.8–1.25). **Thus, medications predominantly metabolized via CYP3A4 may have decreased exposure when administered concomitantly with vemurafenib.**

The clinical significance of this observation depends on the therapeutic index of the specific CYP3A4 substrate administered concomitantly with vemurafenib. If CYP3A4 substrates must be co-administered with vemurafenib, the Investigator should monitor the signs of reduced benefit of CYP3A4 drugs due to potential decrease in their plasma concentration. Doses of the concomitant CYP3A4 drug, but not the dose of vemurafenib, may be adjusted as necessary to alleviate the impact of drug interaction.

Appendix 2 includes a non-exhaustive list of CYP3A4 substrates.

4.4.1.2.2 CYP1A2 substrates

In the CYP450 probe study NP22676, vemurafenib inhibited CYP1A2 in metastatic melanoma patients by approximately 3-fold, as evidenced by a parent-to-metabolite AUC ratio of 0.32 for xanthine in the presence vs. the absence of vemurafenib. This interaction was statistically significantly outside the customary no-effect boundary (0.8–1.25). Similarly, other pharmacokinetic assessments have demonstrated drug-drug interactions between vemurafenib and caffeine that are consistent with CYP1A2 inhibition. **Thus, medications predominantly metabolized via CYP1A2 may have increased exposure when administered concomitantly with vemurafenib.**

The clinical significance of these observations depends on the therapeutic index of the specific CYP1A2 substrate administered with vemurafenib. The Investigator should assess the safety risk associated with a potential increase in plasma concentrations of any concomitantly administered, CYP1A2 metabolized drug. If there is a concern, doses of the concomitant CYP1A2 drug, but not the dose of vemurafenib, may be adjusted as necessary to alleviate the impact of drug interaction.

Appendix 2 includes a non-exhaustive list of CYP1A2 substrates.

4.4.1.2.3 CYP2C9 substrates

Vemurafenib exhibited a strong signal for CYP2C9 inhibition *in vitro* in human hepatic microsomes (IC50, 5.9 μM). This in vitro inhibition did not appear to be as significant, however, in melanoma patients. Thus, in the NP22676 study, vemurafenib increased

exposure to warfarin, a CYP2C9 substrate, by approximately 20%, which was within the statistical no-effect boundary.

It should be noted, though, that some increase in warfarin exposure and a decrease in clearance were noted in NP22676. Warfarin has a narrow therapeutic index, and the potential increase in warfarin exposure, the *in vitro* evidence of CYP2C9 inhibition, and the inherent propensity for coagulation disorders in patients with malignant disease urge caution when vemurafenib is co-administered with warfarin. The same considerations are true of other medications with narrow therapeutic indices that are metabolized primarily by CYP2C9.

Appendix 2 includes a non-exhaustive list of CYP2C9 substrates.

4.4.1.2.4 CYP2C19 and CYP2D6 substrates

No drug-drug interactions have been observed between with omeprazole (a CYP2C19 substrate) and dextromethorphan (a CYP2D6 substrate).

4.4.1.2.5 Drugs that may cause QTc prolongation or cardiac arrhythmia

In a Good Laboratory Practice patch clamp assay, the IC_{50} for inhibition of the human Ether-à-go-go Related Gene (hERG) channel in serum-free conditions was 1.24 μM. Due to a potential preclinical signal for hERG ion channel blockade by vemurafenib *in vitro* and clinical evidence that vemurafenib may prolong QTc interval, caution should be taken when vemurafenib is co-administered with drugs that cause QTc prolongation or cardiac arrhythmia, or when they have a pre-exiting cardiac disease or ECG abnormality that may predispose them to cardiac dysrhythmia.

Investigators should closely monitor patients who are on medications and/or supplements that may affect QT interval prolongation. Such agents include, but are not limited to, terfenadine, quinidine, procainamide, disopyramide, sotalol, probucol, bepridil, haloperidol, risperidone, indapamide, and other drugs with disrythmic potential. Alternative treatment options for medications known to affect QT interval should be discussed with each patient prior to their inclusion into this study. Please refer to QT Drug List by Risk Groups (http://www.azcert.org/) for additional information and **Appendix 3**.

4.5 Criteria for Premature Withdrawal

Patients have the right to withdraw from the study at any time for any reason. Patients who discontinue the study will be asked to return to the clinic for an End of Treatment visit and a Safety Follow-Up Visit 28 (± 5) days after the last dose of vemurafenib.

If lost to follow-up, the Investigator should make all possible efforts to contact the patient or a responsible relative by telephone followed by registered mail or through a personal visit to establish as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made with an explanation of why the patient is withdrawing from the study.

When applicable, patients should be informed of circumstances under which their participation may be terminated by the Investigator without the patient's consent. The

Investigator may withdraw patients from the study in the event of intercurrent illness, adverse events, treatment failure after a prescribed procedure, lack of compliance with the study and/or study procedures (e.g., dosing instructions, study visits), cure or any reason where it is felt by the Investigator that it is in the best interest of the patient to be terminated from the study. Any administrative or other reasons for withdrawal must be documented and explained to the patient.

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

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

4.6 Replacement Policy (Ensuring Adequate Numbers of Evaluable Patients)

4.6.1 For Patients

Patients enrolled into the study will not be replaced

4.6.2 For Centers

A center may be replaced for the following administrative reasons:

Excessively slow recruitment

Poor protocol adherence

5. SCHEDULE OF ASSESSMENTS AND PROCEDURES

Table 7

Schedule of Assessments

	Screening Period[1]	Treatment Period [2] (Allowed visit window: –4 days / +1 day from cycle 2 onwards)										End of Treatment Visit [3]	Safety-Follow-Up Visit[4]	Survival Follow-Up[5]
Cycle		1		2	3	4	5	6	7	8	9 onwards			
Day	–28 to –1	1	15	29	57	85	113	141	169	197	Every 28 Days			
Informed consent[6]	X													
Documentation of BRAF V600 mutation and test performed	X													
Medical history and demographics	X													
Physical examination[7]	X	X	X	X	X	X	X	X	X	X	X (every 8 weeks)	X		
Vital signs[8]	X	X	X	X	X	X	X	X	X	X	X (every 8 weeks)	X		
12-lead ECG[9]	X			X	X	X	X			X	X (every 12 weeks)	X	X	
ECOG performance status	X	X	X	X	X	X	X	X	X	X	X (every 8 weeks)	X		
Hematology[10]	X	X[11]	X	X	X	X	X	X	X	X	X	X		
Biochemistry[12]	X	X[11]	X	X	X	X	X	X	X	X	X	X		
Serum pregnancy test[13]	X													
Solid tumor assessments (CT/MRI)[14]	X				X		X		X		X (every 8 weeks)	X		
Assesments for Multiple	X				X[16]	X[16]	X[16]	X[16]	X[16]	X[16]	X[16]	X[16]		

	Screening Period[1]	Treatment Period [2] (Allowed visit window: –4 days / +1 day from cycle 2 onwards)										End of Treatment Visit [3]	Safety-Follow-Up Visit[4]	Survival Follow-Up[5]
Cycle		1		2	3	4	5	6	7	8	9 onwards			
Day	–28 to –1	1	15	29	57	85	113	141	169	197	Every 28 Days			
Myeloma[15]														
Dermatology evaluation[17]	X			X			X			X	X (every 12 weeks)	X	X	
Head and neck assessment for SCC[18]	X					X			X		X (every 12 weeks)	X	X	
Chest CT for evaluation of SCC[19]	X								X		X (every 6 months)		X[20]	
Drug dispensation		X		X	X	X	X	X	X	X	X			
Drug accountability				X	X	X	X	X	X	X	X	X		
Drug Dosing Exception Diary[21]				X	X	X	X	X	X	X	X	X		
Concomitant medications[22]	X	X										X	X	
AEs / SAEs[23]	X	X										X	X	
Vemurafenib administration		X												
Follow-up for disease progression													X	
Survival status[5)]													X	X
Next anticancer therapy														X

Notes Day 1 = first dose of study drug (vemurafenib)

1. Apart from obtaining written informed consent, no screening procedure may be performed before the patient has been confirmed to be positive for the BRAF V600 mutation. All efforts should be made to collect a tumor sample (formalin-fixed paraffin-embedded tumor tissue [FFPET] or 3-5 serially cut unstained 5-µm sections from one FFPET block) for retrospective confirmation of the BRAF mutation using the cobas 4800 V600 mutation kit. This tumor sample should preferably be from the original specimen used to detect the BRAF mutation. The original tumour block will be returned to the site.
2. Visits during the Treatment Period are to be completed on Day 1, Day 15, Day 29 and every 28 days thereafter until study drug discontinuation. A window of 4 days prior to the scheduled visit date and one day after the scheduled visit date (–4 days / + 1 day) is allowed for each visit from Cycle 2 onwards.

	Screening Period[1]	Treatment Period [2] (Allowed visit window: –4 days / +1 day from cycle 2 onwards)										End of Treatment Visit [3]	Safety-Follow-Up Visit[4]	Survival Follow-Up[5]
Cycle		1		2	3	4	5	6	7	8	9 onwards			
Day	–28 to –1	1	15	29	57	85	113	141	169	197	Every 28 Days			

3. The End of Treatment Visit will be performed when the patient discontinues vemurafenib regardless of when it occurs.
4. The Safety Follow-Up Visit will be performed after 28 (±5) days from discontinuation of vemurafenib for any reason other than disease progression (such as AE).
5. The Survival Follow-Up period will extend from the last dose until death or for a maximum of 12 months for each patient after his/her last dose of study medication, withdrawal of consent or loss to follow-up (whichever occurs first).
6. Informed consent must be obtained prior to performing any study procedure including Screening assessments.
7. Includes the evaluation of the head, eyes, ears, nose, and throat (HEENT); cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal and neurological systems examination; and height (cm) and weight (kg). Height will only be measured during screening.
8. Includes blood pressure, heart rate, temperature and respiratory rate.
9. Includes heart rate, PR interval, QRS duration, QT and QTc intervals and ECG findings.
10. Includes hemoglobin, hematocrit, platelet count, white blood cell count (WBC) and absolute neutrophil count (ANC)
11. Hematology and biochemistry assessments do not need to be repeated on Day 1 if performed within 7 days of first vemurafenib administration. NB: if it is necessary to repeat these blood tests, the results must be known before the patient receives first dose of vemurafenib to ensure that the inclusion and exclusion criteria related to these tests are met.
12. Includes glucose, blood urea nitrogen [BUN], creatinine or creatinine clearance, sodium, potassium, calcium, magnesium, bicarbonate ([if routinely performed on venous blood samples],), total bilirubin with fractionation into direct and indirect (if total bilirubin elevated during the study), alkaline phosphatase, AST ([SGOT]], ALT ([SGPT]],
13. Serum pregnancy test to be performed within 7 days prior to first vemurafenib administration for women with childbearing potential.
14. Includes for solid tumour patients only: CT/MRI of the chest, abdomen and pelvis [C/A/P]). The same imaging technique (CT or MRI) should be used for these patients throughout the study. CT/MRI of the brain may also be performed as per standard of care.
15. Skeletal survey, Serum protein electrophoresis (SPEP), Urine protein electrophoresis (UPEP), Serum free light chains, 24 hour urine proteins, Bone marrow for histology, cytogenetics and FISH, and flow cytometery with or without biopsy, Beta 2 microglobulin, albumin and lactate dehydrogenase (LDH)
16. Bone marrow assessments only to be done to confirm complete remission after two consecutaive immunofluorescence analyses are negative.
17. Performed by a dermatologist. For patients who develop any suspicious new skin lesion during treatment with vemurafenib. Further confirmation by a designated central pathology laboratory.
18. Performed by the treating physician as part of the evaluation for SCC.
19. CT of the chest for the evaluation of noncutaneous SCC (for all patients, solid tumors and MM). For patients with solid tumours, the routinely scheduled

	Screening Period[1]	Treatment Period [2] (Allowed visit window: –4 days / +1 day from cycle 2 onwards)										End of Treatment Visit [3]	Safety-Follow-Up Visit[4]	Survival Follow-Up[5]
Cycle		1		2	3	4	5	6	7	8	9 onwards			
Day	–28 to –1	1	15	29	57	85	113	141	169	197	Every 28 Days			

radiographic assessment for tumor burden may be used (if available) as the chest CT for the evaluation of noncutaneous SCC while the patient is taking vemurafenib.

20. Must be performed 6 months following study drug discontinuation or until initiation of another anti-neoplastic therapy.
21. Patients will keep a diary to record ONLY those occasions when a vemurafenib dose was missed (morning or evening, each day of treatment). The patient will bring this diary with him/her to each study visit to allow missed doses to be recorded by the Investigator.
22. All concomitant medications during the study started within 14 days prior to the screening visit and up to the end of study visit must be recorded.
23. During screening AEs are not recorded in the eCRF unless they are SAEs which are related to protocol-mandated procedures. ALL AEs (including SAEs) must be recorded from the time of first vemurafenib administration. After the last dose of vemurafenib any new, non-serious AEs which the Investigator considers may be related to vemurafenib should be reported up to 28 days after last dose. Any SAEs reported after last dose which the Investigator considers related to vemurafenib must be reported indefinitely.

All screening assessments as outlined in **Table 7. Schedule of Assessments** must be performed within 28 days prior to the first administration of vemurafenib on Day 1. Results of tests or examinations performed as standard of care before obtaining informed consent and within the 28 days prior to commencing vemurafenib may be used.

Eligibility for the study will be determined by the Investigator from the mandatory screening assessments performed during the Screening Period and according to the study inclusion/exclusion criteria. First dosing of vemurafenib will be determined by the patient's eligibility and the laboratory assessments done on Day 1 prior to dosing on Day 1.

The Investigator/Designee will collect and document in the eCRFs whether the patient has progressed or not.

Patients who discontinue study drug for any reason (disease progression, AEs, etc.) other than consent withdrawal will continue to be followed for survival and new anti-cancer therapy every 3 months after last dose until death or for a maximum of 12 months for each patient after their last dose of study mediaction, withdrawal of consent, or lost to follow-up.

5.1 Screening Examination and Eligibility Screening Form

All patients must provide written informed consent before any study specific assessments or procedures are performed. The patient who has provided a written informed consent will be allocated a patient number by the IxRS system which has been established for the purpose of this study. Each identifying number will be unique to the patient for whom it is issued.

All screening evaluations must be performed between Day –28 and Day –1. Patients who fulfill all the inclusion and none of the exclusion criteria will be accepted into the study.

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

A log must be maintained by the Investigator of all patients who fail screening. For consented patients who fail to meet the inclusion and exclusion criteria, only the Screening Log pages, demographics, and reason for screening failure will be collected.

5.1.1 Procedures for Screening Patients for the BRAF V600 Mutation

Patients with BRAF V600 mutation-positive cancers will be identified through mutation analysis assays as routinely performed at each participating site (the BRAF V600 mutation and the assay used for its detection will be recorded in the eCRFs).

5.2 Procedures for Enrollment of Eligible Patients

A patient who has fulfilled the entry criteria will attend on the morning of Day 1. The same patient number allocated to the patient during screening will be used throughout the study. A patient number will not be re-used if the patient leaves the study.

Under no circumstances will patients who enroll in this study and have completed treatment as specified be permitted to re-enroll in the study.

A Patient Enrollment and Identification Code List must be maintained by the Investigator.

5.3 Clinical Assessments and Procedures

The following clinical assessments and procedures must be completed for all patients enrolled in this study.

Please refer to **Table 7. Schedule of Assessments** for specific details and time points related to the clinical assessments and procedures outlined below:

5.3.1 Screening Period

The following assessments should be performed within 28 days before the first administration of vemurafenib on Day 1 (unless they have already been conducted during this time period as part of the patient's routine clinical care):

- Signed written informed consent approved by the relevant Independent Ethics Committee (IEC) / Institutional Review Board (IRB) must be obtained prior to performing any study-related procedures
- Documentation of BRAF V600 mutation and test used for the identification of the mutation.
- All efforts should be made to collect a tumor sample (formalin-fixed paraffin-embedded tumor tissue [FFPET] or 3-5 serially cut unstained 5-µm sections from one FFPET block) for retrospective confirmation of the BRAF mutation using cobas 4800 V600 mutation kit. This tumor sample should preferably be from the original specimen used to detect the BRAF mutation. The original tumour block will be returned back to the site. Any slides sent from the tumour sample will be sent to Roche Molecular Systems and stored for up 5 years.
- Medical history (including demographics)
- Physical examination, including the evaluation of the head, eyes, ears, nose, and throat (HEENT); cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and a neurological systems examination; and height and weight (height will only be measured during screening)
- Vital signs (blood pressure, heart rate, temperature, respiratory rate)
- 12-lead ECG, including heart rate, PR interval, QRS duration, QT and QTc intervals, and ECG findings
- ECOG Performance Status
- Hematology, including hemoglobin, hematocrit, platelet count, white blood cell count (WBC), and absolute neutrophil count (ANC)

- Biochemistry (including glucose, blood urea nitrogen [BUN], creatinine or creatinine clearance, sodium, potassium, calcium, magnesium, bicarbonate [if routinely performed on venous blood samples], total bilirubin with fractionation into direct and indirect (if total bilirubin elevated during the study), alkaline phosphatase, AST [SGOT], ALT [SGPT].
- Serum pregnancy test within 7 days prior to commencement of dosing for women of child-bearing potential. Women surgically sterile or postmenopausal for ≥ 1 year are not to be considered for a pregnancy test.
- Tumor assessments for solid tumours (CT/MRI of the chest, abdomen, and pelvis [C/A/P]). CT/MRI of the brain may also be performed as per standard of care
- Assessments for mutliple myeloma (Skeletal survey, Serum protein electrophoresis (SPEP) with quantitation of M-protein by immunofixation Urine protein electrophoresis (UPEP) using 24 hours urine protein electrophoresis, Serum free light chains, Bone marrow for histology, cytogenetics and FISH, and flow cytometery with or without biopsy, Beta 2 microglobulin albumin and lactate dehydrogenase (LDH))
- Dermatology evaluation by a dermatologist
- Head and neck examination (as part of the evaluation for SCC) performed by the treating physician
- CT of chest for evaluation of noncutaneous SCC (for all patients, solid tumors and MM.
- Concomitant medications
- AEs (including SAEs) related to study-mandated procedures from time signed

5.3.2 Treatment Period

Visits during the treatment period are to be completed on Day 1, Day 15, Day 29, and every 28 days thereafter. A window of 4 days prior to the scheduled visit date and one day after the scheduled visit date (–4 days / + 1 day) is allowed for each visit from Cycle 2 onwards (28-day cycle). The following assessments should be performed during the Treatment Period:

- Physical examination (as described previously) on Day 1, Day 15, Day 29, and every 28 days for the first 8 cycles and then every 8 weeks thereafter until study drug discontinuation
- Vital signs (as described previously) on Day 1, Day 15, Day 29, and every 28 days for the first 8 cycles and then every 8 weeks thereafter until study drug discontinuation

- 12-lead ECG (as described previously) 28 days after starting vemurafenib, every 28 days for the following 3 months, and every 12 weeks thereafter until study drug discontinuation

- ECOG performance status on Day 1, Day 15, Day 29, and every 28 days for the first 8 cycles and then every 8 weeks thereafter until study drug discontinuation

- Hematology (as described previously) on Day 1, Day 15, Day 29, and every 28 days thereafter until study drug discontinuation.
  Hematology assessments do not need to be repeated on Day 1 if performed within 7 days of the first vemurafenib administration

- Biochemistry (as described previously) on Day 1, Day 15, Day 29, and every 28 days thereafter until study drug discontinuation
  Biochemistry assessments do not need to be repeated on Day 1 if performed within 7 days of the first vemurafenib administration

- Dermatology evaluation by a dermatologist 28 days after starting vermurafenib and every 12 weeks thereafter until study drug discontinuation

- Head and neck examination (as part of the evaluation for SCC) performed by the treating physician every 12 weeks after starting vemurafenib

- CT of the chest for the evaluation of noncutaneous SCC (for all patients, solid tumors and MM). For patients with solid tumours, the routinely scheduled radiographic assessment for tumor burden may be used (if available) as the chest CT for the evaluation of noncutaneous SCC while the patient is taking vemurafenib.

- Drug dispensation on Day 1 and every 28 days thereafter until study drug discontinuation

- Drug accountability every 28 days after starting vemurafenib until study drug discontinuation

- Review of the Drug Dosing Exception Diary every 28 days after starting vemurafenib until study drug discontinuation

- Concomitant medications throughout the Treatment Period

- AEs (including SAEs) throughout the Treatment Period Vemurafenib administration throughout the Treatment Period

- Vemurafenib administration throughout the Treatment Period

The following tumor assessments are to be performed for patients with solid tumors;

- CT/MRI of the chest/abdomen/pelvis (C/A/P) every 8 weeks after starting vemurafenib. The same imaging technique (CT or MRI) should be used for each patients throughout the study
- CT/MRI of the brain as per standard care

The following asssements are to be performed for patients with MM 8 weeks after starting vemurafenib and every 4 weeks thereafter;

- Serum protein electrophoresis (SPEP) with quantitation of M-protein level by immunofixation, urine protein electrophoresis (UPEP) using 24-hour urine protein electrophoresis, Serum free light chains , LDH, and beta 2 microglobulin. Bone marrow analsyis only to be done only to confirm complete remission after two consecutaive immunofixation analyses are negative.

5.3.3 End-of-Treatment Visit

The End-of-Treatment Visit will occur when the patient discontinues vemurafenib for any reason, unless the patient withdraws consent and refuses, or is lost to follow up. The following assessments will be conducted at the End-of-Treatment Visit:

- Physical examination (as described previously)
- Vital signs (as described previously)
- 12-lead ECG (as described previously)
- ECOG Performance Status
- Hematology (as described previously)
- Biochemistry (as described previously)
- Tumor assessments (as described previously) if not done within the last 8 weeks
- Response assessments for multiple myeloma if not done within the last 28 days
- Dermatology evaluation by a dermatologist if not done within the previous 12 weeks
- Head and neck examination (as part of the evaluation for SCC) performed by the treating physician every 12 weeks after starting vemurafenib Drug accountability
- Review of the Drug Dosing Exception Diary

- Concomitant medications
- AEs (including SAEs)

5.3.4 Safety-Follow-Up Visit

The Follow-Up Visit will occur 28 (± 5) days after discontinuation of vemurafenib. The following assessments will be conducted at the Follow-Up Visit:

- 12-lead ECG (as previously described)
- Dermatology evaluation by a dermatologist
- Head and neck examination (as part of the evaluation for SCC) performed by the treating physician
- CT of the chest for evaluation of SCC must be performed in all patients (both solid tumour and MM) 6 months following study drug discontinuation or until initiation of another anti-neoplastic therapy
- Concomitant therapy
- AEs (including SAEs)
- Follow up for disease progression for those patients who have discontinued study drug for any reason (i.e., AEs, etc.) other than disease progression
- Survival status

5.3.5 Survival Follow-Up

The following assessments will be conducted during the Survival Follow-Up Period:

- Survival status every 3 months after the last dose until death or for a maximum of 12 months for each patient from their last dose of study medication, withdrawal of consent, or loss to follow-up (whichever occurs first).
- Furthermore, new anticancer therapy will be documented.

5.3.6 Response Criteria

5.3.6.1 Solid tumors

Response of measurable solid tumors to study treatment will be evaluated by the Investigator according to RECIST, v1.1 criteria (**Appendix 4**) (75).

Tumor evaluations will occur once during the Screening Period (Days –28 and –1), every 8 weeks after starting vemurafenib during the Treatment Period, and at the End of Treatment Visit. A window of ± 5 days of scheduled visit is allowed to complete the tumor assessments at the required intervals.

Radiological tumor assessments to measure extent of disease will be carried out by CT/MRI of the chest/abdomen/pelvis (C/A/P), and by CT/MRI of the brain if clinically indicated and as per standard care.

Patients should be assessed at the designated time points using a consistent imaging modality. The same imaging technique must be used for a patient throughout the study. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. If more than one method of assessment is used at baseline, the most accurate method according to RECIST should be selected when recording data; in addition, this method should be performed in all subsequent evaluations. Tumor measurements should be made by the same Investigator/radiologist for each patient during the study to the extent that this is feasible.

For solid tumors to be assigned a status of partial response (PR) or complete response (CR) (i.e., a responder), changes in tumor measurements must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met, i.e., patients need to have two consecutive assessments of PR or CR to be a responder.

Sympomatic deterioration may indicate progressive disease (PD). However, radiological confirmation of PD is strongly recommended.

5.3.6.2 Multiple myeloma

Response of MM to study treatment will be evaluated according to IMWG uniform response criteria (**Appendix 5**) (76, 77).

Evaluations will occur once during the Screening Period (Days –28 and –1), 8 weeks after starting vemurafenib, every 28 days thereafter during the Treatment Period, and at the End of Treatment Visit.

Serum M-protein level will be quantitated using densitometry on serum protein electrophoresis (SPEP) by immunofixation

Urine M-protein measurement will be estimated using 24-hour urine protein electrophoresis (UPEP) only. Random or 24-hour urine tests measuring kappa and lambda light chain levels are not reliable and are not recommended. For oligosecretory and light chain myeloma patients, serum free light chains will be measured.

Patients will need to have two consecutive assessments of CR, sCR, VGPR or PR to be considered a responder.

5.3.7 ECOG Performance Status

Performance Status will be measured using the Eastern Cooperative Oncology Group (ECOG) Performance Status Scale (**Appendix 6**) at each visit.

It is recommended that the same person assess a patient's performance status throughout the study, whenever possible.

5.3.8 Clinical Safety Assessments

The National Cancer Institute's Cancer Toxicity Criteria for Adverse Events, Version 4.0 (NCI-CTCAE, v4.0) will be used to quantify the intensity of AEs occurring during treatment in this study (**Appendix 7**).

Patients will be assessed for AEs at each clinic visit and as necessary throughout the study. Incidence, type, and severity of AEs, serious adverse events (SAEs), incidence of AEs and SAEs leading to vemurafenib interruption or discontinuation, and cause of death will be reported.

All other safety monitoring will occur by the reporting of AEs, by the assessment of routine laboratory values (blood counts and differential and serum chemistries), vital signs, electrocardiograms (ECGs), dermatology, and head & neck evaluations for cutaneous squamous cell carcinoma (SCC) and noncutaneous SCC, respectively, chest CT scans for noncutaneous SCC surveillance, and findings on physical examinations.

The schedule for safety assessments is presented in **Table 1.** Schedule of Assessments Individual assessments are described further below:

5.3.8.1 Medical history and demographics

As part of the physical exam, a medical history will be collected, including demographics, relevant medical history, previous and current diseases, prior therapies including surgeries and relative responses, prior skin cancer history, therapies and procedures, all medications started within 14 days prior to screening visit, and measurements for weight (kilograms, kg) and height (cm, screening visit only).

5.3.8.2 Physical examination

The initial (Screening) complete physical examination should include the evaluation of the head, eyes, ears, nose, and throat (HEENT) and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Subsequent physical examinations during the study for safety assessment may be restricted to evaluation of specific systems or areas of interest, including those with previously abnormal findings or associated with symptomatic or laboratory evidence of toxicity. A skin examination by the treating physician should, however, be performed at each visit.

5.3.8.3 Vital signs

Vital signs will be recorded for all patients and will include blood pressure, temperature (degrees Celsius, °C), heart rate, and respiratory rate.

5.3.8.4 Squamous cell carcinoma assessments

5.3.8.4.1 Cutaneous SCC

Cutaneous squamous cell carcinoma (cSCC) is defined as an event requiring close monitoring. These events must always be designated as SAEs in order to ensure their reporting to the Health Authorities in an appropriate and timely manner. Patients are required to have ongoing full skin examinations by a dermatologist to screen and monitor for SCC, basal cell carcinoma (BCC), actinic keratosis, and keratoacanthoma (KA). Dermatology evaluation will be performed at Screening/Baseline (anytime up to 28 days

prior to Day 1), approximately 28 days on therapy, every 12 weeks thereafter while the patient is on the study, when the patient discontinues vemurafenib unless done within the prior 12 weeks, and at the end of study Safety-Follow-Up Visit 28 days after discontinuing vemurafenib. Patients should report to their physician any new skin lesion or change, including rash and photosensitivity, while on study treatment, and any suspicious lesions should be referred to a dermatologist for further evaluation as required.

The initial examination by the dermatologist should include a complete dermatological history of prior medications, and cutaneous SCC risk factors (i.e., radiation therapy, sun exposure, immunosuppression, prior SCC, use of tanning beds, precursor lesions and photochemotherapy for psoriasis).

Any lesion suspected of representing a new SCC, BCC, actinic keratosis, or keratoacanthoma identified by the dermatologist should be treated as per local standard of care. Skin biopsies of any suspicious lesions identified at baseline and during the study must be biopsied/excised and sent for pathological examination. Available blocks/sections should also be sent to a designated central pathology laboratory for confirmation of diagnosis.

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

5.3.8.4.2 Noncutaneous SCC

A head and neck examination must be performed by the treating physician or other qualified physician at baseline and during the study for all patients enrolled. The head and neck examination will consist of at least a visual inspection of the oral mucosa and lymph node palpation. This will be done at Screening/Baseline (anytime up to 28 days prior to Day 1), every 12 weeks while the patient is on study, when the patient discontinues vemurafenib unless done within the prior 12 weeks, and at the end of study Safety-Follow-Up visit 28 days after discontinuing vemurafenib. Any suspicious findings will be referred to an appropriate specialist

A CT scan of the chest is required for noncutaneous SCC screening and surveillance for all patients. MRI may be used if a CT scan is contra-indicated for the patient. Because radiologic assessments for tumor burden are a standard requirement for patients with solid tumours, it is not necessary to perform a separate chest CT/MRI. Instead, the same (routine tumor assessment CT/MRI) should suffice for monitoring of noncutaneous SCC as well for solid tumour patients only. However, chest CT for the evaluation of SCC are required at a minimum of every 6 months for each patient.

5.3.8.5 Electrocardiographic assessments

Prolongation of the corrected QT (QTc) interval (change from baseline) has been reported in vemurafenib clinical trials. As a result of these findings, mandatory ECG assessments, with a focus on QTc interval, will be conducted during the Screening Period, 4 weeks after starting vemurafenib treatment, every 4 weeks for the next 3 months, every 12 weeks thereafter during the Treatment Period, at the End-of-Treatment

Visit, and at the Safety-Follow-Up Visit. The following parameters will be collected: heart rate, PR interval, QRS duration, QT and QTc intervals, and ECG findings.

Please refer to Section 6.1.1 for dose modifications guidelines to minimize the risk of ventricular arrhythmia in patients with metastatic melanoma treated with vemurafenib.

5.3.8.6 Photosensitivity

Photosensitivity has been reported in patients treated with vemurafenib in clinical trials. The majority of cases were mild or moderate in severity. All patients should be advised to avoid sun exposure and/or wear protective clothing with sun block and lip balm (minimum of SPF 30, re-applied every 2 to 3 hours) during vemurafenib treatment and for at least 5 to 10 days after study drug discontinuation.

5.4 Laboratory Assessments

Samples for hematology, serum biochemistry, and pregnancy will be analyzed at the study site's local laboratory as part of regular safety assessments. Protection of patient confidentiality (See Section 17) will extend to any data generated from the assaying of these samples.

Normal ranges for the study laboratory parameters must be supplied to Roche before the study starts. Changes to the normal ranges during the course of the study should be notified to Roche as soon as possible.

Laboratory assessments will be performed at screening/baseline, at each every 28-Day visit and at the end of the study visit.

5.4.1 Safety Laboratory Assessments

Hematology and biochemistry will be done as part of regular safety assessments. Specifically

Hematology: Hemoglobin, hematocrit, white blood cell count (WBC), absolute neutrophil count (ANC), and platelet count

Biochemistry: glucose, blood urea nitrogen (BUN), creatinine or creatinine clearance (CrCl), sodium, potassium, calcium, magnesium, bicarbonate (if routinely performed on venous blood samples), total bilirubin with fractionation into direct and indirect bilirubin (if total bilirubin is elevated), alkaline phosphatase, and AST (SGOT), ALT (SGPT)

Serum pregnancy test in all women of child-bearing potential at screening (within 7 days prior to first administration of vemurafenib.

6. INVESTIGATIONAL MEDICINAL PRODUCT

The formulated drug product vemurafenib is provided as 240-mg film-coated tablets packed in bottles for oral administration. For additional batch-specific instructions and information, vemurafenib will be labeled in compliance with Good Manufacturing Procedures (GMP). The drug label will include the contents, protocol number, batch number, and storage conditions, as well as any required statements that the drug is: "For

Clinical Trial Use Only." Patients will be requested to store the vemurafenib at the recommended storage conditions noted on the label out of the reach of children or other cohabitants. For further details, please see the Investigator Brochure.

6.1 Dose and Schedule of Vemurafenib

Patients will receive continuous oral doses of vemurafenib 960 mg b.i.d. without scheduled dose interruption starting on Day 1 of the Treatment Period until the development of progressive disease, unacceptable toxicity, consent withdrawal, protocol violation endangering the patient's safety, death, reasons deemed by the Investigator, or study termination by the Sponsor. Vemurafenib is supplied in 240 mg film-coated tablets packed in bottles for oral administration. Patients should be instructed to take four tablets in the morning and four tablets approximately 12 hours later in the evening (total daily dose of 1920 mg [960 mg b.i.d.]). Each dose should always be taken in the same manner i.e. either with or without a meal.

If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. However if a patient forgets to take a dose, it can be taken up to 4 hours prior to the next dose.

If a patient misses a dose (e.g., due to emesis), he or she should be instructed not to take or make up that dose and to resume dosing with the next scheduled dose. Missed doses will not be made up. Patients will be instructed to bring all unused tablets to each study visit for assessment of compliance.

Patients who develop disease progression and, in the opinion of the Investigator, would still benefit from continuing vemurafenib may continue treatment with vemurafenib after discussion with the Sponsor.

Patients will be given a dosing exception diary to record the time and date of *missed* study medication doses. Any such data provided by the patient will be transcribed from the diary to the eCRF by the study coordinators.

A 4-week supply of study medication will be given to the patient on Day 1 of each dosing cycle. From Cycle 8 onwards a 12-week supply of study medication will be given to the patient on Day 1 of each dosing cycle. Patients will be instructed not to open a new bottle until the previous bottle has been finished and to bring their study medication and bottles (used or unused) back to the clinic at the next study visit for reconciliation.

6.1.1 Dose Modifications, Interruptions, and Delays

Management of symptomatic adverse drug reactions (e.g., arthralgia, fatigue, rash) may require temporary interruption and/or dose reduction of vemurafenib treatment. When needed, dose reduction in 240-mg b.i.d. increments is recommended based on individual safety and tolerability. Up to two dose reductions of vemurafenib will be allowed, i.e., to 720 mg p.o. b.i.d., and then to 480 mg p.o. b.i.d. There will be no dosage reductions or interruptions for skin cancer.

Dose escalation after dose reduction is generally not recommended unless under special circumstances, i.e., increased likelihood of clinical benefit for the dose increase and no

safety concerns. This should only be done after discussion with the Sponsor. Dose increases above 960 mg b.i.d. are NOT allowed.

Dosage modification criteria should occur as follows (also see **Table 8**):

Table 8.
Dose Interruption/Modification Criteria for Vemurafenib

Toxicity Grade (CTCAE, v4.0)[a]	Vemurafenib dose changes during current treatment period	Dose adjustments for resumption of treatment
Grade 1	100% of starting dosage	100% of starting dosage
Tolerable Grade 2	100% of starting dosage	100% of starting dosage
Intolerable Grade 2		
First appearance	Interrupt until resolved to Grade 0 – 1	Reduce by 240 mg b.i.d.
Second appearance	Interrupt until resolved to Grade 0 – 1	Reduce by 240 mg b.i.d.
Third appearance	Discontinue permanently	
Grade 3		
First appearance	Interrupt until resolved to Grade 0 – 1	Reduce by 240 mg b.i.d.
Second appearance	Interrupt until resolved to Grade 0 – 1	Reduce by 240 mg b.i.d.
Third appearance	Discontinue permanently	–
Grade 4		
First appearance	Discontinue permanently or interrupt until resolved to Grade 0 – 1	Reduce to 50% of starting dosage
Second appearance	Discontinue permanently	–

[a]Common Terminology Criteria for Adverse Events, Version 4.0.

Prolongation of the corrected QT (QTc) interval (change from baseline) was observed in a substudy of the NP22657/BRIM-2 phase II trial. As a result of these findings, the following recommendations have been developed to minimize the risk of ventricular arrhythmia in patients with metastatic melanoma treated with vemurafenib:

Avoid combination with other agents with known potential to lead to prolongation of QTc interval, if possible.

ECG monitoring, with a focus on QTc interval, should occur during the Screening/Baseline period, 28 days after starting vemurafenib, every 28 days for the following 3 months, and every 12 weeks thereafter until study drug discontinuation at the End-of-Treatment Visit, and at the Safety-Follow-Up Visit.

If QTc interval exceeds 500 ms or the change from baseline is > 60 ms, vemurafenib treatment should be temporarily interrupted. The Investigator should check electrolytes (K+, Mg++, and Ca++) with a focus on hypokalemia, correct any electrolyte abnormalities prior to reinstitution of therapy, recheck concomitant medications to insure that none has been implicated in QTc prolongation, and rule out or control other cardiac risk factors (i.e., ischemia). ECG should be monitored weekly until QTc decreases to less than 500 ms, at which point treatment should be reinitiated at one reduced dose level, i.e., from 960 mg b.i.d. to 720 mg b.i.d. If a subsequent increase in QTc to > 500 ms or change from baseline is > 60 ms is observed, vemurafenib may be reduced to 480 mg b.i.d.

Vemurafenib should be permanently discontinued if a QTc increase meets both criteria of > 500 ms and > 60 ms change from pre-treatment values or if QTc > 500 ms or change from baseline > 60 ms is observed on two separate prior occasions.

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

For patients required to have tumor surgery, radiotherapy or other procedures, treatment with vemurafenib must be interrupted prior to these procedures. The treating physician must contact the Sponsor for guidelines as when study drug is to be stopped and re-started after the procedure.

Temporary discontinuation longer than 4 weeks should be discussed with the Sponsor. If a treatment interruption occurs for reasons other than an AE, and it is determined that vemurafenib will be re-started, no dose reduction is required.

6.2 Preparation and Administration of Vemurafenib

Vemurafenib will be supplied as 240-mg film-coated tablets packed in bottles for oral administration. No further preparation is required.

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

Vemurafenib should be stored at room temperature < 25°C and should be protected from excessive exposure to sunlight. Patients will be requested to store vemurafenib at the recommended storage conditions noted on the label, out of the reach of children or other vulnerable persons. Under hot weather conditions storage in the refrigerator is possible to not exceed storage conditions above 25°C.

For additional batch-specific instructions and information for vemurafenib film-coated tablets, please refer to the packaging.

Vemurafenib should be taken at approximately the same times each day, the first dose is to be taken in the morning and the second dose is to be taken approximately 12 hours later in the evening. Each dose should always be taken in the same manner i.e. either with or without a meal

If a patient misses a dose (e.g., due to emesis), he or she should be instructed not to take or make up that dose and to resume dosing with the next scheduled dose. Missed doses will not be made up.

6.3 Packaging, and Labeling

Study drug packaging will be overseen by the Roche clinical trial supplies department and will bear a label with the identification required by local law, the protocol number, batch number, storage conditions, drug identification, and dosage, and the statements:

"Do Not Store above 25°C" and "Keep Container Tightly Closed," as well as any required statements that the drug is "For Clinical Trial Use Only."

The packaging and labeling of the study medication will be in accordance with Roche standards and local regulations and in compliance with Good Manufacturing Procedures (GMP). Local packaging in some countries may be different.

6.4 Blinding and Unblinding

Not applicable, study is open label.

6.5 Accountability of IMP and Assessment of Compliance

6.5.1 Accountability of Vemurafenib

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

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

Documentation of drug shipments received from the sponsor (date received, batch number and quantity)

Disposition of unused study drug not dispensed to patient

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

Identification of the patient to whom the study medication was dispensed

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

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

All records and drug supplies must be available for inspection by the Monitor at every monitoring visit.

Patients will be asked to return all used and unused drug supply containers at the end of the treatment as a measure of compliance.

This inventory must be available for inspection by the Monitor. All supplies, including partially used or empty containers and copies of the dispensing & inventory logs, must be returned to the Monitor at the end of the study, unless alternate destruction has been authorized by Roche, or required by local or institutional regulations (Section 6.6).

6.5.2 Assessment of Compliance

Patient compliance will be assessed by maintaining adequate study drug dispensing records. The Investigator is responsible for ensuring that dosing is administered in compliance with the protocol. Delegation of this task must be clearly documented and approved by the Investigator.

6.6 Destruction of Vemurafenib

Local or institutional regulations may require immediate destruction of used investigational medicinal product (IMP) for safety reasons e.g., cytotoxicity. In these cases, it may be acceptable for investigational site staff to destroy dispensed IMP before a monitoring inspection provided that source document verification is performed on the remaining inventory and reconciled against the documentation of quantity shipped, dispensed, returned and destroyed. Written authorization must be obtained from the sponsor at study start up before destruction.

Written documentation of destruction must contain the following:

Identity (batch numbers and patient numbers) of investigational product(s) destroyed

Quantity of investigational product(s) destroyed

Date of destruction (date discarded in designated hazardous container for destruction)

Method of destruction (the site must provide the sponsor with documentation of their institutional policy and procedures for handling and disposing of hazardous drugs)

Name and signature of responsible person who discarded the investigational product in a hazardous container for destruction

7. SAFETY INSTRUCTIONS AND GUIDANCE

7.1 Warnings and Precautions

Investigators and patients should be aware of the risks of photosensitivity reactions, SCC, and potential drug–drug interactions during treatment with vemurafenib (see Section 4.4 and **Appendix 2** for advice on which concomitant treatments should be avoided while taking vemurafenib).

Mild to severe photosensitivity has been reported in patients treated with vemurafenib. All patients should be advised to avoid prolonged sun exposure while taking vemurafenib and for at least 5 days after study drug discontinuation. Patients should also be advised to use a broad spectrum sun screen of at least SPF >30 to help protect against sunburn. For acneiform rash, Investigators should consider treatment with minocycline.

Section 5.3.8.4 of this protocol outlines a detailed surveillance plan for SCC which includes a thorough skin evaluation by a dermatologist, head and neck exam, and CT scan of the chest for all patients who participate in the study. Please see Schedule of Assessments in Table 7 for specific details on when assessments for SCC risk management plan are to be conducted at screening and throughout study.Owing to the possible tumor biopsy requirement (for screening or evaluation of suspicious skin lesions) in this study, risks such as infection of the surgical site, excessive bleeding, or

injury to adjacent tissues, should be considered for patients who undergo tumor tissue biopsies.

7.2 Adverse Events and Laboratory Abnormalities

7.2.1 Clinical Adverse Events

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

7.2.1.1 Intensity

Intensity of all adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events, Version 4.0 (CTCAE, v4.0) on a five-point scale (Grade 1 to 5) and reported in detail on the eCRF.

Adverse events not listed on the CTCAE v4.0 should be graded as described in **Table 9**.

Table 9.
Adverse Event Grading (Severity) Scale

CTC Grade	Equivalent to:	Definition
Grade 1	Mild	Discomfort noticed but no disruption of normal daily activity
Grade 2	Moderate	Discomfort sufficient to reduce or affect daily activity; no treatment or medical intervention is indicated although this could improve the overall well-being or symptoms of the patient
Grade 3	Severe	Inability to work or perform normal daily activity; treatment or medical intervention is indicated in order to improve the overall well-being or symptoms; delaying the onset of treatment is not putting the survival of the subject at direct risk.
Grade 4	Life threatening/ disabling	An immediate threat to life or leading to a permanent mental or physical conditions that prevents work or performing normal daily activities; treatment or medical intervention is required in order to maintain survival.
Grade 5	Death	AE resulting in death

7.2.1.2 Drug – Adverse Event relationship

The causality relationship of study drug to the adverse event will be assessed by the Investigator as either:

Yes or No

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

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

Reasonable temporal association with drug administration

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

Known response pattern to suspected drug

Disappears or decreases on cessation or reduction in dose

Reappears on rechallenge

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

It does <u>not</u> follow a reasonable temporal sequence from administration of the drug.

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

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

It does not reappear or worsen when the drug is readministered.

7.2.1.3 Serious Adverse Events (Immediately Reportable to Roche)

A serious adverse event is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any Adverse Event that at any dose fulfils at least one of the following criteria:

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

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

required in-patient hospitalization or prolongation of existing hospitalization;

results in persistent or significant disability/incapacity;

is a congenital anomaly/birth defect;

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

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

The study will comply with all local regulatory requirements and adhere to the full requirements of the **ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2.**

After informed consent, but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies, medication washout, or no treatment run-in).

7.2.1.4 Progression of Underlying Malignancy

Progression of underlying malignancy is not reported as an adverse event if it is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST criteria, or other criteria as determined by protocol. This includes also deaths solely due to underlying malignancy. An SAE with outcome death solely due to progression of the underlying malignancy does not need to be reported as an SAEs. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as a serious adverse event. Clinical symptoms of progression may be reported as adverse events if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.

Symptomatic deterioration may indicate progressive disease (PD), hoever radiological confirmation of PD is strongly recommended. In this situation, progression is evident in the subject's clinical symptoms, but is not supported by the tumor measurements. Or, the disease progression is so evident that the Investigator may elect not to perform further disease assessments. In such cases, the determination of clinical progression is based on

symptomatic deterioration. These determinations should be a rare exception as every effort should be made to document the objective progression of underlying malignancy.

If there is any uncertainty about an adverse event being due only to the disease under study, it should be reported as an AE or SAE.

7.2.2 Treatment and Follow-up of AEs

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

Related AEs: Follow until one of the following occurs:

Resolved or improved to baseline

Relationship is reassessed as unrelated

Death

Start of new anti-cancer regimen

Investigator confirms that no further improvement can be expected

Clinical or safety data will no longer be collected, or final database closure

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

Resolved or improved to baseline

Severity improved to Grade 2

Death

Start of new anti-cancer regimen

Investigator confirms that no further improvement can be expected

Clinical or safety data will no longer be collected, or final database closure

Unrelated Grade 1 or Grade 2 AEs: Follow until **28 days from the last dose of study drug.**

The final outcome of each adverse event must be recorded on the eCRF

7.2.3 Laboratory Test Abnormalities

Local laboratories will be used for all laboratory tests. Laboratory test results will be recorded on the laboratory results form of the eCRF.

Any laboratory result abnormality fulfilling the criteria for a serious adverse event (SAE) should be reported as such, in addition to being recorded as an AE in the eCRF.

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

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

7.2.3.1 Follow-up of Abnormal Laboratory Test Values

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

Handling of Safety Parameters

7.3.1 Reporting of Adverse Events

All adverse events (either related to study specific procedures or otherwise) experienced after the patient has signed the Informed Consent form but before they have received study treatment, should be recorded as medical history.

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

All AEs and SAEs regardless of the relationship to the trial drug will be recorded in the eCRF.

All AE reports should contain a brief description of the event, date and time of onset, date and time of resolution, intensity, treatment required, relationship to trial drug, action taken with the trial drug, outcome, and whether the AE is classified as serious.

All adverse events experienced after the patient has started study treatment must be recorded on the AE form of the eCRF, as well as all new adverse events experienced during the study and up to 28 days after the last dose of study treatment. SAEs considered related to study drug are to be reported indefinitely.

A pre-existing medical condition that is present at the start of the study should be recorded on the Medical History eCRF.

AEs ill be reported and graded following NCI CTCAE, v4.0. Accordingly, intensity of all AEs will be graded on a five-point scale (Grade 1 to 5) and reported in detail on the CRF. Reporting of AE based on CTCAE terms and corresponding grading are an integral part of safety/AE/SAE reporting in this study and will have to be strictly followed. The causality relationship of study 'treatment' to the adverse event will be assessed by the Investigator as either **Yes or No**.

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

The Investigator should provide his/her assessment as to whether an AE is related to the study treatment regimen.

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

Reasonable temporal association with drug administration

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

Known response pattern to suspected drug

Disappears or decreases on cessation or reduction in dose

Reappears on rechallenge

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

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

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

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

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

7.3.2 Reporting of Serious Adverse Events (immediately reportable)

Only SAEs caused by a protocol mandated intervention that are experienced after the patient has signed the Informed Consent form but before they have received study treatment should be reported as SAEs. Any clinical adverse event or abnormal laboratory test value that is *serious* and which occurs during the course of the study (as defined in section 7.2.1.3 above), must be reported to Roche **within *one* working day** (24 hours) of the Investigator becoming aware of the event (expedited reporting).

Related Serious Adverse Events ***MUST*** be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed. Related SAEs must be collected and reported indefinitely.

Suspected Unexpected Serious Adverse Reactions (SUSARs) are reported to Investigators at each site and associated IRB/IEC when the following conditions occur:

The event must be a SAE.

There must be a certain degree of probability that the event is an adverse reaction from the administered drug.

The adverse reaction must be unexpected, that is to say, not foreseen in the Investigator's Brochure.

When all subjects at a particular site are off treatment as defined by the protocol:

only individual SUSAR reports originating in that particular trial will be forwarded to the site and associated IRB/IEC on an expedited basis;

individual SUSARs considered to be a significant safety issue and/or which result in Roche recommending a change to the Informed Consent Form (ICF), will be reported in an expedited manner to all Investigators and IRBs/IECs;

SUSAR reports originating from other trials using the same IMP will be provided as six monthly SUSAR Reports (SSRs) to Investigators and IRBs/IECs where long-term follow-up studies are carried out, unless they are considered significant.

Unrelated Serious Adverse Events must be collected and reported during the study and for up to 28 days after the last dose of study medication.

This study adheres to the definition and reporting requirements of **ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2.** Complete information can be found in **Appendix 8**.

7.3.3 Reporting of Protocol-Defined Events of Special Interest

7.3.3.1 Abortion, Congenital Anomaly, and Birth Defects

Abortions, congenital anomalies, and birth defects are events of special interest and will need to be reported to the Sponsor expeditiously.

Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious (as the Sponsor considers these medically significant), recorded on an SAE eCRF page, and expeditiously reported to the Sponsor.

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to the investigational product should be recorded and reported as an SAE.

7.3.3.2 Cutaneous Squamous Cell Carcinoma / Keratoacanthoma & Second Primary Malignancies

Cutaneous squamous cell carcinoma (cSCC) is defined as an event requiring close monitoring. These events must always be designated as SAEs in order to ensure their reporting to the Health Authorities in an appropriate and timely manner. The treating physician is asked to perform regular (at each study visit) skin exams of the patient. A full skin examination by a dermatologist is requested during the Screening Period, after 28 days of vemurafenib treatment, every 12 weeks thereafter during the Treatment Period, at the End of Treatment Visit, and at the Safety-Follow-Up Visit. Any lesion at baseline or during treatment clinically suspected of representing cutaneous SCC, basal cell carcinoma, actinic keratosis, keratoacanthoma or other skin conditions identified by the dermatologist should be treated as per local standard of care.

If more than one SCC lesion occurs in more than one location on the skin, and the multiple lesions are detected during the same observation period (i.e., clinic visit), then these SCC lesions should be reported together as one event on the same **SAE or AE** form and also reported as one event on the **SAE or AE** page of the eCRF. Locations of each lesion can be listed in the event term and narrative for SAE and AE reporting.

If more than one SCC lesion occurs in more than one location on the skin and the lesions are detected during separate observation periods (i.e., separate clinic visits), then these SCC lesions should be reported as separate events on separate **SAE or AE** forms and also as separate events on the **SAE or AE** page of the eCRF.

Cases in which patients rapidly develop multiple lesions within a limited time-frame (e.g., 5–10 lesions over a 2-week period) will be handled on a case by case basis in terms of reporting. Please contact the Medical Monitor when these cases occur, for additional discussion.

Skin biopsies should be performed by a dermatologist, as necessary, with histopathologic interpretation of suspected lesions. Biopsy-proven non-melanoma skin cancers should be excised. Available excised cutaneous SCC/KA specimen block/sections should be sent to a designated central dermatopathology laboratory for confirmation of diagnosis.

Details including histological findings should be reported within the eCRF (see also Section 5.3.8.4).

SCC events should be reported in any case as an SAE as follows:

(a) In the SAE form in the eCRF

Cutaneous SCC events should be reported using the event term of "Squamous Cell Carcinoma of the skin" or "Cutaneous Squamous Cell Carcinoma".

The term "Squamous Cell Carcinoma" should only be used if there is a confirmed non-cutaneous squamous cell carcinoma.

If the SCC is confirmed to be cutaneous the term "Cutaneous Squamous Cell Carcinoma" or "Squamous Cell Carcinoma of the skin" should be used. Do not report the event term of "treatment related secondary malignancy".

(b) In the eCRF AE form

Cutaneous SCC events should be reported using the event term of "Squamous Cell Carcinoma of the skin" or "Cutaneous Squamous Cell Carcinoma" and should be designated as Grade 3 severity.

The term "Squamous Cell Carcinoma" should only be used if there is a confirmed non-cutaneous squamous cell carcinoma.

SCC events should be reported as "Squamous Cell Carcinoma".

If the SCC is confirmed to be cutaneous the term "Cutaneous Squamous Cell Carcinoma" or "Squamous Cell Carcinoma of the skin" should be used with a Grade 3 designation

Any second primary malignancies should be reported in any case as an SAE as follows:

(a) In the SAE form in the eCRF

Second primary malignancies should be reported with the type of malignancy. Do not report the event term of "treatment related secondary malignancy".

(b) In the eCRF AE form
Second primary malignancies should be reported with the type of malignancy and a Grade 3 designation.

7.4 Pregnancy

A female subject must be instructed to stop taking the test "drug" and immediately inform the investigator if she becomes pregnant during the study. The investigator should report all pregnancies within 24 hours to the sponsor, using the Clinical Trial Pregnancy Reporting Form, [gcp_for000023]. The investigator should counsel the subject; discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Pregnancies occurring up to 90 days after the completion of the study medication must also be reported to the investigator.

Pregnancy occurring in the partner of a male subject participating in the study should be reported to the investigator and the sponsor. The partner should be counseled, the risks of continuing the pregnancy discussed, as well as the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

NOTE: The Investigator should fill out a *Pregnancy Reporting Form* only if the pregnant partner has signed a Pregnant Partner Data Release Form.

7.5 Warnings and Precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the Investigators' Brochure and described in this Protocol.

8. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

8.1 Primary and Secondary Study Variables

8.1.1 Primary Variable

Response Rate at Week 8, as assessed by the Investigator using RECIST, v1.1 for patients with solid tumors or IMWG uniform response criteria for patients with MM, is the primary endpoint for each cohort. For patients with solid tumors, responders at Week 8 will be defined based on tumor assessment status of PR or CR at Week 8. For patients with MM, responders at Week 8 will be defined based on tumor assessment status of CR, sCR, VGPR or PR. Only patients with measurable disease at baseline will be included in the analysis of the RR. Patients without a post-baseline tumor assessment will be considered to be non-responders.

8.1.2 Secondary Efficacy Variables

Secondary endpoints for each cohort and for patients with solid tumors and MM will include:

- duration of response (DOR),

- time to response,

- time to progression,

- clinical benefit rate (CR (or sCR), PR (or VGPR)) and stable disease [SD]),

- best overall response (BOR),

- PFS, and

- overall survival (OS).

PFS is defined as the time from enrollment into the study, i.e. date of first visit, until the first documented progression of disease or death from any cause, whichever occurs first. Patients with no PFS events will be censored at the time of the last evaluable tumor assessment. Patients with no tumor assessment after the baseline visit will be censored at the time of randomization plus 1 day.

Overall survival (time to death) is defined as time between enrollment and date of death of any cause. Patients for whom no death is captured on the clinical database are censored at the most recent date they were known to be alive.

Time to progression is defined as time from enrollment to the first occurrence of progressive disease. Patients who have not progressed at the time of study completion (including patients who have died before progressive disease) or who are lost to follow-up are censored at the date of the last tumor assessment.

Clinical benefit response includes patients whose best response was:

- PR (or VGPR) or

- CR (or sCR) or

- Stable disease (SD) that have lasted at least 6 weeks.

For patients with response at Week 8, duration of response (unconfirmed) is defined as the period from the date of initial PR or CR until the date of progressive disease or death from any cause. Patients with no documented progression after CR or PR will be censored at the last date at which they are known to have had the CR or PR, respectively. The method for handling censoring is the same as described for the PFS.

For patients with a response at Week 8 of CR or PR, time to response is defined as the time from the date of randomization to the date of first CR or PR. The censoring rules will be similar to those of the PFS.

For patients with MM, responders will be defined as patients with CR, sCR, PR and VGPR status. All other definitions for secondary endpoints for these patients will be similar to definitions above.

The best (confirmed) overall response (BOR) will be also assessed at the end of Stage II for each cohort. BOR is defined as the best response recorded from the start of trial treatment until disease progression/recurrence or death. To be assigned a status of PR or CR (i.e., a responder), changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met, i.e., patients need to have two consecutive assessments of PR or CR to be a responder. Only patients with measurable disease at baseline will be included in the analysis of the BOR. Patients without a post-baseline tumor assessment will be considered to be non-responders .

Duration of confirmed response is defined as the period from the date of initial PR or CR that contributed for the BOR status until the date of progressive disease or death from any cause. Patients with no documented progression after CR or PR will be censored at the last date at which they are known to have had the CR or PR, respectively. The method for handling censoring is the same as described for the PFS.

For responders in BOR, time to response is defined as the time from the date of randomization to the date of first CR or PR. The censoring rules will be similar to those of the PFS.

8.1.3 Safety Variables

Adverse events (AEs), all AEs, AEs grade 3 or 4, AEs leading to treatment interruption and discontinuation, serious adverse events (SAEs), premature discontinuation from study and treatment, laboratory parameters, exposure to study medication and skin evaluation, head/neck evaluations, chest CT scan will be the primary safety variables for each cohort. Vital signs, electrocardiogram, ECOG performance status, and physical examination will be the secondary safety variables.

8.2 Study Populations

The main analysis population for the efficacy analysis will be the intent-to-treat (ITT) population, which will include all patients enrolled in the study irrespective of whether they have received study medication or not. ITT1 to ITT8 will correspond to the ITT population for each cohort (Cohort 1 to Cohort 8, respectively).

The per-protocol (PP) population will not be defined due to the small number of patients per cohort, but protocol deviations will be listed.

The safety populations SP1 to SP8 will correspond to the the safety populations for Cohort 1 to Cohort 8, respectively, and will include, for each cohort, all patients who have received at least one dose of study medication.

8.3 Statistical and Analytical Methods

8.3.1 Statistical Model

The main analysis for RR will use an adaptive design based on Simon's two stage design for a single proportion (78).

Stage I will be defined as when a pre-specified number of patients (as determined in the Sample Size section) will have a minimum of 8 weeks of treatment, develop progressive disease, prematurely withdraw from the study medication, or die, whichever occurs first.

If a pre-specified minimal RRwill not be achieved in certain cohorts in the first stage of the study, this cohort will be closed and no further enrollment of patients will be performed for that cohort. Otherwise, enrollment will continue into Stage II until a pre-determined number of additional patients has been reached (as explained in the Sample Size section). At the conclusion of this study, vemurafenib will be declared effective or ineffective for each indication (cohort) based on rules for Stage II.

The analysis at Stage II (for lower or higher desirable response) for each cohort will be performed when all patients enrolled in the study, as estimated in the Sample Size section, will have a minimum of 8 weeks of treatment, develop progressive disease, withdraw, or are lost to follow-up, whichever occurs first.

The final analysis for OS for each cohort will take place when all patients in that cohort have been followed for survival for a maximum of 12 months for each patient after their last dose of study drug, have died, have withdrawn consent, or are lost to follow up, whichever occurs first. More details are provided in Efficacy Data Analysis (see below).

The final analysis for RR for each cohort will be at the end of Stage II.

8.3.1.1 Hypothesis Testing

The adaptive two-stage design allows the original estimation of the Stage II RR to be reassessed, based on information at Stage I, in the event that it was too optimistic or too sceptical to be the true RR.

For example, for patients in each cohort, we assume that an RR of 15% would be a very low RR and vemurafenib would be "under-performing" for this cohort. An RR of 45%

would be a high desirable RR, whereas an RR of 35% would be a low desirable RR, for Stage II.

The hypotheses for all cohorts for Stage I are:

H_0: $\pi_{N1} < \pi_0$ where $\pi_0 = 15\%$
H_1: $\pi_{N1} \geq \pi_0$ where $\pi_0 = 15\%$

If H0 is rejected (and H1 is accepted at Stage I), further patients will be enrolled based on the number of responders in Stage I and their data will be collected in the second stage.

The hypotheses for all cohorts at the end of Stage II for a low desirable response, π1L, are:

H_0: $\pi_N \leq \pi_{1L}$ where $\pi_{1L} = 35\%$
H_1: $\pi_N > \pi_{1L}$ where $\pi_{1L} = 35\%$

The N notifies the total number of patients for each cohort.

The hypotheses for all cohorts at the end of Stage II for a high desirable response, π1H, are:

H_0: $\pi_N \leq \pi_{1H}$ where $\pi_{1H} = 45\%$
H_1: $\pi_N > \pi_{1H}$ where $\pi_{1H} = 45\%$

8.3.1.2 Stopping Rules for Enrollment and Screening

If no patients are enrolled within any cohort after one year from the start of the study, as described above, then that particular cohort will be closed and enrollment for that cohort will be stopped.

Rules for Stage 1

Stage I will be stopped if the number of responders is less than the pre-specified number assessed (e.g. if there is none or only one responder out of first seven patients). However if a clear clinical benefit has been observed for patients in the cohort, e.g. majority of patients recorded SD at Week 8 and no CR or PR is recorded, then enrolment into Stage II might be allowed for this cohort.

If there is the required response during Stage I or a good clinical benefit is observed for particular cohort as mentioned above, then additional patients will be enrolled in the second stage of the corresponding cohort, in order to achieve total number of patients as specified in the Tables 10 and 11 below (Sample Size estimation section).

Cohort 8 will be closed to enrollment when all other cohorts are closed, regardless of the number of patients recruited at that time. This cohort may be quite heterogeneous and will be examined primarily to seek efficacy signals in the relatively rare BRAF V600 mutation-positive tumors.

Rules for Stage 2

A study treatment will be considered to be non-efficacious in a cohort in Stage 2 if the number of responders is

- less than specified in the sample size calculations, as presented in the Table below or-unacceptable toxicity occurs or

- best overall response, BOR (confirmed) is lower than 15%.

8.3.2 Efficacy Data Analysis

The primary efficacy endpoint is RR at Week 8 in each cohort, as assessed by the Investigator using RECIST, v1.1 or IMWG response criteria. This is an early phase II study and cohorts are independent, hence there will be no adjustment for multiplicity. Number and percentage of responders with corresponding Clopper-Pearson 95% confidence intervals will be provided for each cohort. The clinical benefit, BOR and RR at the end of Stage II will be analyzed in a similar way to RR at Week 8. Estimates for the survivor function for the time-to-event variables, such as time to progression (TTP), PFS, OS, duration of response, and time to response, will be obtained by using the Kaplan-Meier (KM) approach together with associated 95% CI.

8.3.3 Safety Data Analysis

The safety variables will be summarized for the safety population where the safety population is SP1 to SP8. All safety variables will be summarized for each cohort.

All AEs will be assessed according to the NCI CTCAE, v4.0, grading system. The analysis of AEs will focus on treatment-emergent AEs, i.e., AEs occurring on the day of or after first administration of study drug (vemurafenib). Non-treatment emergent AEs (i.e., those occurring before commencement of study medication) will only be listed.

The incidence, type, and severity of AEs will be summarized according to the primary system-organ class (SOC) and within each SOC, by MedDRA preferred term. Summary tables may be presented for time to first onset of the AE of special interest.

AEs leading to treatment interruption and discontinuation and SAEs will be analyzed in a similar way to all AEs. Cause of death will also be summarized and listed.

Results from skin evaluation, head and neck evaluations, chest CT scan (e.g., number of lesions, SCC - keratoacanthoma type, etc.) will be summarized using frequencies and percentages. The number of patients prematurely discontinued from the treatment with corresponding reason for discontinuation will be summarized and listed. The discontinuation from study will be also summarized and listed.

Descriptive statistics will be presented for cumulative vemurafenib doses and duration of exposure.

Laboratory parameters, hematology, and serum biochemistry will be presented in shift tables of NCI-CTCAE grade at baseline versus worst grade during the Treatment Period. The summary of laboratory parameters presented by means, standard deviation, minimum, and maximum will be also presented.

Vital signs (blood pressure, temperature, heart rate, and respiratory rate) and ECG (heart rate, PR interval, QRS duration, QT interval and QTc interval) will be summarized over time by means of mean, median, and range (mean and maximum). The ECG findings will be also presented by frequency tables over time. The ECOG PS will be summarized by frequency tables over time and percentage of patients in different categories will be presented by bar charts at different time points. Physical examination variables collected only at baseline (e.g., height) will be summarized for baseline only while other physical examination variables will be summarized over time by visits and reported in patients' listings. Concomitant therapy will be summarized by frequency tables and percentages.

8.3.4 Interim Analysis

There will be no further interim efficacy analysis, except the efficacy analysis of response rate at Stage I

8.3.5 Other Analyses

Demographics and medical history will be summarized for each cohort..

8.4 Sample Size Estimation

The sample size estimation is based on the method of Lin and Shih (78) and corresponding SAS program.

There will be 8 cohorts. The estimated number of patients required for this study will be in the range of 104 to 152 patients (depending on response in Stage I).

Cohorts will have a minimum of 13 and a maximum of 19 patients (depending on results in Stage I).

A proportion of 15% is chosen for a low response, based on Section XX in the protocol and on our present knowledge

However, if the number of responders are 2, 3, or 4 out of 7 patients in Stage I, then the study medication is possibly efficacious for that cohort and further data will be collected based on the "low desirable response at Stage II" Sample Size estimation, i.e., an additional 12 patients will be enrolled in order to have a total of 19 patients for that cohort.

If there are 5 or more responders out of 7, then further data will be collected based on "high desirable response at Stage II" Sample Size estimation, i.e., an additional 6 patients will be enrolled in order to have a total of 13 patients for that cohort.

Assuming RRs as specified in the prior hypothesis testing, a power of 80% for high desirable response and 70% for low desirable response and two-sided alpha of 0.1, the number of patients required in each cohort is presented in **Table 10**.

Table 10.
Sample Size for Each Cohort

	At the end of Stage Two

	Low desirable response	High desirable response
NSCLC	19	13
Ovarian cancer	19	13
Colorectal cancer	19	13
Cholangiocarcinoma/cancer of biliary tract	19	16
Breast cancer	19	13
Prostate cancer	19	13
MM	19	13
Other tumors	19	13
Total number of patients	**152**	**104**

Details regarding Stage I and number of responders are presented in **Table 11**.

Table 11. Sample Size for Each Cohort and Each Stage

	Stage (Two-Stage Design)		Total Number of Patients in Each Cohort	Two-Sided Alpha Level / Power
	Stage I	**Stage II** [a]		
All Cohorts				
Low response at the end of Stage I				
Number of patients	7	19	19	10% / 70%
Number of responders [b]	≥ 2 and ≤ 4	≥ 5		
High response at the end of Stage I				
Number of patients	7	13	13	10% / 80%
Number of responders [b]	≥ 5	≥ 6		

The sample size was estimated using the method of Lin and Shih (78) and corresponding SAS program.

[a] This column displays the maximum number of patients required for each cohort and the number of responders that should be present at the end of Stage II in order to declare efficacious treatment.

[b] Number of patients needed to respond in order to continue into Stage II or have a positive result at the end of the trial.

9. DATA COLLECTION, MANAGEMENT AND QUALITY ASSURANCE

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

Accurate and reliable data collection will be assured by verification and cross–check of the eCRFs against the Investigator's records by the study monitor (source document verification), by checks through data management and the maintenance of a drug–dispensing log by the Investigator.

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

A comprehensive validation check program utilizing front-end checks in the eCRF will verify the data and discrepancy reports will be generated accordingly and transferred electronically to the eCRF at the site for resolution by the Investigator.

9.1 Assignment of Preferred Terms and Original Terminology

For classification purposes, preferred terms will be assigned by the Sponsor to the original terms entered on the eCRF, using the most up-to-date version of the Medical Dictionary for Regulatory Activities (MedDRA) terminology for adverse events and diseases and the International Non-proprietary Name (INN) Drug Terms and Procedures Dictionary for treatments and surgical and medical procedures.

10. REFERENCES

1. Alberts B, Johnson A, Lewis J, Raff M, Roberts K, Walter P. Mechanisms of Cell Communication. Molecular biology of the cell. 5th ed. New York: Garland Science; 2008.

2. Forbes SA, Bhamra G, Bamford S, Dawson E, Kok C, Clements J, et al. The Catalogue of Somatic Mutations in Cancer (COSMIC). Curr Protoc Hum Genet. 2008;Chapter 10:Unit 10 1.

3. Forbes SA, Bindal N, Bamford S, Cole C, Kok CY, Beare D, et al. COSMIC: mining complete cancer genomes in the Catalogue of Somatic Mutations in Cancer. Nucleic Acids Res. 2011;39:D945-50.

4. Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, et al. Mutations of the BRAF gene in human cancer. Nature. 2002;417:949-54.

5. Helfrich I, Edler L, Sucker A, Thomas M, Christian S, Schadendorf D, et al. Angiopoietin-2 levels are associated with disease progression in metastatic malignant melanoma. Clin Cancer Res. 2009;15:1384-92.

6. Sumimoto H, Hirata K, Yamagata S, Miyoshi H, Miyagishi M, Taira K, et al. Effective inhibition of cell growth and invasion of melanoma by combined suppression of BRAF (V599E) and Skp2 with lentiviral RNAi. Int J Cancer. 2006;118:472-6.

7. Rubinstein JC, Sznol M, Pavlick AC, Ariyan S, Cheng E, Bacchiocchi A, et al. Incidence of the V600K mutation among melanoma patients with BRAF mutations, and potential therapeutic response to the specific BRAF inhibitor PLX4032. J Transl Med. 2010;8:67.

8. Deschoolmeester V, Baay M, Specenier P, Lardon F, Vermorken JB. A review of the most promising biomarkers in colorectal cancer: one step closer to targeted therapy. Oncologist. 2010;15:699-731.

9. Michor F, Iwasa Y, Lengauer C, Nowak MA. Dynamics of colorectal cancer. Semin Cancer Biol. 2005;15:484-93.

10. Jass JR. Colorectal cancer: a multipathway disease. Crit Rev Oncog. 2006;12:273-87.

11. Goel A, Arnold CN, Niedzwiecki D, Chang DK, Ricciardiello L, Carethers JM, et al. Characterization of sporadic colon cancer by patterns of genomic instability. Cancer Res. 2003;63:1608-14.

12. Lee S, Cho NY, Choi M, Yoo EJ, Kim JH, Kang GH. Clinicopathological features of CpG island methylator phenotype-positive colorectal cancer and its

adverse prognosis in relation to KRAS/BRAF mutation. Pathol Int. 2008;58:104-13.

13. Maestro ML, Vidaurreta M, Sanz-Casla MT, Rafael S, Veganzones S, Martinez A, et al. Role of the BRAF mutations in the microsatellite instability genetic pathway in sporadic colorectal cancer. Ann Surg Oncol. 2007;14:1229-36.

14. Barault L, Veyrie N, Jooste V, Lecorre D, Chapusot C, Ferraz JM, et al. Mutations in the RAS-MAPK, PI(3)K (phosphatidylinositol-3-OH kinase) signaling network correlate with poor survival in a population-based series of colon cancers. Int J Cancer. 2008;122:2255-9.

15. Ogino S, Nosho K, Kirkner GJ, Kawasaki T, Meyerhardt JA, Loda M, et al. CpG island methylator phenotype, microsatellite instability, BRAF mutation and clinical outcome in colon cancer. Gut. 2009;58:90-6.

16. Price TJ, Hardingham JE, Lee CK, Weickhardt A, Townsend AR, Wrin JW, et al. Impact of KRAS and BRAF Gene Mutation Status on Outcomes From the Phase III AGITG MAX Trial of Capecitabine Alone or in Combination With Bevacizumab and Mitomycin in Advanced Colorectal Cancer. J Clin Oncol. 2011;29:2675-82.

17. Richman SD, Seymour MT, Chambers P, Elliott F, Daly CL, Meade AM, et al. KRAS and BRAF mutations in advanced colorectal cancer are associated with poor prognosis but do not preclude benefit from oxaliplatin or irinotecan: results from the MRC FOCUS trial. J Clin Oncol. 2009;27:5931-7.

18. Roth AD, Tejpar S, Delorenzi M, Yan P, Fiocca R, Klingbiel D, et al. Prognostic role of KRAS and BRAF in stage II and III resected colon cancer: results of the translational study on the PETACC-3, EORTC 40993, SAKK 60-00 trial. J Clin Oncol. 2010;28:466-74.

19. Samowitz WS, Sweeney C, Herrick J, Albertsen H, Levin TR, Murtaugh MA, et al. Poor survival associated with the BRAF V600E mutation in microsatellite-stable colon cancers. Cancer Res. 2005;65:6063-9.

20. Saridaki Z, Papadatos-Pastos D, Tzardi M, Mavroudis D, Bairaktari E, Arvanity H, et al. BRAF mutations, microsatellite instability status and cyclin D1 expression predict metastatic colorectal patients' outcome. Br J Cancer. 2010;102:1762-8.

21. Tol J, Nagtegaal ID, Punt CJ. BRAF mutation in metastatic colorectal cancer. N Engl J Med. 2009;361:98-9.

22. Di Nicolantonio F, Martini M, Molinari F, Sartore-Bianchi A, Arena S, Saletti P, et al. Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. J Clin Oncol. 2008;26:5705-12.

23. Kopetz S, Desai J, Chan E, Hecht JR, O'Dwyer PJ, Lee RJ, et al. PLX4032 in metastatic colorectal cancer patients with mutant BRAF tumors. J Clin Oncol (Meeting Abstracts) 2010;28:3534.

24. Brose MS, Volpe P, Feldman M, Kumar M, Rishi I, Gerrero R, et al. BRAF and RAS mutations in human lung cancer and melanoma. Cancer Res. 2002;62:6997-7000.

25. Marchetti A, Felicioni L, Malatesta S, Grazia Sciarrotta M, Guetti L, Chella A, et al. Clinical features and outcome of patients with non-small-cell lung cancer harboring BRAF mutations. J Clin Oncol. 2011;29:3574-9.

26. Garon EB, Finn RS, Hosmer W, Dering J, Ginther C, Adhami S, et al. Identification of common predictive markers of in vitro response to the Mek inhibitor selumetinib (AZD6244; ARRY-142886) in human breast cancer and non-small cell lung cancer cell lines. Mol Cancer Ther. 2010;9:1985-94.

27. Hollestelle A, Elstrodt F, Nagel JH, Kallemeijn WW, Schutte M. Phosphatidylinositol-3-OH kinase or RAS pathway mutations in human breast cancer cell lines. Mol Cancer Res. 2007;5:195-201.

28. Gonzalez-Bosquet J, Calcei J, Wei JS, Garcia-Closas M, Sherman ME, Hewitt S, et al. Detection of somatic mutations by high-resolution DNA melting (HRM) analysis in multiple cancers. PLoS One. 2011;6:e14522.

29. Ueda M, Toji E, Nunobiki O, Izuma S, Okamoto Y, Torii K, et al. Mutational analysis of the BRAF gene in human tumor cells. Hum Cell. 2008;21:13-7.

30. Janku F, Lee JJ, Tsimberidou AM, Hong DS, Naing A, Falchook GS, et al. PIK3CA Mutations Frequently Coexist with RAS and BRAF Mutations in Patients with Advanced Cancers. PLoS One. 2011;6:e22769.

31. Hollestelle A, Nagel JH, Smid M, Lam S, Elstrodt F, Wasielewski M, et al. Distinct gene mutation profiles among luminal-type and basal-type breast cancer cell lines. Breast Cancer Res Treat. 2010;121:53-64.

32. Cho KR. Ovarian cancer update: lessons from morphology, molecules, and mice. Arch Pathol Lab Med. 2009;133:1775-81.

33. Nakayama N, Nakayama K, Yeasmin S, Ishibashi M, Katagiri A, Iida K, et al. KRAS or BRAF mutation status is a useful predictor of sensitivity to MEK inhibition in ovarian cancer. Br J Cancer. 2008;99:2020-8.

34. Pohl G, Ho CL, Kurman RJ, Bristow R, Wang TL, Shih Ie M. Inactivation of the mitogen-activated protein kinase pathway as a potential target-based therapy in ovarian serous tumors with KRAS or BRAF mutations. Cancer Res. 2005;65:1994-2000.

35. Sieben NL, Macropoulos P, Roemen GM, Kolkman-Uljee SM, Jan Fleuren G, Houmadi R, et al. In ovarian neoplasms, BRAF, but not KRAS, mutations are restricted to low-grade serous tumours. J Pathol. 2004;202:336-40.

36. Singer G, Oldt R, 3rd, Cohen Y, Wang BG, Sidransky D, Kurman RJ, et al. Mutations in BRAF and KRAS characterize the development of low-grade ovarian serous carcinoma. J Natl Cancer Inst. 2003;95:484-6.

37. Dansonka-Mieszkowska A, Ludwig AH, Kraszewska E, Kupryjanczyk J. Geographical variations in TP53 mutational spectrum in ovarian carcinomas. Ann Hum Genet. 2006;70:594-604.

38. Kohler MF, Marks JR, Wiseman RW, Jacobs IJ, Davidoff AM, Clarke-Pearson DL, et al. Spectrum of mutation and frequency of allelic deletion of the p53 gene in ovarian cancer. J Natl Cancer Inst. 1993;85:1513-9.

39. Salani R, Kurman RJ, Giuntoli R, 2nd, Gardner G, Bristow R, Wang TL, et al. Assessment of TP53 mutation using purified tissue samples of ovarian serous carcinomas reveals a higher mutation rate than previously reported and does not correlate with drug resistance. Int J Gynecol Cancer. 2008;18:487-91.

40. Kupryjanczyk J, Thor AD, Beauchamp R, Merritt V, Edgerton SM, Bell DA, et al. p53 gene mutations and protein accumulation in human ovarian cancer. Proc Natl Acad Sci U S A. 1993;90:4961-5.

41. Wen WH, Reles A, Runnebaum IB, Sullivan-Halley J, Bernstein L, Jones LA, et al. p53 mutations and expression in ovarian cancers: correlation with overall survival. Int J Gynecol Pathol. 1999;18:29-41.

42. Quaye L, Gayther SA, Ramus SJ, Di Cioccio RA, McGuire V, Hogdall E, et al. The effects of common genetic variants in oncogenes on ovarian cancer survival. Clin Cancer Res. 2008;14:5833-9.

43. Quaye L, Song H, Ramus SJ, Gentry-Maharaj A, Hogdall E, DiCioccio RA, et al. Tagging single-nucleotide polymorphisms in candidate oncogenes and susceptibility to ovarian cancer. Br J Cancer. 2009;100:993-1001.

44. Nelson WG, De Marzo AM, Isaacs WB. Prostate cancer. N Engl J Med. 2003;349:366-81.

45. Agell L, Hernandez S, Salido M, de Muga S, Juanpere N, Arumi-Uria M, et al. PI3K signaling pathway is activated by PIK3CA mRNA overexpression and copy gain in prostate tumors, but PIK3CA, BRAF, KRAS and AKT1 mutations are infrequent events. Mod Pathol. 2011;24:443-52.

46. Burger M, Denzinger S, Hammerschmied C, Tannapfel A, Maderstorfer A, Wieland WF, et al. Mitogen-activated protein kinase signaling is activated in

prostate tumors but not mediated by B-RAF mutations. Eur Urol. 2006;50:1102-9; discussion 9-10.

47. Liu T, Willmore-Payne C, Layfield LJ, Holden JA. Lack of BRAF activating mutations in prostate adenocarcinoma: a study of 93 cases. Appl Immunohistochem Mol Morphol. 2009;17:121-5.

48. Cho NY, Choi M, Kim BH, Cho YM, Moon KC, Kang GH. BRAF and KRAS mutations in prostatic adenocarcinoma. Int J Cancer. 2006;119:1858-62.

49. Palanisamy N, Ateeq B, Kalyana-Sundaram S, Pflueger D, Ramnarayanan K, Shankar S, et al. Rearrangements of the RAF kinase pathway in prostate cancer, gastric cancer and melanoma. Nat Med. 2010;16:793-8.

50. Gioeli D, Mandell JW, Petroni GR, Frierson HF, Jr., Weber MJ. Activation of mitogen-activated protein kinase associated with prostate cancer progression. Cancer Res. 1999;59:279-84.

51. Jeong JH, Wang Z, Guimaraes AS, Ouyang X, Figueiredo JL, Ding Z, et al. BRAF activation initiates but does not maintain invasive prostate adenocarcinoma. PLoS One. 2008;3:e3949.

52. Kyle RA, Rajkumar SV. Multiple myeloma. N Engl J Med. 2004;351:1860-73.

53. Fonseca R, Bergsagel PL, Drach J, Shaughnessy J, Gutierrez N, Stewart AK, et al. International Myeloma Working Group molecular classification of multiple myeloma: spotlight review. Leukemia. 2009;23:2210-21.

54. Chng WJ, Glebov O, Bergsagel PL, Kuehl WM. Genetic events in the pathogenesis of multiple myeloma. Best Pract Res Clin Haematol. 2007;20:571-96.

55. Bezieau S, Devilder MC, Avet-Loiseau H, Mellerin MP, Puthier D, Pennarun E, et al. High incidence of N and K-Ras activating mutations in multiple myeloma and primary plasma cell leukemia at diagnosis. Hum Mutat. 2001;18:212-24.

56. Liu P, Leong T, Quam L, Billadeau D, Kay NE, Greipp P, et al. Activating mutations of N- and K-ras in multiple myeloma show different clinical associations: analysis of the Eastern Cooperative Oncology Group Phase III Trial. Blood. 1996;88:2699-706.

57. Bonello L, Voena C, Ladetto M, Boccadoro M, Palestro G, Inghirami G, et al. BRAF gene is not mutated in plasma cell leukemia and multiple myeloma. Leukemia. 2003;17:2238-40.

58. Chapman MA, Lawrence MS, Keats JJ, Cibulskis K, Sougnez C, Schinzel AC, et al. Initial genome sequencing and analysis of multiple myeloma. Nature. 2011;471:467-72.

59. Kim K, Kong SY, Fulciniti M, Li X, Song W, Nahar S, et al. Blockade of the MEK/ERK signalling cascade by AS703026, a novel selective MEK1/2 inhibitor, induces pleiotropic anti-myeloma activity in vitro and in vivo. Br J Haematol. 2010;149:537-49.

60. Hezel AF, Deshpande V, Zhu AX. Genetics of biliary tract cancers and emerging targeted therapies. J Clin Oncol. 2010;28:3531-40.

61. Zhu AX, Hezel AF. Development of molecularly targeted therapies in biliary tract cancers: reassessing the challenges and opportunities. Hepatology. 2011;53:695-704.

62. Hori H, Ajiki T, Mita Y, Horiuchi H, Hirata K, Matsumoto T, et al. Frequent activation of mitogen-activated protein kinase relative to Akt in extrahepatic biliary tract cancer. J Gastroenterol. 2007;42:567-72.

63. Saetta AA, Papanastasiou P, Michalopoulos NV, Gigelou F, Korkolopoulou P, Bei T, et al. Mutational analysis of BRAF in gallbladder carcinomas in association with K-ras and p53 mutations and microsatellite instability. Virchows Arch. 2004;445:179-82.

64. Tannapfel A, Sommerer F, Benicke M, Katalinic A, Uhlmann D, Witzigmann H, et al. Mutations of the BRAF gene in cholangiocarcinoma but not in hepatocellular carcinoma. Gut. 2003;52:706-12.

65. Goldenberg D, Rosenbaum E, Argani P, Wistuba, II, Sidransky D, Thuluvath PJ, et al. The V599E BRAF mutation is uncommon in biliary tract cancers. Mod Pathol. 2004;17:1386-91.

66. Stevens G, Fife K. Cerebral metastases. In: Thompson JF, Morton DL, Kroon BBR, editors. Textbook of Melanoma: Pathology, Diagnosis, and Management. Independence, KY: Taylor & Francis; 2004. p. 519-29.

67. Bollag G, Hirth P, Tsai J, Zhang J, Ibrahim PN, Cho H, et al. Clinical efficacy of a RAF inhibitor needs broad target blockade in BRAF-mutant melanoma. Nature. 2010;467:596-9.

68. Yang H, Higgins B, Kolinsky K, Packman K, Go Z, Iyer R, et al. RG7204 (PLX4032), a selective BRAFV600E inhibitor, displays potent antitumor activity in preclinical melanoma models. Cancer Res. 2010;70:5518-27.

69. Flaherty KT, Puzanov I, Kim KB, Ribas A, McArthur GA, Sosman JA, et al. Inhibition of mutated, activated BRAF in metastatic melanoma. N Engl J Med. 2010;363:809-19.

70. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011;364:2507-16.

71. Sosman J, Kim K, Schuchter L, Gonzalez R, Pavlick A, Weber J, et al. An open-label, multicenter phase II study of continuous oral dosing of RG7204 (PLX4032) in previously treated patients with BRAF V600E mutation-positive metastatic melanoma. Pigment Cell Melanoma Res. 2010;23:886.

72. Ribas A, Kim KB, Schuchter LM, Gonzalez R, Pavlick AC, Weber JS, et al. BRIM-2: An open-label, multicenter phase II study of vemurafenib in previously treated patients with BRAF V600E mutation-positive metastatic melanoma. J Clin Oncol (Meeting Abstracts). 2011;29:Abstract 8509.

73. Mandrell JC, Santa Cruz D. Keratoacanthoma: hyperplasia, benign neoplasm, or a type of squamous cell carcinoma? Semin Diagn Pathol. 2009;26:150-63.

74. Kopetz S, Desai J, Chan E, Hecht JR, O'Dwyer PJ, Lee RJ, et al. PLX4032 in metastatic colorectal cancer patients with mutant BRAF tumors. J Clin Oncol (Meeting Abstracts). 2010;28:3534.

75. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-47.

76. Durie BG, Harousseau JL, Miguel JS, Blade J, Barlogie B, Anderson K, et al. International uniform response criteria for multiple myeloma. Leukemia. 2006;20:1467-73.

77. Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. Leukemia. 2009;23:3-9.

78. Lin Y, Shih WJ. Adaptive two-stage designs for single-arm phase IIA cancer clinical trials. Biometrics. 2004;60:482-90.

79. Amaravadi R et al, Society for Melanoma Research 2011 (Abstract #SMR-P3)

PART II: ETHICS AND GENERAL STUDY ADMINISTRATION

11. ETHICAL ASPECTS

11.1 Local Regulations/Declaration of Helsinki

The Investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline [January 1997] or with local law if it affords greater protection to the subject. For studies conducted in the EU/EEA countries, the Investigator will ensure compliance with the EU Clinical Trial Directive [2001/20/EC]. For studies conducted in the USA or under US IND, the Investigator will additionally ensure adherence to the basic principles of "Good Clinical Practice" as outlined in the current version of 21 CFR, subchapter D, part 312, "Responsibilities of Sponsors and Investigators", part 50, "Protection of Human Subjects", and part 56, "Institutional Review Boards".

In other countries where "Guideline for Good Clinical Practice" exist Roche and the Investigators will strictly ensure adherence to the stated provisions.

11.2 Informed Consent

11.2.1 Main study Informed Consent

It is the responsibility of the Investigator, or a person designated by the Investigator [if acceptable by local regulations], to obtain signedwritten informed consent from each patient prior to participating in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. For patients not qualified or incapable of giving legal consent, written consent must be obtained from the legally acceptable representative. In the case where both the patient and her legally acceptable representative are unable to read, an impartial witness should be present during the entire informed consent discussion. After the patient and representative have orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood.

The Investigator or designee must also explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, for any reason.

The electroninc Case Report Forms (eCRFs) for this study contain a section for documenting patient informed consent, and this must be completed appropriately. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All patientss (including those already being treated) should be informed of the new information, given a copy of the revised form and give their consent to continue in the study.

For US-IND studies: In a life-threatening situation where a subject is unconscious or otherwise unable to communicate, the emergency is such that there is not enough time to obtain consent from the subject's legally acceptable representative, and there is no other

or better treatment available, it is permissible to treat the subject under protocol with consent of both the investigator and another physician not involved in the study, with appropriate documentation submitted to the IRB within 5 days. If this collaboration is not immediately possible, there must be a written evaluation by a physician independent of the study and the appropriate documentation be submitted to the IRB within 5 days of treating the subject. In addition, the subject or his/her legally acceptable representative should be informed about the trial as soon as possible and consent to continue, giving written consent as described above.

For non-US-IND studies: In a life-threatening situation where a subject is unconscious or otherwise unable to communicate, the emergency is such that there is not enough time to obtain consent from the subject's legally acceptable representative, and there is no other or better treatment available, it is permissible to treat the subject under protocol with consent of the investigator, with appropriate documentation that the IEC had approved the procedures used to enroll subjects in such situations. In addition, the subject or his/her legally acceptable representative should be informed about the trial as soon as possible and consent to continue, giving written consent as described above.

11.3 Independent Ethics Committees(IEC)/Institutional Review Board (IRB)

The protocol, informed consent form and any accompanying material provided to the patient in the U.S. will be submitted by the Investigator to an IRB for review. For EEA member states, the sponsor will submit to the Competent Authority and IEC, the protocol and any accompanying material provided to the patient. In both the US and EEA member states, the accompanying material may include patient information sheets, descriptions of the study used to obtain informed consent and terms of any compensation given to the patient as well as advertisements for the trial.

An approval letter or certificate (specifying the protocol number and title) from the IEC/IRB must be obtained before study initiation by the Investigator specifying the date on which the committee met and granted the approval. This applies whenever subsequent amendments/modifications are made to the protocol.

Any modifications made to the protocol, informed consent or material provided to the patient after receipt of the IEC/IRBapproval must also be submitted by the Investigator in the U.S. and by the Sponsor in the EEA member states in accordance with local procedures and regulatory requirements.

When no local review board exists, the Investigator is expected to submit the protocol to a regional committee. If no regional committee exists, Roche will assist the Investigator in submitting the protocol to the European Ethics Review Committee.

Roche shall also submit an Annual Safety Report once a year to the IEC and Competent Authorities (CAs) according to local regulatory requirements and timelines of each country participating in the study. In the U.S. Roche submits an IND Annual Report to the FDA according to local regulatory requirements and timelines.

11.4 Financial Disclosure

The Investigator(s) will provide the Sponsor with sufficient accurate financial information (PD35) to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. The Investigator is responsible to promptly update any information provided to the Sponsor if relevant changes occur in the course of the investigation and for 1 year following the completion of the study (last patient, last visit).

12. CONDITIONS FOR MODIFYING THE PROTOCOL

Requests from Investigators to modify the protocol to ongoing studies will be considered only by consultation between an appropriate representative of the sponsor and the Investigator [Investigator representative[s] in the case of a multicenter trial]. Protocol modifications must be prepared by a representative of the sponsor and initially reviewed and approved by the International Medical Leader and Biostatistician.

All protocol modifications must be submitted to the appropriate Independent Ethics Committee or Institutional Review Board for information and approval in accordance with local requirements, and to Regulatory Agencies if required. Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial patients, or when the change[s] involves only logistical or administrative aspects of the trial.

13. CONDITIONS FOR TERMINATING THE STUDY

Both the sponsor and the Investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange the procedures on an individual study basis after review and consultation. In terminating the study, Roche and the Investigator will assure that adequate consideration is given to the protection of the patient's interests. The appropriate IRB/IEC and Regulatory Agencies should be informed accordingly.

14. STUDY DOCUMENTATION, CRFS AND RECORD KEEPING

14.1 Investigator's Files / Retention of Documents

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two different separate categories: 1) Investigator's Study File, and 2) patient clinical source documents.

The Investigator's Study File will contain the protocol/amendments, Case Report and Query Forms, schedule of assessments, Independent Ethics Committee/Institutional Review Board and governmental approval with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms and other appropriate documents/correspondence, etc.

Patient clinical source documents [usually defined by the project in advance to record key efficacy/safety parameters independent of the eCRFs] would include patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, EEG, X-ray, pathology and special assessment reports, signed informed consent forms, consultant letters, and patient screening and enrollment logs.

The Investigator must keep the two categories of documents on file as described above (including the archival CD) on file for at least 15 years after completion or discontinuation of the study. After that period of time the documents may be destroyed, subject to local regulations.

Should the Investigator wish to assign the study records to another party or move them to another location, Roche must be notified in advance.

If the Investigator can not guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the Investigator and Roche to store these in a sealed container[s] outside of the site so that they can be returned sealed to the Investigator in case of a regulatory audit. Where source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the site.

ICH GCP guidelines require that Investigators maintain information in the study subject's records which corroborate data collected on the eCRF(s). Completed eCRF will be forwarded to Roche.

14.2 Source Documents and Background Data

The Investigator shall supply the sponsor on request with any required background data from the study documentation or clinic records. This is particularly important when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

14.3 Audits and Inspections

The Investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Roche Quality Assurance or its designees, or to health authority inspectors after appropriate notification. The verification of the eCRF data must be by direct inspection of source documents.

14.4 Case Report Forms or Electronic Case Report Forms

Data for this study will be captured via an Electronic Data Capture (EDC) system by using an online eCRFs.. An audit trail will maintain a record of initial entries and changes made; reasons for change; time and date of entry; and user name of person authorizing entry or change. For each patient enrolled, an eCRF must be completed and electronically signed by the principal Investigator or authorized delegate from the study staff. This also applies to records for those patients who fail to complete the study [even during a pre-enrollment screening period if an eCRF was initiated]. If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

The Investigator should ensure the accuracy, completeness and timeliness of the data reported to the sponsor in the eCRFs and in all required reports.

15. MONITORING THE STUDY

It is understood that the responsible Monitor will contact and visit the Investigator and will be allowed, on request, to inspect the various records of the trial [eCRFs and other pertinent data] provided that patient confidentiality is maintained in accord with local requirements.

It will be the monitor's responsibility to inspect the eCRFs throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them. The monitor should have access to laboratory test reports and other patient records needed to verify the entries on the eCRF. The Investigator [or deputy] agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

16. CONFIDENTIALITY OF TRIAL DOCUMENTS AND PATIENT RECORDS

The Investigator must assure that patients' anonymity will be maintained and that their identities are protected from unauthorized parties. On eCRFs or other documents submitted to the sponsor, patients should not be identified by their names, but by an identification code. The Investigator should keep a patient enrollment log showing codes, names and addresses.

17. CLINICAL STUDY REPORT (CSR)

A clinical study report will be written and distributed to Health Authorities as required by applicable regulatory requirements.

18. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Roche will comply with the requirements for publication of study results.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to Roche prior to submission. This allows the sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator. In accordance with standard editorial and ethical practice, Roche will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors (ICMJE) authorship requirements. Any formal publication of the study in which input of Roche personnel exceeded that of conventional monitoring will be considered as a joint publication by the Investigator and the appropriate Roche personnel.

Appendix 1 Cockroft and Gault Method for Calculated Creatinine Clearance

$$\text{Calculated creatinine clearance (mL/min)} = \frac{(140 - \text{age [yrs]}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/100mL)}}$$

Female patients**:** multiply by 0.85

Cockcroft DW, Gault MH. Prediction of Creatinine Clearance from Serum Creatinine. Nephron 1976; 16: 31-41.

Appendix 2 Agents Metabolized by CYP1A2, CYP2C9, and CYP3A4

Substrate		
CYP1A2[a]	**CYP2C9[a]**	**CYP3A4[b]**
amitriptyline	NSAIDs:	Macrolide antibiotics:
caffeine	diclofenac	clarithromycin
clomipramine	ibuprofen	erythromycin
clozapine	lornoxicam	telithromycin
cyclobenzaprine	meloxicam	
estradiol	S-naproxen	Anti-arrhythmics:
fluvoxamine	Norpiroxicam	quinidine 3OH
haloperidol	suprofen	
imipramine N-DeMe		Benzodiazepines:
mexilletine	Oral Hypoglycemic:	alprazolam
naproxen	tolbutamide	diazepam 3OH
olanzapine	glipizide	midazolam
ondansetron	glyburide	triazolam
phenacetin_	glibenclamide/glyburide	
acetaminophen	glipizide	Immune Modulators:
propranolol	glimepiride	cyclosporine
riluzole	nateglinide	tacrolimus (FK506)
ropivacaine	rosiglitazone	
tacrine		HIV Antivirals:
theophylline	Angiotensin II	indinavir
tizanidine	Blockers:	nelfinavir
verapamil	losartan	ritonavir
(R) warfarin	irbesartan	saquinavir
zileuton		
zolmitriptan	Miscellaneous:	Prokinetic:
	amitriptyline	cisapride
	celecoxib	
	fluoxetine	Antihistamines:
	fluvastatin	astemizole
	phenytoin-4-OH2	chlorpheniramine
	tamoxifen	terfenadine
	torsemide	
	S-warfarin	Calcium Channel Blockers:
		amlodipine
		diltiazem
		felodipine
		lercanidipine
		nifedipine2
		nisoldipine
		nitrendipine
		verapamil
		HMG CoA Reductase Inhibitors:
		atorvastatin
		cerivastatin
		lovastatin
		simvastatin
		Steroid 6beta-OH:
		estradiol
		hydrocortisone

Substrate		
CYP1A2[a]	**CYP2C9[a]**	**CYP3A4[b]**
		progesterone testosterone <u>Miscellaneous:</u> alfentanyl aprepitant aripiprazole buspirone cafergot caffeine cilostazol cocaine codeine-N demethylation dapsone dexamethasone dextromethorphan docetaxel domperidone eplerenone fentanyl finasteride gleevec haloperidol irinotecan lidocaine methadone nateglinide ondansetron pimozide propranolol quetiapine quinine risperidone salmeterol sildenafil sirolimus tamoxifen taxol terfenadine trazodone vincristine zaleplon ziprasidone zolpidem

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

Appendix 3 Medications Affecting QT Interval[a]

Albuterol	Doxepin	Lithium	Quinidine
Alfuzosin	Droperidol	Mesoridazine	Ranolazine
Amantadine	Ephedrine	Metaproterenol	Risperidone
Amiodarone	Epinephrine	Methadone	Ritodrine
Amitriptyline	Erythromycin	Methylphenidate	Roxithromycin
Amphetamine	Felbamate	Mexiletine	Salmeterol
Arsenic trioxide	Fenfluramine	Midodrine	Sertindole
Astemizole	Flecainide	Moexipril	Sertraline
Atazanavir	Fluconazole	Moxifloxacin	Sibutramine
Atomoxetine	Fluoxetine	Nicardipine	Sibutramine
Azithromycin	Foscarnet	Nilotinib	Solifenacin
Bepridil	Fosphenytoin	Norepinephrine	Sotalol
Chloral hydrate	Galantamine	Nortriptyline	Sparfloxacin
Chloroquine	Gatifloxacin	Octreotide	Sunitinib
Chlorpromazine	Gemifloxacin	Ofloxacin	Tacrolimus
Ciprofloxacin	Granisetron	Ondansetron	Tamoxifen
Cisapride	Halofantrine	Oxytocin	Telithromycin
Citalopram	Haloperidol	Paliperidone	Terbutaline
Clarithromycin	Ibutilide	Paroxetine	Terfenadine
Clomipramine	Imipramine	Pentamidine	Thioridazine
Clozapine	Indapamide	Perflutren lipid microspheres	Tizanidine
Cocaine	Isoproterenol	Phentermine	Tolterodine
Desipramine	Isradipine	Phenylephrine	Trimethoprim-Sulfa
Dexmethylphenidate	Itraconazole	Phenylpropanolamine	Trimipramine
Disopyramide	Ketoconazole	Pimozide	Vardenafil
Dobutamine	Lapatinib	Probucol	Venlafaxine
Dofetilide	Levafloxacin	Procainamide	Voriconazole
Dolasetron	Levalbuterol	Protriptyline	Ziprasidone
Domperidone	Levomethadyl	Pseudoephedrine	
Dopamine	Lisdexamfetamine	Quetiapine	

[a]Information available at http://www.azcert.org.

Appendix 4 New Response Evaluation Criteria in Solid Tumors – Version 1.1 – Modified Excerpt From Original Publication with Supplementary Explanations [1]

1. MEASURABILITY OF TUMOR AT BASELINE

1.1 DEFINITIONS

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

1.1.1 MEASURABLE TUMOR LESIONS

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

10 mm by CT or MRI scan (CT/MRI scan slice thickness/interval no greater than 5 mm).

10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).

20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be not greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also section 2.2 below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

1.1.2 NON-MEASURABLE TUMOR LESIONS

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

1.1.3 SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, *with identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

1.2 TARGET LESIONS: SPECIfiCATIONS BY METHODS OF MEASUREMENTS

1.2.1 MEASUREMENT OF LESIONS

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

1.2.2 METHOD OF ASSESSMENT

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during study. Imaging based evaluation should always be the preferred option.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and $\geq$ 10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

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

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor markers, Cytology, Histology: The utilization of these techniques for objective tumor evaluation can not generally be advised but will be dependent on the study design.

2.2.2 <u>TUMOR RESPONSE EVALUATION</u>

2.1. ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

Measurable disease is defined by the presence of at least one measurable lesion (as detailed above in Section 1.1.1).

2.2. BASELINE DOCUMENTATION OF 'TARGET' AND 'NON-TARGET' LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

This means in instances where patients have only one or two organ sites involved a maximum of two (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in that organ will be recorded as non-measurable lesions. (even if size is greater than 10mm by CT scan).

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

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As noted in section 1.1.1, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geq$ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis $\geq$ 10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

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

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (see also section 2.3.4).

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2.3. RESPONSE CRITERIA

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

2.3.1. EVALUATION OF TARGET LESIONS

- *Complete Response (CR):* Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- *Partial Response (PR):* At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- *Progressive Disease (PD):* At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study including baseline (nadir). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- *Stable Disease (SD):* Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

2.3.2. SPECIAL NOTES ON THE ASSESSMENT OF TARGET LESIONS

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

Target lesions that become *'too small to measure'*: while on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and BML (below measurable limit)

should be ticked (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm and in that case BML should not be ticked (BML is equivalent to a less than sign <).

Lesions that split or coalesce on treatment: when non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.3.3. EVALUATION OF NON-TARGET LESIONS

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions (and, if applicable, normalization of tumor marker level). All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression (see section 2.3.4) of existing non-target lesions. The appearance of one or more new lesions is also considered progression.

2.3.4. SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET DISEASE

When the patient also has measurable disease: **in this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.** A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for **unequivocal progression** status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease: this circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The

same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as **'sufficient to require a change in therapy'**. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be **substantial**.

2.3.5. NEW LESIONS

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

2.4 EVALUATION OF RESPONSE

2.4.1 TIME POINT RESPONSE (OVERALL RESPONSE)

It is assumed that at each protocol specified time point, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Table 1 Time Point Response – Target (w/wo non- target) Lesions

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

Table 2 Time Point Response – Non-Target Lesions only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.

a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

2.4.2 MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

For example, if a patient had a baseline sum of 50 mm with three measured lesions and during study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done, or could not be assessed because of poor image quality or obstructed view, the Response for Target Lesions should be "Unable to Assess" since the patient is not evaluable. Similarly, if one or more non-target lesions are indicated as 'not assessed', the response for non-target lesions should be "Unable to Assess" (except where there is clear progression). Overall response would be "Unable to Assess" if either the target response or the non-target response is "Unable to Assess" (except where this is clear evidence of progression) as this equates with the case being not evaluable at that time point.

Table 3 Best Overall Response when Confirmation is required

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

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

2 SPECIAL NOTES ON RESPONSE ASSESSMENT

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

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1–3.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled

assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

In studies where patients with advanced disease are eligible (i.e. primary disease still or partially present), the primary tumor should be also captured under target or non-target lesions as appropriate. This is to avoid wrong assessments of complete overall response by statistical programs while the primary is still present but not evaluable.

Appendix 5 International Melanoma Working Group (IMWG) Uniform Response and Relapse Criteria for Multiple Myeloma

	IMWG criteria[2]
Response	
sCR[2]	CR as defined below plus: o Normal FLC ratio and o Absence of clonal cells in bone marrow[3] by immunohistochemistry or immunofluorescence[4]
CR[2]	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and ≤ 5% plasma cells in bone marrow[3]
VGPR[2,5]	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥ 90% or reduction in serum M-protein plus urine M-protein level < 100 mg per 24 hour
PR[2,5]	≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hours If the serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30% In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
MR	NA
No change / SD	Not meeting criteria for CR, VGPR, PR or progressive disease
Plateau	NA
Relapse	
Progressive disease[6]	Increase of ≥ 25% from lowest response value in any one or more of the following: o Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dL)[7] o Urine M-component and/or (the absolute increase must be ≥ 200 mg per 24 hours)

	○ Only in patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL ○ Bone marrow plasma cell percentage. The absolute percentage must be ≥ 10%[8] ○ Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas ○ Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder
Relapse[6]	Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features).[7] It is not used in calculation of time to progression or progression-free survival but is listed here as something that can be reported optionally or for use in clinical practice. 1. Development of new soft tissue plasmacytomas or bone lesions 2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion 3. Hypercalcemia (> 11.5 mg/dL) [2.65 mmol/L] 4. Decrease in hemoglobin of ≥ 2 g/dL [1.25 mmol/L] 5. Rise in serum creatinine by 2 mg/dL or more [177 μ-mol/L or more]
Relapse from CR[6] (to be used only if the end point studied is DFS)[9]	Any one or more of the following: ○ Reappearance of serum or urine M-protein by immunofixation or electrophoresis ○ Development of ≥ 5% plasma cells in the bone marrow[8] ○ Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia)

CR, complete response; DFS, disease-free survival; FLC, free light chain; PR, partial response; SD, stable disease; sCR, stringent complete response; VGPR, very good partial response.

1 Adapted from Durie BGM, et al. Leukemia 2006;20:1467-1473; and Kyle RA, Rajkumar SV. Leukemia 2008;23:3-9.

2 All response categories require two consecutive assessments made at anytime before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.

3 Confirmation with repeat bone marrow biopsy not needed.

4 Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is kappa/lambda of > 4:1 or < 1:2.

5 A clarification to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients is defined as a normal FLC ratio of 0.26–1.65 in addition to CR criteria listed above. VGPR in such patients is defined as a > 90% decrease in the difference between involved and uninvolved free light chain (FLC) levels.

6 All relapse categories require two consecutive assessments made at anytime before classification as relapse or disease progression and/or the institution of any new therapy. In the IMWG criteria, CR patients must also meet the criteria for progressive disease shown here to be classified as progressive disease for the purposes of calculating time to progression and progression-free survival. The definitions of relapse, clinical relapse and relapse from CR are not to be used in calculation of time to progression or progression-free survival.

7 For progressive disease, serum M-component increases of ≥1 gm/dL are sufficient to define relapse if starting M-component is ≥5 g/dL.

8 Relapse from CR has the 5% cut-off versus 10% for other categories of relapse.

9 For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease.

Appendix 6 ECOG Performance Status Scale

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

Appendix 7 National Cancer Institute-Common Toxicity Criteria for Adverse Events, v4.0

The Common Terminology Criteria for Adverse Events v4.0, updated June 14, 2010, is available at: http://evs.nci.nih.gov/ftp1/CTCAE/About.html

Appendix 8 ICH Guidelines for Clinical Safety Data Management, Definitions, and Standards for Expedited Reporting, Topic E2

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

is fatal; [results in death] [NOTE: death is an outcome, not an event]

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

required in-patient hospitalization or prolongation of existing hospitalization;

results in persistent or significant disability/incapacity;

is a congenital anomaly/birth defect;

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

Medical and scientific judgment should be exercised in deciding whether expedited reporting to the sponsor is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definitions above. These situations should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

An unexpected AE is one, the nature or severity of which is not consistent with the applicable product information.

Causality is initially assessed by the Investigator. For Serious Adverse Events, possible causes of the event **are** indicated by selecting one or more options. (Check all that apply)

Pre-existing/Underlying disease - specify

Study treatment – specify the drug(s) related to the event

Other treatment (concomitant or previous) – specify

Protocol-related procedure

Other (e.g. accident, new or intercurrent illness) - specify

The term severe is a measure of intensity, thus a severe AE is not necessarily serious. For example, nausea of several hours' duration may be rated as severe, but may not be clinically serious.

A serious adverse event occurring during the study or which comes to the attention of the Investigator within 15 days after stopping the treatment or during the protocol-defined follow-up period, if this is longer, whether considered treatment-related or not, must be reported. In addition, a serious adverse event that occurs after this time, if considered related to test "drug", should be reported.

Such preliminary reports will be followed by detailed descriptions later which will include copies of hospital case reports, autopsy reports and other documents when requested and applicable.

For serious adverse events, the following must be assessed and recorded on the AEs page of the eCRF: intensity, relationship to test substance, action taken, and outcome to date.

The Investigator must notify the Ethics Review Committee/Institutional Review Board of a serious adverse event in writing as soon as is practical and in accordance with international and local laws and regulations.

ROCHE LOCAL COUNTRY CONTACT for SAEs: Local Monitor

The local Monitor will be the initial point of contact for all study related issues. The local monitor is responsible to provide administrative details and contact information of the Roche study team as required.

ROCHE HEADQUARTERS CONTACT for SAEs and other medical emergencies: Clinical Operations

The local Monitor will be the initial point of contact for all study related issues. The local monitor is responsible to provide administrative details and contact information of the Roche study team as required.

See the attached *Protocol Administrative and Contact Information & List of Investigators form [gcp_for000227]*, for details of administrative, contact information, and Emergency Medical Call Center Help Desk toll-free numbers.

24 HOUR MEDICAL COVERAGE

Please refer to the Emergency Medical Call Center Help Desk toll-free numbers provided by your local Monitor.

3 APPENDICES REFERENCES

1. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;**45**:228-47.

2. Bogaerts J, Ford R, Sargent D, et al, Individual patient data analysis to assess modifications to the RECIST criteria Eur J Cancer 2009;45:

PROTOCOL

TITLE:	**AN OPEN-LABEL, PHASE II STUDY OF VEMURAFENIB IN PATIENTS WITH BRAF V600 MUTATION-POSITIVE CANCERS**
PROTOCOL NUMBER:	MO28072
VERSION NUMBER:	6
EUDRACT NUMBER:	2011-004426-10
IND NUMBER:	73,620
TEST PRODUCT:	Vemurafenib (RO5185426)
MEDICAL MONITOR:	Dr. Vladan Antic
SPONSOR:	F. Hoffmann-La Roche Ltd.
DATE FINAL:	13 January 2015
DATES AMENDED:	Version 1: 30 November 2011 Version 2: 9 August 2012 Version 3: 7 January 2013 *for U.S. sites only* Version 3: 12 June 2013 *for ex-U.S. sites only* Version 4: 10 September 2013 *for U.S. sites only* Version 5: 18 March 2014 Version 6: See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
Antic, Vladan	Company Signatory	16-Jan-2015 09:36:16

SYNOPSIS OF PROTOCOL MO28072

TITLE

An open-label, phase II study of vemurafenib in patients with BRAF V600 mutation-positive cancers.

SPONSOR

F. Hoffmann-La Roche Ltd.

CLINICAL PHASE

II

INDICATION

Patients with cancers (excluding melanoma and papillary thyroid cancer) harbouring BRAF V600 mutations as identified by the routinely performed mutation analysis assays at each individual participating site.

OBJECTIVES

Primary objective:

To evaluate the efficacy of vemurafenib in patients with cancers harbouring BRAF V600 mutations as response rate (RR) at Week 8 determined by the Investigator using Response Evaluation Criteria In Solid Tumors, Version 1.1 (RECIST, v1.1)* in solid tumours or International Myeloma Working Group (IMWG) uniform response criteria for multiple myeloma and to identify tumour types for further development.

*For prostate cancer, Erdheim-Chester disease (ECD) and/or Langerhans cell histiocytosis (LCH) specific response criteria see Appendix 9 and Appendix 10, respectively.

Secondary objectives:

- To evaluate the safety and tolerability of vemurafenib in this patient population.
- To evaluate in solid tumours and multiple myeloma (MM) overall response rate (ORR) clinical benefit rate (Clinical response (CR) or Stringent Complete Response (sCR)) partial response (PR) or very good partial response (VGPR) and stable disease [SD]) of vemurafenib, duration of response (DOR), time to response, time to tumour progression (TTP), progression free survival (PFS) and overall survival (OS).
- To determine the maximum tolerated dose (MTD) and recommended dose for stage I/II of the combination of vemurafenib and cetuximab in BRAF V600-positive metastatic CRC patients (Cohort 3b only).
- To investigate the safety, tolerability, efficacy of the combination of vemurafenib and cetuximab in BRAF V600-positive metastatic CRC patients (Cohort 3b only).
- To evaluate tumour assessment scans by an IRC for Cohort 1 (NSCLC) and other cohorts that demonstrate clinically meaningful efficacy per investigator assessment.

Exploratory objectives:

- To perform concordance testing for the detection of BRAF V600 mutation in tumour samples via either the Roche Companion Diagnostic (CoDx) cobas 4800 BRAF V600 Test or other standard methodology.
- To examine the previous line of treatment's TTP (plTTP) in relation to the TTP achieved during study treatment
- For all newly enrolled patients in all cohorts:
    - To explore the PK characteristics of vemurafenib
    - To assess the correlation of BRAF V600 mutation between tissue samples and plasma samples

TRIAL DESIGN

Open-label, multicentre, multinational, phase II study exploring the efficacy and safety of vemurafenib monotherapy in a diverse population of patients with cancers (excluding melanoma and papillary thyroid cancer) known to harbour BRAF V600 mutations and for whom vemurafenib is deemed the best treatment option in the opinion of the Investigator.

In the population of colorectal cancer patients, the safety and efficacy of vemurafenib in combination with cetuximab will also be explored in addition to vemurafenib.

Patients with BRAF V600 mutation-positive cancers will be identified through mutation analysis assays, as routinely performed at each participating site. BRAF V600 mutation and test used for the detection of the BRAF mutation assay will be recorded in the eCRFs. The presence of BRAF V600 mutation will be retrospectively confirmed in a central laboratory by the Roche CoDx cobas 4800 BRAF V600 Test or other standard methodology.

The trial will consist of a Screening Period (Day –28 to −1), a Treatment Period, an End of Treatment Visit occurring when study medication is discontinued for any reason, a Safety Follow-Up Visit occurring 28 days (± 5 days) after the last dose of study medication and a Survival Follow-Up Period lasting for a minimum of 12 months after enrolment of the last patient or until all patients have died, withdrawn consent or are lost to follow-up (whichever occurs first). Day 1 of the study (baseline) will be defined as the first day a patient receives study medication. One cycle of therapy will be defined as 28 days of treatment. Patients will be asked to attend clinic visits at regular intervals during the study for safety and efficacy assessments.

The study will include 7 cohorts of patients with the following cancers:

Cohort 1:	Non-small cell lung cancer (NSCLC)
Cohort 2:	Ovarian cancer
Cohort 3:	Colorectal cancer
Cohort 3a:	Vemurafenib only
Cohort 3b:	Combination therapy with vemurafenib and cetuximab
Cohort 4:	Cholangiocarcinoma / cancer of the biliary tract
Cohort 5:	Breast cancer
Cohort 6:	Multiple myeloma (MM)
Cohort 7:	Solid tumours other than the above

Colorectal cancer patients with BRAF V600 mutation-positive cancers will receive vemurafenib as a single agent (Cohort 3a) or the combination of vemurafenib and cetuximab (Cohort 3b).

The Cohort 3b is designed to investigate the safety, tolerability, efficacy and determine the MTD and the recommended dose for stage I/II of the combination of vemurafenib and cetuximab. Cohort 3b has two parts:

- Part 1 is a dose finding phase of vemurafenib in combination with cetuximab (based on a classical 3+3 design)
- Part 2 is investigating the efficacy and safety of the recommended dose for stage I/II of the combination of vemurafenib and cetuximab and the same Stage I/II design as the other cohorts will be used

The decision to carry on enrolment of CRC patients into Cohort 3a (vemurafenib monotherapy) and/or enrol patients into Cohort 3b (combination of vemurafenib and cetuximab) will be based on the stage I analysis for Cohort 3a (vemurafenib monotherapy). This will be decided by the Sponsor in discussion with study Steering Committee.

The decision to continue enrolment in Cohort 3b after the Part I dose escalation phase will be decided by the Sponsor in discussion with the study Steering Committee.

Recruitment/enrolment in any of the above cohorts may present some challenges due to the low frequency of BRAF V600 mutations in the specific disease settings. Therefore the following rule on cohort closure (permanent enrolment stop) will be applied: if no patients are enrolled in the remaining cohorts one year after any of the cohorts has completed enrolment, then enrolment in those remaining cohorts will be stopped. Cohort 7 (Other solid tumours) will be closed to enrolment when all other cohorts are closed, regardless of the number of patients recruited at that time. This cohort is quite heterogeneous and will be examined primarily to seek efficacy signals in the relatively rare BRAF V600 mutation-positive tumours.

Enrolled patients will receive:

- Cohorts 1 – 7 (except patients in the Cohort 3b): continuous oral dosing of vemurafenib at 960 mg twice daily (b.i.d.)
- Cohort 3b: Part 1 vemurafenib and cetuximab at the doses allocated for dose escalation (see Section 6.3.1) or Part 2 at the dose recommended for stage I/II of vemurafenib and cetuximab

until the development of progressive disease (as per Investigator assessment), unacceptable toxicity, withdrawal of consent, protocol violation endangering the patient's safety, death, reasons deemed critical by the treating physician, or study termination by the Sponsor.

Patients who develop disease progression but, in the opinion of the Investigator, would still benefit from continuing study treatment may continue treatment with study treatment after discussion with the Sponsor.

Patients with ECD/LCH have the option of discontinuing vemurafenib treatment after one year, if the investigator considers it to be in the best interest of the patient. Patients can then resume vemurafenib treatment if they become symptomatic or if their scans show worsening of their disease.

NUMBER OF PATIENTS

It is estimated that up to 170 patients with solid tumours or multiple myeloma will be enrolled in this study for the Stage I/II analysis. Approximately 13–37 patients per indication (cohort) will be

included. The number of patients in a cohort can be less than 13 if a cohort is closed earlier as a result of stopping rules for the cohort.

Recruitment into any cohort/indication can be expanded up to 70 patients if a response rate has been demonstrated in Stage II of that cohort per stopping rules defined in the protocol or a clear clinical benefit for patients is observed. This will be decided by the Sponsor in discussion with the study's Steering Committee. The maximum number of patients in this study is therefore 490 (7 cohorts up to 70 patients each).

TARGET POPULATION

Adult patients with BRAF V600 mutation-positive cancers (excluding melanoma and papillary thyroid cancer). BRAF V600 mutations will be identified by mutation analysis assays as routinely performed at each individual participating site.

Eligibility Criteria

For solid tumours only*

1. Histologically confirmed cancers (excluding melanoma and papillary thyroid cancer) that harbour a BRAF V600 mutation and are refractory to standard therapy or for which standard or curative therapy does not exist or is not considered appropriate by the Investigator.

   Note: for the patient to be eligible, they must be able to provide a tumour sample (preferably tissue; alternatively DNA) for retrospective confirmation of the BRAF mutation by a central laboratory. This tumour sample should preferably be from the original specimen used to detect the BRAF mutation. If archival samples are not available, the patient should be biopsied in order to obtain adequate tissue. Exceptions may be considered upon discussion with the Sponsor (e.g. ≥ 250 ng of DNA may be sent instead of tissue samples).
2. Measurable disease according to RECIST, v1.1
3. Adequate hematologic function, as defined by the following laboratory values; test performed within 7 days prior to the first dose of vemurafenib:
   a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
   b. Platelet count ≥ 100 x 10^9/L

For multiple myeloma only:

4. Patients with a confirmed diagnosis of MM harbouring a BRAF V600 mutation

   Note: for the patient to be eligible, they must be able to provide a tumour sample (preferably tissue; alternatively DNA) for retrospective confirmation of the BRAF mutation by a central laboratory. This tumour sample should preferably be from the original specimen used to detect the BRAF mutation. If archival samples are not available, the patient should be biopsied in order to obtain adequate tissue. Exceptions may be considered upon discussion with the Sponsor (e.g. ≥ 250 ng of DNA may be sent instead of tissue samples).
5. Patients must have received at least one line of prior systemic therapy for the treatment of MM. A line of treatment is sequential treatment without interruption for response and subsequent progression
6. Patients treated with local radiotherapy (with or without concomitant exposure to steroids for pain control or management of cord/nerve root compression); two weeks must have elapsed since the last date of radiotherapy, which is recommended to be a limited field. Patients who

require concurrent radiotherapy should have entry into the Study deferred until the radiotherapy is completed and two weeks have passed since the last date of therapy

7. Patients must have relapsed and/or refractory MM with measurable disease, defined as disease that can be measured either by serum or urinary evaluation of the monoclonal component or by serum assay of free light chain (FLC) of at least one of the following three parameters:
   a. Serum M-protein > 0.5 g/dL
   b. Urine M-protein > 200 mg per 24 hours
   c. Involved FLC level > 10 mg/dL (> 100 mg/L) provided serum FLC ratio is abnormal
8. Adequate hematologic function as defined by the following laboratory values performed within 7 days prior to the first dose of vemurafenib:
   a. Absolute neutrophil count (ANC) ≥ 1.0 x 10^9/L
   b. Platelets count ≥ 50 x 10^9/L

For all patients (solid tumours and MM):

9. Signed written informed consent approved by the relevant Independent Ethics Committee (IEC) / Institutional Review Board (IRB) must be obtained prior to performing any study-related procedures
10. Male or female ≥ 16 years of age
11. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2
12. Must have recovered from all side effects of their most recent systemic or local treatment
13. Able to swallow pills
14. Adequate hematologic, renal and liver function as defined by the following laboratory values; tests performed within 7 days prior to the first dose of vemurafenib:
    a. Haemoglobin ≥ 9 g/dL
    b. Serum creatinine ≤ 1.5 times upper limit of normal (ULN) or creatinine clearance (CrCl) > 50 mL/min by Cockroft–Gault formula (Protocol Appendix 1)
    c. Aspartate aminotransferase (AST [SGOT]) and alanine aminotransferase (ALT [SGPT]) ≤ 2.5 times ULN (≤ 5 times ULN if considered due to primary or metastatic liver involvement)
    d. Serum bilirubin ≤ 1.5 times ULN
    e. Alkaline phosphatase ≤ 2.5 times ULN (≤ 5 times ULN if considered due to tumour)
15. Negative serum pregnancy test within 7 days prior to commencement of dosing in premenopausal women. Women of non-childbearing potential may be included without serum pregnancy test if they are either surgically sterile or have been postmenopausal for ≥ 1 year
16. Fertile men and women must use an effective method of contraception during treatment and for at least 6 months after completion of treatment as directed by their physician. Effective methods of contraception are defined as those which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly (for example implants, injectables, combined oral contraception or intra-uterine devices). At the discretion of the Investigator, acceptable methods of contraception may include total abstinence in cases where the lifestyle of the patient ensures compliance. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)

17. Absence of any psychological, familial, sociological, or geographical conditions potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before trial entry

Exclusion Criteria*

1. Melanoma, papillary thyroid cancer or haematological malignancies (with the exception of multiple myeloma)
2. Uncontrolled concurrent malignancy (early stage or chronic disease is allowed if not requiring active therapy or intervention and is under control)
3. For MM, solitary bone or solitary extramedullary plasmacytoma as the only evidence of plasma cell dyscrasia
4. Active or untreated CNS metastases.

   Patients with brain metastasis are eligible if asymptomatic, off corticosteroid therapy, and without evidence of disease progression in brain for ≥ 2 months.

   Patients with incidentally found brain metastases that are asymptomatic and for which no treatment is planned are also eligible.
5. History of or known carcinomatous meningitis
6. Concurrent administration of any anti-cancer therapies (e.g., chemotherapy, other targeted therapy, experimental drug, etc.) other than those administered in this study
7. Known hypersensitivity to vemurafenib or another BRAF inhibitor. In addition, for Cohort 3b only: known hypersensitivity to cetuximab
8. Prior treatment with a BRAF or MEK inhibitor (prior sorafenib is allowed)
9. Pregnant or lactating women
10. Refractory nausea and vomiting, malabsorption, external biliary shunt or significant bowel resection that would preclude adequate absorption.
11. Any of the following within the 6 months prior to first vemurafenib administration:
    - Myocardial infarction, severe/unstable angina, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack
12. Pulmonary embolism within 30 days prior to first study medication administration
13. Hypertension not adequately controlled by current medications within 30 days prior to first study medication administration
14. History or presence of clinically significant ventricular or atrial dysrhythmias ≥ Grade 2 (National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 [NCI CTCAE, v4.0])
15. Corrected QT (QTc) interval ≥ 450 msec at baseline or history of congenital long QT syndrome or uncorrectable electrolyte abnormalities
16. Uncontrolled medical illness (such as infection requiring treatment with intravenous [IV] antibiotics)
17. Other severe, acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study medication administration or may interfere with the interpretation of study results which, in the judgment of the Investigator, would make the patient inappropriate for entry into this study
18. Unwillingness to practice effective birth control

19. Inability to comply with other requirements of the protocol

*For prostate cancer, ECD and/or LCH specific eligibility criteria as part of Cohort 7, see Appendix 9 and Appendix 10, respectively

LENGTH OF STUDY

The trial will consist of a Screening Period (Day -28 to -1), a Treatment Period, an End of Treatment Visit occurring when vemurafenib is discontinued for any reason, a Safety Follow-Up Visit occurring 28 days (± 5 days) after the last dose of study medication and at 6 months following study drug discontinuation or prior to the initiation of another anti-neoplastic therapy (whichever occurs first), and a Survival Follow-Up Period lasting for a minimum of 12 months after the enrolment of the last patient or until all patients have died, withdrawn consent or are lost to follow-up (whichever occurs first) to monitor survival status. Day 1 of the study (baseline) will be defined as the first day a patient receives study medication.

Recruitment period will be approximately 24 - 40 months, depending if any cohort is expanded based on Stage II efficacy.

Enrolled patients will receive:

- Cohorts 1 – 7 (except patients in the Cohort 3b): continuous oral dosing of vemurafenib at 960 mg twice daily (b.i.d)
- Cohort 3b: Part 1 vemurafenib and cetuximab at the doses allocated for dose escalation (see Section 6.3.1) or Part 2 at the dose recommended for stage I/II of vemurafenib and cetuximab

until the development of progressive disease (as per Investigator assessment), unacceptable toxicity, withdrawal of consent, protocol violation endangering the patient's safety, death, reasons deemed critical by the treating physician, or study termination by the Sponsor.

Patients who develop disease progression but, in the opinion of the Investigator, would still benefit from continuing study treatment may continue treatment with study treatment after discussion with the Sponsor.

Patients with ECD/LCH have the option of discontinuing vemurafenib treatment after one year, if the investigator considers it to be in the best interest of the patient. Patients can then resume vemurafenib treatment if they become symptomatic or if their scans show worsening of their disease.

Patients who discontinue study medication for any reason (e.g., disease progression, an adverse event [AE], etc.) other than withdrawal of consent will continue to be followed for survival and new anti-cancer therapy every 3 months after last dose until death, for a minimum of 12 months after the last patient has been enrolled or until all patients have died, withdrawn consent or are lost to follow-up (whichever occurs first).

END OF STUDY

The end of study will occur when all patients have been followed for survival for a minimum period of 12 months after the last patient has been enrolled or until all patients have died, withdrawn consent or are lost to follow up, whichever occurs first.

At this time, the trial will end and no further data will be collected on the clinical database for this study. The end of the MO28072 study is defined as the last patient last visit at the end of the follow-up period.

INVESTIGATIONAL MEDICAL PRODUCT(S): DOSE/ ROUTE/ REGIMEN

Patients will receive:

- Cohorts 1 to 7 (except the Cohort 3b): continuous oral doses of vemurafenib 960 mg b.i.d. starting on Day 1 of the study Treatment Phase until the development of progressive disease (as per Investigator assessment), unacceptable toxicity, consent withdrawal, protocol violation endangering patient's safety, death, reasons deemed critical by the treating physician or study termination by the Sponsor.
- Cohort 3b. cetuximab intravenous (IV) weekly (see Appendix 1 for body surface area calculation) starting on Day 1 of the study Treatment Phase and continuous oral doses of vemurafenib b.i.d. starting on Day 2 of the study Treatment Phase

until the development of progressive disease (as per Investigator assessment), unacceptable toxicity, consent withdrawal, protocol violation endangering patient's safety, death, reasons deemed critical by the treating physician or study termination by the Sponsor.

Patients with ECD/LCH have the option of discontinuing vemurafenib treatment after one year, if the investigator considers it to be in the best interest of the patient. Patients can then resume vemurafenib treatment if they become symptomatic or if their scans show worsening of their disease.

For Part 1 of Cohort 3b, the dose escalation levels of vemurafenib and cetuximab combination will be as follows:

Dose Level	Vemurafenib	Cetuximab
1	720 mg b.i.d. starting on Day 2 of cycle 1	Cetuximab: 300 mg/m^2 loading dose on Day 1 of Treatment Phase, then 200 mg/m^2 weekly
2	720 mg b.i.d. starting on Day 2 of cycle 1	Cetuximab: 400 mg/m^2 loading dose on Day 1 of Treatment Phase, then 250 mg/m^2 weekly
3	960 mg b.i.d. starting on Day 2 of cycle 1	Cetuximab: 400 mg/m^2 loading dose on Day 1 of Treatment Phase, then 250 mg/m^2 weekly

If the dose levels above are not tolerated then the following provisional dose levels may be considered as alternative to any of the above dose levels after discussion between the Sponsor and study Steering Committee (see Section 6.3.1).

Dose Level	Vemurafenib	Cetuximab
1A	720 mg b.i.d. starting on Day 2 of cycle 1	Cetuximab: 200 mg/m^2 loading dose on Day 1 of Treatment Phase, then 125 mg/m^2 weekly
2A	720 mg b.i.d. starting on Day 2 of cycle 1	Cetuximab: 300 mg/m^2 loading dose on Day 1 of Treatment Phase, then 250 mg/m^2 weekly
3A	960 mg b.i.d. starting on Day 2 of cycle 1	Cetuximab: 300 mg/m^2 loading dose on Day 1 of Treatment Phase, then 250 mg/m^2 weekly

Patients included in Part 2 of Cohort 3b of the study will receive vemurafenib and cetuximab at the doses recommended during the dose escalation part.

If recruitment is expanded in any cohort (due to promising efficacy seen in Stage II), patients who are part of this expansion will receive the same treatment as patients who were treated in Stage II of that cohort.

Patients who develop disease progression but, in the opinion of the Investigator, would still benefit from continuing study treatment may continue treatment with study treatment after discussion with the Sponsor.

NON-INVESTIGATIONAL MEDICAL PRODUCT(S)

N/A

COMPARATOR "DRUG" (OR STANDARD OF CARE): DOSE/ ROUTE/ REGIMEN

N/A

CENTRES

This is a multinational, multicentre study with approximately 30 centres.

EFFICACY

Efficacy of vemurafenib for solid tumours and MM and vemurafenib in combination with cetuximab in colorectal cancer will be captured by Response Rate (RR), clinical benefit rate ([CR or sCR, PR or VGPR and stable disease (SD)], and time-dependent endpoints (DOR), overall response rate assessed via best overall response (BOR), time to response, time to tumour progression, PFS and OS).

The primary endpoint will be RR at Week 8 in each indication. For solid tumours to be assigned a status of partial response (PR) or complete response (CR) (i.e., a responder), changes in tumour measurements must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met, i.e., patients need to have two consecutive assessments of PR or CR to be responders.

For patients with solid tumours, response will be assessed according to RECIST, v1.1, criteria (Eisenhauer EA et al. Eur J Cancer 2009;45(2):228-47). Assessments will be performed by the Investigator using computed tomography (CT) or magnetic resonance imaging (MRI) scan every 8 weeks (see Appendix 4).

For prostate cancer, ECD and or LCH specific response criteria see Appendix 9 and Appendix 10, respectively.

For patients with MM, response will be assessed according to International Myeloma Working Group [IMWG] uniform response criteria (Durie BGM et al. Leukemia 2006;20:1467-73.), e.g., patients need to have two consecutive assessments of CR, sCR, VGPR or PR to be responders. Assessments will be performed by the Investigator 8 weeks after starting vemurafenib and every 28 days thereafter. Bone marrows assessments will be performed only once to confirm CR or sCR.

Secondary endpoints for solid tumours and MM will include duration of response (DOR), time to response, time to progression (TTP), overall response rate (ORR), clinical benefit rate [CR or sCR, PR or VGPR and stable disease (SD)], time to tumour progression, PFS, and overall survival (OS).

For patients in Cohort 1, all CT scans during the patient's last therapy prior to this study, as well as CT scans made during this study, will be collected and reviewed retrospectively by an IRC. Scans from the prior therapy will be used to establish plTTP, and this may be examined in relation to the TTP achieved from study treatment. During the study, the investigator-assessed response rate will remain as the primary efficacy endpoint and the IRC assessment will be a supportive secondary endpoint. The concordance tables between Investigator and IRC assessment will be produced. The collection of scans and IRC review may also be considered for confirmation of efficacy assessments for other cohorts where clinically meaningful efficacy is demonstrated with Investigator assessment.

SAFETY

The NCI-CTCAE, v4.0, will be used to quantify the intensity of AEs occurring during treatment in this study.

Patients will be assessed for AEs at each clinical visit and as necessary throughout the study. Incidence, type, and severity of AEs, serious adverse events (SAEs), incidence of AEs and SAEs leading to vemurafenib interruption or discontinuation, and cause of death will be reported.

For Cohort 3b, there will be a summary of dose-limiting toxicities (DLTs) (as defined in Section 6.3.2.2) by dose level.

All other safety monitoring will occur by the reporting of AEs, by the assessment of routine laboratory values (blood counts and differential and serum chemistries), vital signs, electrocardiograms (ECGs), dermatology, and head & neck evaluations for cutaneous squamous cell carcinoma (SCC) and non-cutaneous SCC, respectively, chest CT scans for non-cutaneous SCC surveillance and findings on physical examinations.

Performance Status (PS) will be measured using the ECOG PS Scale at each clinical visit.

As part of the physical exam, a medical history will be collected, including demographics, relevant medical history, previous and current diseases, prior therapies including surgeries and relative responses, prior skin cancer history, therapies and procedures, all medications started within 14 days prior to screening visit, and measurements for weight (kg) and height (cm, screening visit only).

The initial (screening/baseline) complete physical examination should include the evaluation of the head, eyes, ears, nose, and throat (HEENT) and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, neurological systems. Subsequent physical examinations during the study for safety assessment may be restricted to evaluation of specific systems or areas of interest, including those with previously abnormal findings or associated with symptomatic or laboratory evidence of toxicity. A skin examination by the treating physician should, however, be performed at each visit.

Vital signs will be recorded for all patients and will include: blood pressure (BP), temperature (degrees Celsius, °C), heart rate, and respiratory rate.

ECG monitoring will occur at Screening and throughout the study treatment.

Guidelines for dose modification and discontinuation are reported in protocol Section 6.2.1 for vemurafenib monotherapy and Section 6.3.3 for the combination of vemurafenib and cetuximab.

Special Safety Considerations

Cutaneous squamous cell carcinoma (cSCC)

Cutaneous squamous cell carcinoma (cSCC), Keratoacanthoma (KA), basal cell carcinoma (BCC) and any other second primary malignancies and its progression or recurrence are defined as events requiring close monitoring. As based on mechanism of action, vemurafenib may cause progression of cancers associated with RAS mutations, vemurafenib should be used with caution in patients with prior or concurrent cancers associated with RAS mutation. With the exception of events of actinic keratosis, these events must always be designated as SAEs in order to ensure their reporting to the Health Authorities in an appropriate and timely manner. Patients are required to have full skin examination by a dermatologist to screen and monitor for SCC, basal cell carcinoma (BCC), actinic keratosis and keratoacanthoma (KA). Dermatology evaluation will be performed at screening/baseline, approximately Day 28 of therapy, every 12 weeks thereafter while patient is on study, when patient discontinues vemurafenib unless done within the prior 12 weeks and at the Safety Follow-up Visit, 28 (± 5) days after discontinuing study drug and at 6 months following study drug discontinuation or prior to the initiation of another anti-neoplastic therapy (whichever occurs first). Patients should report to their physician any new skin lesion or change, including rash and photosensitivity, while on study treatment and any suspicious lesions should be referred to a dermatologist for further evaluation as required.

The initial examination by the dermatologist should include a complete dermatological history of prior medications and cutaneous SCC risk factors (i.e., radiation therapy, sun exposure, immunosuppression, prior SCC, use of tanning beds, precursor lesions, and photochemotherapy for psoriasis).

Any lesion suspected of representing a new SCC, BCC, actinic keratosis, or keratoacanthoma identified by the dermatologist should be treated as per local standard of care. Skin biopsies of any suspicious lesions identified at baseline and during the study must be biopsied/excised and sent for pathological examination. Available blocks/sections from any suspicious lesion should also be sent to a designated central pathology laboratory for confirmation of diagnosis.

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

Non-cutaneous squamous cell carcinoma (Treating Physician or Other Qualified Physician):

A head and neck examination must be performed by the treating physician at baseline and during the study for all enrolled patients. The head and neck examination will consist of at least a visual inspection of the oral mucosa and lymph node palpation. This will be done at screening/baseline (anytime up to 28 days prior to Day 1), every 12 weeks while the patient is on study, when the patient discontinues vemurafenib unless done within the prior 12 weeks and at the Safety Follow-Up Visit 28 (± 5) days after discontinuing study drug and at 6 months following study drug discontinuation or prior to the initiation of another anti-neoplastic therapy (whichever occurs first). Any suspicious findings will be referred to an appropriate specialist.

For all patients (with solid tumours and MM) a CT scan of the chest is required for non-cutaneous SCC screening and surveillance. As radiologic assessments for tumour burden are a standard requirement for solid tumour patients, it is not necessary to perform a separate chest CT. Instead, the same (routine tumour assessment CT) should suffice for monitoring of non-cutaneous SCC

for patients with solid tumours. However, chest CTs for the evaluation of SCC are required at a minimum of every 6 months for each patient and at 6 months following study drug discontinuation or prior to the initiation of another anti-neoplastic therapy (whichever occurs first).

Pelvic examinations for women (with special attention to cervix) and anal examinations for all patients will be performed at baseline and at Safety Follow-Up Visit 28 (± 5) as part of surveillance for non-cutaneous SCC. The pelvic examination should include a complete external and internal examination (internal examination of uterine cervix may include a Pap smear, which would be a decision of the investigator). The anal examination should include external examination, digital anorectal examination and anoscopy or proctoscopy. However, if in opinion of the investigator the presence of "abnormal lesions including SCC" can be excluded by the external inspection and the manual examination, this is acceptable. However, if the presence of a lesion is suspected, an anoscopy or proctoscopy are recommended.

Photosensitivity

Photosensitivity has been reported in patients treated with vemurafenib in clinical trials. The majority of cases were mild or moderate in severity. All patients should be advised to avoid sun exposure and wear protective clothing and use sun block and lip balm (minimum of SPF 30, re-applied every 2 to 3 hours) during vemurafenib treatment and for at least 5 to 10 days after study drug discontinuation.

See protocol Section 6.3.3 for guidance of cetuximab specific safety considerations.

PHARMACOKINETICS / PHARMACODYNAMICS

For all newly enrolled patients in all cohorts, mandatory blood samples will be taken during Cycle 1 (Day 1 and Day 15) and Cycles 2 – 4 (Day 1) to explore the PK characteristics of vemurafenib. Samples will be taken pre-dose and 2-4 hours post-dose of the morning dose on the corresponding days. Approximately 2 mL of blood will be collected at each time point.

Collected samples will be destroyed no later than five years after the end of the study.

QUALITY OF LIFE AND PHYSICAL SYMPTOMS

N/A

EXPLORATORY BIOMARKERS

In order to perform concordance testing for the detection of BRAF V600 mutation in tumour samples via either the Roche Companion Diagnostic (CoDx) cobas 4800 BRAF V600 Test or other standard methodology, patients must be able to provide a tumour sample (preferably tissue; alternatively DNA) for retrospective confirmation of the BRAF mutation by a central laboratory. This tumour sample should preferably be from the original specimen used to detect the BRAF mutation. If archival samples are not available, the patient should be biopsied in order to obtain adequate tissue. Exceptions may be considered upon discussion with the Sponsor (e.g. ≥ 250 ng of DNA may be sent instead of tissue samples).

For the assessment of the correlation of BRAF V600 mutation between tissue samples and plasma samples, optional blood samples can be collected from any newly enrolled patient in any cohort. Blood samples will be taken at pre-dose Cycle 1 (Day 1) and Cycle 2 (Day 1), as well as at the Safety Follow-up Visit or at time of disease progression (whichever occurs first), with

approximately 10 mL blood being required at each time point. For these patients, BRAF V600 mutations in tissue may be correlated to BRAF V600 mutations in plasma and assessed in relation to clinical parameters and clinical outcome.

Any collected samples will be destroyed no later than five years after the end of the study.

PROCEDURES (SUMMARY):

Patients with BRAF V600 mutation-positive cancers will be identified through mutation analysis assays as routinely preformed at each participating site (the BRAF V600 mutation and test used for the detection of BRAF mutation assay will be recorded in the eCRFs). Sites must submit a tumour sample (preferably tissue; alternatively DNA) for retrospective confirmation of the BRAF mutation using the Roche CoDx cobas 4800 BRAF V600 Test or other standard methodology by a central laboratory. This tumour sample should preferably be from the original specimen used to detect the BRAF mutation. If archival samples are not available, the patient should be biopsied in order to obtain adequate tissue. Exceptions may be considered upon discussion with the Sponsor (e.g. ≥ 250 ng of DNA may be sent instead of tissue samples).

Patients will be assessed for tumour response or progression using the RECIST criteria for solid tumours (current version 1.1)* or IMWG response criteria for MM and monitored for AEs according to the study procedures.

*For prostate, ECD and/or LCH specific response criteria see Appendix 9 and Appendix 10, respectively.

STUDY ASSESSMENTS:

Screening Period*

The following assessments should be performed within 28 days before the first administration of study medication on Day 1 (unless they have already been conducted during this time period as part of the patient's routine clinical care):

- Signed written informed consent approved by the relevant Independent Ethics Committee (IEC) / Institutional Review Board (IRB) must be obtained prior to performing any study-related procedures
- Documentation of BRAF V600 mutation and test used for the identification of the mutation.
- Sites must submit a tumour sample for retrospective confirmation in a central laboratory of the BRAF mutation using the Roche CoDx cobas 4800 BRAF V600 Test or other standard methodology. This tumour sample should preferably be from the original specimen used to detect the BRAF mutation. The original tumour block will be returned back to the site. If archival samples are not available, the patient should be biopsied in order to obtain adequate tissue. Exceptions may be considered upon discussion with the Sponsor (e.g. ≥ 250 ng DNA may be sent instead of tissue samples).
- Medical history (including demographics)
- Physical examination, including the evaluation of the head, eyes, ears, nose, and throat (HEENT); cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and a neurological systems examination; height and weight (height will only be measured during screening)

- Vital signs (blood pressure, heart rate, temperature, respiratory rate)
- 12-lead ECG, including heart rate, PR interval, QRS duration, QT and QTc intervals and ECG findings
- ECOG Performance Status
- Haematology, including haemoglobin, haematocrit, platelet count, white blood cell count (WBC) and absolute neutrophil count (ANC)
- Biochemistry (including amylase, lipase, glucose, blood urea nitrogen ([BUN]], creatinine or creatinine clearance, sodium, potassium, calcium, magnesium, bicarbonate ([if routinely performed on venous blood samples]), total bilirubin with fractionation into direct and indirect (if total bilirubin elevated during the study; if one component is available, the other component can be calculated), alkaline phosphatase, AST ([SGOT]], ALT [(SGPT)].
- Serum pregnancy test within 7 days prior to commencement of dosing for women of child-bearing potential. Women surgically sterile or postmenopausal for ≥ 1 year are not to be considered for a pregnancy test.
- Tumour assessments for patients with solid tumours (CT/MRI of the chest, abdomen and pelvis [C/A/P]). Exception: for patients with a confirmed primary brain tumour, the CT/MRI of C/A/P may be omitted. In addition, CT/MRI of the brain may also be performed as per standard of care.
- For patients in Cohort 1, all CT scans during the patient's last therapy prior to this study will be collected and reviewed retrospectively by an IRC. The collection of scans and IRC review may also be considered for confirmation of efficacy assessments for other cohorts where clinically meaningful efficacy is demonstrated with Investigator assessment.
- Assessments for multiple myeloma (Skeletal survey, Serum protein electrophoresis (SPEP) with quantitation of M-protein by immunofixation, Urine protein electrophoresis (UPEP) using 24 hours urine protein electrophoresis, Serum free light chains, bone marrow for histology, cytogenetics and FISH, and flow cytometry with or without biopsy, Beta 2 microglobulin albumin and lactate dehydrogenase (LDH))
- Dermatology evaluation by a dermatologist.
- Head and neck examination (as part of the evaluation for SCC) performed by the treating physician
- CT of chest for evaluation of non-cutaneous SCC (for all patients, solid tumours and MM. For solid tumours, the routinely performed chest CT for tumour assessment may be used as chest CT for the evaluation of non-cutaneous SCC while the patient is taking vemurafenib)
- Concomitant medications
- AEs (including SAEs) related to study-mandated procedures from time ICF is signed
- Pelvic examinations for women (with special attention to cervix) and anal examinations for all patients for evaluation of SCC

*For patients included in Cohort 7 with Prostate cancer or ECD/LCH, see Appendix 9 and Appendix 10, respectively, for additional assessments.

Treatment Period*

Visits during the treatment period are to be completed on Day 1, Day 15, Day 29, and every 28 days thereafter. A window of ± 2 days will apply for Cycle 1 / Day 15, and ± 5 days is allowed for each visit from Cycle 2 onwards (28-day cycle).

For the patients included in Cohort 3b only, the visits will be weekly throughout the treatment period, and a visit window of ± 1 day will apply starting on Day 8 of Cycle 1 and onwards.

The following assessments should be performed during the Treatment Period:

- Physical examination (as described previously) on Day 1, Day 15, Day 29 and every 28 days thereafter until study drug discontinuation. For Cohort 3b only, physical examination assessments will be done weekly for the first 8 weeks, and then every 2 weeks thereafter from Day 57.
- Vital signs (as described previously) on Day 1, Day 15, Day 29 and every 28 days for the first 8 cycles and then every 8 weeks until study drug discontinuation. For Cohort 3b only, vital sign assessments will be done weekly for the first 8 weeks, and then every 2 weeks thereafter from Day 57.
- 12-lead ECG (as described previously) on Day 29, every 28 days for the following 3 months and every 12 weeks thereafter until study drug discontinuation
- ECOG performance status on Day 1, Day 15, Day 29 and every 28 days for the first 8 cycles and then every 8 weeks thereafter until study drug discontinuation. For Cohort 3b only, ECOG performance status assessments will be done weekly for the first 8 weeks, and then every 2 weeks thereafter from Day 57.
- Haematology (as described previously) on Day 1, Day 15, Day 29 and every 28 days thereafter until study drug discontinuation. For Cohort 3b only, haematology assessments will be done weekly for the first 8 weeks, and then every 2 weeks thereafter from Day 57.
  - Haematology assessments do not need to be repeated on Day 1 if performed within 7 days prior to the first vemurafenib administration (this does not apply to Cohort 3b, where haematology must be done on Day 1 prior to cetuximab administration)
- Biochemistry (as described previously) on Day 1, Day 15, Day 29 and every 28 days thereafter until study drug discontinuation. For Cohort 3b only, biochemistry assessments will be done weekly for the first 8 weeks, and then every 2 weeks thereafter from Day 57
  - Biochemistry assessments do not need to be repeated on Day 1 if performed within 7 days prior to the first vemurafenib administration (this does not apply to Cohort 3b, where biochemistry must be done on Day 1 prior to cetuximab administration)
- The following tumour assessments are to be performed for patients with solid tumours;
  - CT/MRI of the chest/abdomen/pelvis (C/A/P) every 8 weeks after starting study drug. The same imaging technique (CT or MRI) should be used for each patient throughout the study. Exception: for patients with a confirmed primary brain tumour, the CT/MRI of C/A/P may be omitted.
  - In addition, CT/MRI of the brain as per standard care
- For all patients in Cohort 1, the CT scans made during this study will be collected and reviewed retrospectively by an IRC. The collection of scans and IRC review may also be considered for confirmation of efficacy assessments for other cohorts where clinically meaningful efficacy is demonstrated with Investigator assessment.

- The following assessments are to be performed for patients with MM 8 weeks after starting vemurafenib and every 4 weeks thereafter;
  - Serum protein electrophoresis (SPEP) with quantitation of M-protein level by immunofixation, urine protein electrophoresis (UPEP) using 24-hour urine protein electrophoresis, Serum free light chains , LDH, and beta 2 microglobulin. Bone marrow analysis only to be done only to confirm complete remission after two consecutive immunofixation analyses are negative.
- Dermatology evaluation by a dermatologist 28 days after starting study drug and every 12 weeks thereafter until study drug discontinuation
- Head and neck examination (as part of the evaluation for SCC) performed by the treating physician every 12 weeks after starting study drug
- Chest CT for evaluation of SCC every 6 months after starting study drug (for all patients with solid tumours and MM)
- Vemurafenib dispensation on Day 1 and every 28 days thereafter until study drug discontinuation
- Vemurafenib accountability every 28 days after starting vemurafenib until study drug discontinuation
- Review of the vemurafenib Dosing Exception Diary every 28 days after starting vemurafenib until study drug discontinuation.
- Concomitant medications throughout the Treatment Period.
- AEs (including SAEs) throughout the Treatment Period.
- Assessment of dose-limiting toxicities on Day 8, Day 15, Day 22 and Day 29 in the first cycle for patients who are participating in the dose escalation phase of Cohort 3b Part 1(see Section 6.3.2.2)
- For newly enrolled patients in all cohorts, mandatory blood samples will be taken during Cycle 1 (Day 1 and Day 15) and Cycles 2 – 4 (Day 1) for PK analysis. Samples will be taken pre-dose and 2-4 hours post-dose of the morning dose on the corresponding days. For all PK samples, the date and time of the last dose of vemurafenib should be recorded, along with the actual time of PK blood draw. See Section 5.4.2.
- For newly enrolled patients in any cohort, blood samples for exploratory biomarkers are optional. Samples will be taken pre-dose during Cycle 1 (Day 1) and Cycle 2 (Day 1), as well as at the Safety Follow-up Visit or at time of disease progression (whichever occurs first) (see Section 5.4.3).
- Vemurafenib administration throughout the Treatment Period. Note that for patients in Part I of Cohort 3b, vemurafenib will start on Day 2 of Cycle 1 (administered while in hospital).
- Weekly administration of cetuximab throughout the Treatment Period for all patients included in Cohort 3b.

* Patients included in Cohort 7 with Prostate cancer or ECD/LCH see Appendix 9 and Appendix 10, respectively, for additional assessments.

End of Treatment Visit

The End of Treatment Visit will occur when the patient discontinues vemurafenib for any reason, unless the patient withdraws consent or is lost to follow-up. The following assessments will be conducted at the End of Treatment Visit:

- Physical examination (as described previously)
- Vital signs (as described previously)
- 12-lead ECG (as described previously)
- ECOG Performance Status
- Haematology (as described previously)
- Biochemistry (as described previously)
- Tumour assessments (as described previously) if not done within the last 8 weeks
- Response assessments for multiple myeloma if not done within the last 28 days
- Dermatology evaluation by a dermatologist if not done within the previous 12 weeks
- Head and neck examination (as part of the evaluation for SCC) performed by the treating physician if not done within the previous 12 weeks
- Drug accountability
- Review of the Drug Dosing Exception Diary
- Concomitant medications
- AEs (including SAEs)
- For newly enrolled patients in any cohort, blood samples for exploratory biomarkers are optional. Samples will be taken at the Safety Follow-up Visit or at time of disease progression (whichever occurs first). See Section 5.4.3.

Safety Follow-Up Visit

The Safety Follow-Up Visit will occur after 28 (± 5) days from discontinuation of study drug. The following assessments will be conducted at the Safety Follow-Up Visit

- 12-lead ECG (as previously described)
- Dermatology evaluation by a dermatologist
- Head and neck examination (as part of the evaluation for SCC) performed by the treating physician
- CT of the chest, dermatology evaluation by a dermatologist and head and neck examination for evaluation of SCC must be performed at this visit and in all patients (both solid tumour and MM) 6 months following study drug discontinuation or prior to the initiation of another anti-neoplastic therapy (whichever occurs first)
- Concomitant therapy
- AEs (including SAEs)
- Follow up for disease progression for those patients who have discontinued study drug for any reason (AEs, etc.) other than disease progression
- Survival status

- Pelvic examinations for women (with special attention to cervix) and anal examinations for all patients for evaluation of SCC.
- For newly enrolled patients in any cohort, blood samples for exploratory biomarkers are optional. Samples will be taken at the Safety Follow-up Visit or at time of disease progression (whichever occurs first). See Section 5.4.3.

Survival Follow-Up Period

The following assessments will be conducted during the Survival Follow-Up Period:

- Survival status every 3 months after the last dose until death or for a minimum of 12 months after the last patient has been enrolled or until all patients have died, withdrawn consent or are lost to follow-up (whichever occurs first)
- Record of next anti-cancer therapy

STATISTICAL CONSIDERATIONS AND ANALYTIC PLAN

Primary Variable

The primary endpoint is RR at Week 8 for each cohort, as assessed by the Investigator using RECIST, v1.1 for patients with solid tumours or IMWG uniform response criteria for patients with MM. For patients with solid tumours, responders at Week 8 will be defined based on tumour assessment status of PR or CR at Week 8. For MM patients to be assigned the status of a responder, patients need to have CR, sCR, VGPR, or PR. Bone marrows will be performed only to confirm CR or sCR. Patients without a post-baseline tumour assessment will be considered to be non-responders.

There will be 7 cohorts with different cancer types. There will be Cohort 3a and 3b with patients with colorectal cancer treated with vemurafenib or vemurafenib in combination with cetuximab, respectively.

Cohort 3b has two parts:

- Part 1 is a dose finding phase for vemurafenib in combination with cetuximab (based on a classical 3+3 design)
- Part 2 is investigating the efficacy and safety of the recommended dose for stage I/II of the combination of vemurafenib and cetuximab

Secondary Efficacy Variables

The secondary efficacy endpoints for each cohort will include: BOR, clinical benefit rate (CR (or sCR) plus PR (or VGPR) plus SD), duration of response (DOR), time to response, time to tumour progression, PFS, and OS. In addition, secondary endpoints will include the IRC assessment of response rates focussing on Week 8, Week 16 and BOR for Cohort 1 (NSCLC) and other cohorts that demonstrate clinically meaningful efficacy per investigator assessment.

Safety Variables

Adverse events (AEs), all AEs, AEs Grade 3 or 4, AEs leading to treatment interruption and discontinuation, serious adverse events (SAEs), premature discontinuation from study and treatment, haematology and biochemistry parameters, exposure to study medication and skin evaluation, head/neck evaluations, chest CT scan will be the primary safety variables for each

cohort. Vital signs, electrocardiogram, ECOG performance status, concomitant medications and physical examination will be the secondary safety variables.

For Cohort 3b, patients with colorectal cancer, dose-limiting toxicities as defined in Section 6.3.2.2 will be summarized by dose levels.

Study Populations

The main analysis population for the efficacy analysis will be the intent-to-treat (ITT) population, which will include all patients enrolled in the study irrespective of whether they have received study medication or not. ITT1 to ITT7 will correspond to the ITT population for each cohort (Cohort 1 to Cohort 7, respectively).

The per-protocol (PP) population will not be defined due to the small number of patients per cohort, but protocol deviations will be listed (including patients with non-measurable disease at baseline).

The safety populations SP1 to SP7 will correspond to the safety populations for Cohort 1 to Cohort 7, respectively, and will include, for each cohort, all patients who have received at least one dose of study medication.

Cohort 7 (patients with other solid tumour) will include patients with different tumour types and therefore different safety/ITT populations will be defined for different tumour types.

Statistical Model

Primary Efficacy Variable

The main analysis for the RR will be based on Adaptive design based on Simon's two stage design for a single proportion (Ref: Lin and Shih (2004). Adaptive Two-stage design for Single-Arm Phase II A Cancer Clinical Trials, Lin and Biometrics 60, 482-490).

Stage I will be defined as when a pre-specified number of patients (as determined in the Sample Size Section 8.3) will have a minimum of 8 weeks of treatment, develop progressive disease, prematurely withdraw from study, or die, whichever occurs first.

If a pre-specified minimal response rate will not be achieved in certain cohorts in the first stage of the study, this cohort will be closed and no further enrolment of patients will be performed for that cohort. However, if a clear clinical benefit has been observed for patients in the cohort, e.g. majority of patients recorded SD at Week 8 and no CR or PR is recorded, then enrolment into Stage II might be allowed for this cohort after discussion with the Sponsor and study Steering Committee. Otherwise, enrolment continues into Stage II until a pre-determined number of additional patients has been reached (as explained in the Sample Size section). At the conclusion of this study, the study treatment will be declared effective or ineffective for each indication (cohort) based on rules for Stage II.

The analysis at Stage II (for lower or higher desirable confirmed response) for each cohort will be performed when all patients enrolled in the study, as estimated in the Sample Size section, will have a minimum of 8 weeks of treatment, develop progressive disease, withdraw, or are lost to follow-up, whichever occurs first.

In case a cohort/indication is expanded up to 70 patients, the primary analysis for efficacy will occur once all patients have been followed up for 9 months after last patient had been enrolled in that cohort, or the patient develops progressive disease, withdraws consent, or is lost to follow-up, whichever occurs first.

Secondary efficacy variables (final analysis)

The final analysis for each cohort will take place when all patients in that cohort have been followed for survival for a minimum of 12 months after the last patient has been enrolled or until all patients have died, withdrawn consent or are lost to follow up, whichever occurs first. More details are in Efficacy Analysis Data (Section 8.3.2).

Hypothesis Testing

The adaptive two-stage design allows the original estimation of the Stage II response rate to be reassessed, based on information at Stage I, in the event that it was too optimistic or too sceptical to be the true response rate.

For example, for patients in each cohort, we assume that RR of 15% would be a very low RR and vemurafenib will be "under-performing" for this cohort. A RR of 45% would be a high desirable RR, while a RR of 35% would be a low desirable RR, for Stage II.

The hypotheses for all cohorts for Stage I are:

a. H_0: $\pi_{N1} < \pi_0$ where $\pi_0 = 15\%$

b. H_1: $\pi_{N1} \geq \pi_0$ where $\pi_0 = 15\%$

where N_1 is a number of patients in Stage I and π_0 is a very low, undesirable RR.

If H_0 is rejected (and H_1 is accepted at Stage I), further patients will be enrolled based on the number of responders in Stage I and their data will be collected in the second stage.

The hypotheses for all cohorts at the end of Stage II for a low desirable response, π1L, are:

i) H_1 is accepted at Stage I and

ii) H_0: $\pi_N \leq \pi_{1L}$ where $\pi_{1L} = 35\%$
H_1: $\pi_N > \pi_{1L}$ where $\pi_{1L} = 35\%$

The N notifies the total number of patients for each cohort.

The hypotheses for all cohorts at the end of Stage II for a high desirable response, π_{1H}, are:

i) H_1 is accepted at Stage I and

ii) H_0: $\pi_N \leq \pi_{1H}$ where $\pi_{1H} = 45\%$
H_1: $\pi_N > \pi_{1H}$ where $\pi_{1H} = 45\%$

Cohort 3b

For this cohort, first, the recommended dose for Stage I/II part should be established based on 3+3 classical design. Then the second part will include a stage I and II parts similar to what is planned for the other cohorts and same statistical hypotheses at Stage I and Stage II will be applied.

Stopping rules for enrolment and screening

If no patients are enrolled in the remaining cohorts one year after any of the cohorts has completed enrolment, then enrolment in those remaining cohorts will be stopped (patients already in screening will be allowed to enrol if eligible).

Individual cohorts may temporarily stop enrolment to allow for the stage I analysis before progressing to stage II.

Individual cohorts may temporarily stop screening to allow for the stage I analysis before progressing to stage II.

The decision to carry on enrolment of CRC patients into Cohort 3a (vemurafenib monotherapy) and/or enrol patients into Cohort 3b (combination of vemurafenib and cetuximab) will be based on the stage I analysis for Cohort 3a (vemurafenib monotherapy). This will be decided by the Sponsor in discussion with study Steering Committee.

The decision to continue enrolment in Cohort 3b after the Part I dose escalation phase will be decided by the Sponsor in discussion with study Steering Committee.

Stopping rules for each cohort:

Rules for Stage I:

Stage I will be stopped if the number of responders (unconfirmed) is less than the pre-specified number in Table 2 (e.g. if there is none or only one responder out of first seven patients). However if a clear clinical benefit has been observed for patients in the cohort, e.g. majority of patients recorded SD at Week 8 and no CR or PR is recorded, then enrolment into Stage II might be allowed for this cohort.

If there is the required response during Stage I or a good clinical benefit is observed for particular cohort as mentioned above, then additional patients will be enrolled in the second stage of the corresponding cohort, in order to achieve total number of patients as specified in the Table 1 and Table 2 below (Sample Size estimation section).

Cohort 7 will be closed to enrolment when all other cohorts are closed regardless of the number of patients recruited at that time. This cohort may be quite heterogeneous and will be examined primarily to seek efficacy signals in the relatively rare BRAF V600 mutation-positive tumours.

Rules for Stage II:

A study treatment will be considered to be efficacious in a cohort in Stage II if

- there is no unacceptable toxicity and
- the number of responders is equal or above the specified number in the sample size calculations, as presented in Table 2 or
- best overall response, BOR (confirmed) is higher than 15%.

Cohort Expansion

There will be no formal statistical hypothesis tested as part of the expansion cohort analysis. The analysis of the expanded cohort will allow estimation of RR and other efficacy parameters and other efficacy parameters (please refer to secondary efficacy parameters in Section 8.1.2) with increased precision and more insight concerning the safety profile.

Efficacy Data Analyses

The primary efficacy endpoint is RR at Week 8 in each cohort, as assessed by the Investigator using RECIST, v1.1 or IMWG response criteria. This is an early phase II study and cohorts are independent, hence there will be no adjustment for multiplicity. Number and percentage of responders with corresponding Clopper-Pearson 95% confidence intervals will be provided for each cohort. The overall response rate will be assessed via BOR. The clinical benefit rate and BOR will be analysed in a similar way to RR.

Duration and time of response in each indication will be summarized only for responders, i.e., for the patients whose confirmed response is CR or PR for patients with solid tumours and CR, sCR, VGPR or PR for patients with MM.

Estimates for the survivor function for the time-to-event variables, such as time to progression (TTP), PFS,

OS, duration of response, and time to response, will be obtained by using the Kaplan-Meier (KM) approach together with associated 95% CI.

Due to the small sample size in Cohort 7 (patients with other solid tumours), only descriptive statistics will be applied. If there are at least 5 patients with the same tumour type, number (percentage) of patients will be summarized in the frequency table and listed for RR at Week 8, clinical benefit rate and BOR. If there are fewer patients, only listings will be provided. For response criteria for patients with prostate cancer, ECD and/or LCH enrolled in this cohort, see Appendix 9 and Appendix 10, respectively.

For all patients in Cohort 1, the CT scans during the patient's last therapy prior to this study, as well as CT scans made during this study, will be collected and reviewed retrospectively by an IRC. Scans from the prior therapy will be used to establish plTTP, and this may be examined in relation to the TTP achieved from study treatment. During the study, the investigator-assessed response rate will remain as the primary efficacy endpoint and the IRC assessment will be a supportive secondary endpoint. The concordance tables between Investigator and IRC assessment will be produced. The IRC assessment of response rates will focus on Week 8, Week 16 and BOR. The collection of scans and IRC review may also be considered for confirmation of efficacy assessments for other cohorts where clinically meaningful efficacy is demonstrated with Investigator assessment.

Interim Analysis:

The study will be analysed for efficacy at Stage I and Stage II and the dose escalation for Part 1 of Cohort 3b (Section 6.3.2.1) and at week 16 for expanded cohorts. All cohorts will be analysed at the end of the study.

Other analyses

Demographics and medical history will be summarized for each cohort.

Safety Data Analysis

The safety variables will be summarized for the safety population where the safety population is SP1 to SP7. All safety variables will be summarized for each cohort.

All AEs will be assessed according to the NCI CTCAE, v4.0, grading system. The analysis of AEs will focus on treatment-emergent AEs, i.e., AEs occurring on the day of or after first administration of study drug (vemurafenib). Non-treatment emergent AEs (i.e., those occurring before commencement of study medication) will only be listed.

The incidence, type, and severity of AEs will be summarized according to the primary system-organ class (SOC) and within each SOC, by MedDRA preferred term. Summary tables will be presented for time to first onset of the AE of special interest, e.g. SCC.

AEs leading to treatment interruption and discontinuation as well as SAEs will be analysed in a similar way to all AEs. Cause of death will also be summarized and listed.

Results from skin evaluation, head and neck evaluations, chest CT scan (e.g., number of lesions, SCC - keratoacanthoma type, etc.) will be summarized using frequencies and percentages. Premature discontinuation of treatments with corresponding reason for discontinuation will be summarized by frequency tables and listed. The discontinuation from study will be also summarized and listed.

Descriptive statistics will be presented for cumulative vemurafenib doses and duration of exposure.

Laboratory parameters, haematology, and serum biochemistry will be presented in shift tables of NCI-CTCAE grade at baseline versus worst grade during the Treatment Period. The summary of laboratory parameters presented by means, standard deviation, minimum, and maximum will be also presented.

Vital signs (blood pressure, temperature, heart rate, and respiratory rate) and ECG (heart rate, PR interval, QRS duration, QT interval and QTc interval) will be summarized over time by means of mean, median, and range (mean and maximum). The ECG findings will be also presented by frequency tables over time. The ECOG PS will be summarized by frequency tables over time and percentage of patients in different categories will be presented by bar charts at different time points. Physical examination variables collected only at baseline (e.g., height) will be summarized for baseline only while other physical examination variables will be summarized over time by visits and reported in patients' listings. Concomitant therapy will be summarized by frequency tables and percentages.

For the dose escalation phase Cohort 3b, there will be a summary of DLT safety parameters (as defined in Section 6.3.2.2) by dose levels.

For Cohort 7, if there are at least 5 patients with the same tumour type, number (percentage) of patients for safety parameters will be summarised and listed. If there are fewer patients, only listings will be provided for this cohort.

Pharmacokinetic Analysis

The population PK model developed in melanoma patients will be used to obtain individual vemurafenib PK parameters from the sparse sampling collected in newly enrolled patients. Summary statistics will be used as appropriate for the vemurafenib plasma concentrations and PK parameters.

The relationship between appropriate clinical and pharmacodynamic endpoints and the plasma concentrations of vemurafenib will be explored.

Exploratory Analyses

The correlation between plasma and tissue BRAF V600 mutation status as well as the concordance of the Roche CoDx cobas 4800 BRAF V600 Test or other standard methodologies may be explored. The relationship between appropriate clinical endpoints and the mutation status (including, but not limited to, allelic frequencies of the BRAF V600 mutation and its dynamic changes from pre-dose to on-treatment) in tissue and/or plasma will be explored. Mutation status in tissue and/or plasma will also be correlated to demographics, medical history and clinical parameters.

Sample Size Estimation

The sample size estimation is based on Lin and Shih's paper and corresponding SAS program.

There will be 7 cohorts with patients with different indications. There will be two sub-cohorts with patients with colorectal cancer, one treated only with vemurafenib and the other treated with vemurafenib and cetuximab.

Cohorts (except Cohort 3b and Cohort 7) will have a minimum of 13 and a maximum of 19 patients (depending on results in Stage I).

If there are enough patients enrolled in individual tumour type, Cohort 7 will have 13 or 19 patients and Lin and Shin's method of Stage I and Stage II design will be applied.

If there are not enough patients in individual tumour type, data for cohort 7 will be only listed.

Cohort 3b will have a dose escalation phase based on a classical 3+3 design and will enrol a maximum of 18 patients. The dose level recommended for the combination of vemurafenib and cetuximab will be expanded to 7 patients as per rule of Stage I design. Then a further 6 or 12 patients will be enrolled to a maximum of 13 or 19 patients depending on the results for stage I (see Table 2). The maximum number of patients for this cohort might be up to 37 patients.

A proportion of 15% is chosen for a low response, based on Section 8.3.1.1 in the protocol and on our present knowledge.

However, if the number of responders are 2, 3, or 4 out of 7 patients in Stage I, then the study medication is possibly efficacious for that cohort and further data will be collected based on "low desirable response at Stage II" Sample Size estimation, i.e., an additional 12 patients will be enrolled in order to have a total of 19 patients for that cohort.

Stage I will be stopped if the number of responders is less than the pre-specified number in Table 2 (e.g. if there is none or only one responder out of first seven patients). However, if a clear clinical benefit has been observed for patients in the cohort, e.g. majority of patients recorded SD at Week 8 and no CR or PR is recorded, then enrolment into Stage II will be allowed for this cohort after discussion with Sponsor and study Steering Committee.

If there are 5 or more responders out of 7 patients, then further data will be collected based on "high desirable response at Stage II" Sample Size estimation, i.e., an additional 6 patients will be enrolled in order to have a total of 13 patients for that cohort.

Assuming, RRs as specified in the prior hypothesis testing, a power of 80% for high desirable response and 70% for low desirable response and two-sided alpha of 0.1, the following number of patients is required for each cohort.

Table 1:
Sample Size for Each Cohort – Stage I/II

	Dose Finding [a]	Sample size following Stage I analysis	
		Low desirable response	High desirable response
NSCLC		19	13
Ovarian cancer		19	13
Colorectal cancer (Cohort 3a vemurafenib only)		19	13
Colorectal cancer (Cohort 3b vemurafenib and cetuximab)	3+3 Design up to 18	19	13
Cholangiocarcinoma/cancer of biliary tract		19	13
Breast Cancer		19	13
Multiple Myeloma		19	13
Other tumours[b]		19	13
Total number for Stage I/II	**up to 170 patients [c]**		

a. Cohort 3b Part 1 only
b. The n's presented are for each individual tumour type, with enough patients available to follow the 2 stage study design
c. The total number of patients may exceed the original estimate of 170 patients if any cohort is expanded (see Table 2).

Details regarding Stage I and number of responders are presented in Table 2.

Table 2:
Sample Size for Each Cohort (except Cohort 6) and Stage I/II

	Stage (Two-Stage Design)		Total Number of Patients in Each Cohort	Two-Sided Alpha Level / Power
	Stage I	Stage II [b]		
All Cohorts				
Low response at the end of Stage I				
Number of patients	7	19	19	10% / 70%
Number of responders [a]	≥ 2 and ≤ 4	≥ 5		
High response at the end of Stage I				
Number of patients	7	13	13	10% / 80%
Number of responders [a]	≥ 5	≥ 6		

The sample size was estimated using the method of Lin and Shih's paper (Biometrics. 2004;60:482-490) and corresponding SAS program.

a. Number of patients needed to respond in order to continue into Stage II or have a positive result at the end of trial.

b. This columns display a maximum number of patients required for each cohort and number of responders that should be present at end of Stage II in order to declare efficacious treatment.

Cohort expansion

Recruitment into any cohort/indication can be expanded up to a total of 70 patients if a response rate has been demonstrated in Stage II of that cohort as per stopping rules defined in the protocol or a clear clinical benefit for patients is observed. This will be decided by the Sponsor in discussion with study Steering Committee.

Assuming a preferable BOR of 40% in the cohort with promising Stage II results and aiming at a distance from the estimated proportion to the CI limits of 12%, a total of 70 patients would need to be enrolled. The observed BOR of 40% could then be estimated to be within 28% and 52%, with a probability of 95% (Clopper-Pearson exact confidence intervals). Details are presented in Table 3.

Table 3:
Estimation of Sample Size

Sample Size	BOR	95% Clopper Pearson Exact Confidence Intervals
70 patients	36% (25 patients)	25% – 48%
	40% (28 patients)	28% – 52%
	46% (32 patients)	34% – 58%
	50% (35 patients)	38% – 62%

Table 4a:
Schedule of Assessments for Cohorts 1, 2, 3a, 4 – 7 (Cohorts with Vemurafenib Study Treatment Only)

	Screening Period [1]	Treatment Period [2]										End of Treatment Visit [3]	Safety Follow-Up Visit [4]	Survival Follow-Up [5]
Cycle		**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9 onwards**		**Post treatment d/c**	**Every 3 months**
Day	**–28 to –1**	**1**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**Every 28 Days**		**28 (± 5) days**	
Allowed Visit Window (days)			**± 2**	**± 5**										
Informed consent [6]	X													
Documentation of BRAF V600 mutation via local test; sample taken for retrospective confirmation [7]	X													
Medical history and demographics	X													
Physical examination [8]	X	X	X	X	X	X	X	X	X	X	X	X		
Vital signs [9]	X	X	X	X	X	X	X	X	X	X	X (Q8 weeks)	X		
12-lead ECG [10]	X			X	X	X	X			X	C11 (then Q12 weeks)	X	X	
ECOG performance status	X	X	X	X	X	X	X	X	X	X	X (Q8 weeks)	X		
Haematology [11]	X	X[12]	X	X	X	X	X	X	X	X	X	X		
Biochemistry [13]	X	X[12]	X	X	X	X	X	X	X	X	X	X		

	Screening Period [1]	Treatment Period [2]										End of Treatment Visit [3]	Safety Follow-Up Visit [4]	Survival Follow-Up [5]
Cycle		**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9 onwards**		**Post treatment d/c**	**Every 3 months**
Day	**–28 to –1**	**1**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**Every 28 Days**		**28 (± 5) days**	
Allowed Visit Window (days)			**± 2**	**± 5**										
Serum pregnancy test [14]	X													
Solid tumour assessments (CT/MRI) [15]	X				X		X		X		X (Q8 weeks)	X		
Assessments for Multiple Myeloma [16]	X				X[17]	X[17]	X[17]	X[17]	X[17]	X[17]	X[17]	X[17]		
Dermatology evaluation [18]	X			X			X			X	C11 (then Q12 weeks)	X	X[19]	At 6 months
Head and neck assessment for SCC [20]	X					X			X		C10 (then Q12 weeks)	X	X[19]	At 6 months
Chest CT for evaluation of SCC [21]	X								X		C13 (then Q6 months)		X[19]	At 6 months
Drug dispensation		X		X	X	X	X	X	X	X	X			
Drug accountability				X	X	X	X	X	X	X	X	X		
Drug Dosing Exception Diary [22]				X	X	X	X	X	X	X	X	X		
Prostate Cancer patients only – PSA Assessment [23]	X				X		X		X		X (Q8 weeks)	X		

	Screening Period [1]	Treatment Period [2]										End of Treatment Visit [3]	Safety Follow-Up Visit [4]	Survival Follow-Up [5]
Cycle		**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9 onwards**		**Post treatment d/c**	**Every 3 months**
Day	**–28 to –1**	**1**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**Every 28 Days**		**28 (± 5) days**	
Allowed Visit Window (days)			**± 2**	**± 5**										
Prostate Cancer patients only – Bone Scans [24]	X				X		X		X		X (Q8 weeks)	X		
ECD/LCH patients only – C-reactive protein[25]		X		X	X		X		X		X (Q8 weeks)	X		
ECD/LCH patients only – additional tumour assessments [26]	X				X		X		X		X (Q8 weeks)	X		
Mandatory PK sampling (all newly enrolled patients) [27]		X	X	X	X	X								
Biomarker assessment (optional) [28]		X		X	at time of PD, if applicable								X (if no PD)	
Concomitant medications [29]	X	X										X	X	
AEs / SAEs [30]	X	X										X	X	
Vemurafenib administration		X												
Follow-up for disease progression														X
Survival status [5]													X	X
Next anticancer therapy														X

	Screening Period [1]	Treatment Period [2]										End of Treatment Visit [3]	Safety Follow-Up Visit [4]	Survival Follow-Up [5]
Cycle		1		2	3	4	5	6	7	8	9 onwards		Post treatment d/c	Every 3 months
Day	–28 to –1	1	15	29	57	85	113	141	169	197	Every 28 Days		28 (± 5) days	
Allowed Visit Window (days)			± 2	± 5										
Anal and pelvic exam [31]	X												X	

Notes Day 1 = first dose of study drug (vemurafenib)

1. Apart from obtaining written informed consent, no screening procedure may be performed before the patient has been confirmed to be positive for the BRAF V600 mutation (see footnote 7).
2. Visits during the Treatment Period are to be completed on Day 1, Day 15, Day 29 and every 28 days thereafter until study drug discontinuation. A window of ± 2 days will apply for Cycle 1 / Day 15, and ± 5 days is allowed for each visit from Cycle 2 onwards (28-day cycle).
3. The End of Treatment Visit will be performed when the patient discontinues vemurafenib regardless of when it occurs.
4. The Safety Follow-Up Visit will be performed after 28 (± 5) days from discontinuation of vemurafenib.
5. The Survival Follow-Up period will last for a minimum of 12 months after the last patient has been enrolled or until all patients have died, withdrawn consent or are lost to follow-up (whichever occurs first). The head and neck exam and chest CT for evaluation of SCC, and the dermatology evaluation should be done either 6 months following study drug discontinuation or prior to the initiation of another anti-neoplastic therapy, whichever occurs first.
6. Informed consent must be obtained prior to performing any study procedure including Screening assessments. The date of signature on the informed consent form signifies the beginning of the 28-day Screening Period.
7. Patients with BRAF V600 mutation-positive cancers will be identified through mutation analysis assays, as routinely performed at each participating site. BRAF V600 mutation and test used for the detection of the BRAF mutation assay will be recorded in the eCRFs. Note: for the patient to be eligible, they must be able to provide a tumour sample (preferably tissue; alternatively DNA) for retrospective confirmation of the BRAF mutation by a central laboratory. This tumour sample (formalin-fixed paraffin-embedded tumour tissue [FFPET] or 3-5 serially cut unstained 5-µm sections from one FFPET block) should preferably be from the original specimen used to detect the BRAF mutation. The original tumour block will be returned to the site. If archival samples are not available, the patient should be biopsied in order to obtain adequate tissue. Exceptions may be considered upon discussion with the Sponsor (e.g. ≥ 250 ng of DNA may be sent instead of tissue samples).
8. Includes the evaluation of the head, eyes, ears, nose, and throat (HEENT); cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal and neurological systems examination; and height (cm) and weight (kg). Height will only be measured during screening.
9. Includes blood pressure, heart rate, temperature and respiratory rate.

10. Includes heart rate, PR interval, QRS duration, QT and QTc intervals and ECG findings.
11. Includes haemoglobin, haematocrit, platelet count, white blood cell count (WBC) and absolute neutrophil count (ANC)
12. Haematology and biochemistry assessments do not need to be repeated on Day 1 if performed within 7 days of first vemurafenib administration. NB: if it is necessary to repeat these blood tests, the results must be known before the patient receives first dose of vemurafenib to ensure that the inclusion and exclusion criteria related to these tests are met.
13. Includes amylase, lipase, glucose, blood urea nitrogen [BUN], creatinine or creatinine clearance, sodium, potassium, calcium, magnesium, bicarbonate ([if routinely performed on venous blood samples],), total bilirubin with fractionation into direct and indirect (if total bilirubin elevated during the study; if one component is available, the other component can be calculated), alkaline phosphatase, AST ([SGOT]], ALT ([SGPT]],
14. Serum pregnancy test to be performed within 7 days prior to first vemurafenib administration for women with childbearing potential.
15. Includes for solid tumour patients only: CT/MRI of the chest, abdomen and pelvis [C/A/P]). The same imaging technique (CT or MRI) should be used for these patients throughout the study. Exception: for patients with a confirmed primary brain tumour, the CT/MRI of C/A/P may be omitted. In addition, CT/MRI of the brain may also be performed as per standard of care. For all patients in Cohort 1, the CT scans during the patient's last therapy prior to this study, as well as CT scans made during this study, will be collected and reviewed retrospectively by an Independent Review Committee (IRC). The collection of scans and IRC review may also be considered for confirmation of efficacy assessments for other cohorts where clinically meaningful efficacy is demonstrated with Investigator assessment.
16. Serum protein electrophoresis (SPEP), Urine protein electrophoresis (UPEP), Serum free light chains, 24 hour urine proteins, Bone marrow for histology, cytogenetics and FISH, and flow cytometry with or without biopsy, Beta 2 microglobulin, albumin and lactate dehydrogenase (LDH). A skeletal survey is done during Screening only; thereafter it should be done as per routine clinical practice.
17. Bone marrow assessment only to be done to confirm complete remission after two consecutive immunofluorescence analyses are negative.
18. Performed by a dermatologist. For patients who develop any suspicious new skin lesion during treatment with vemurafenib. Further confirmation by a designated central pathology laboratory. Only required at the End of Treatment Visit if not performed in the previous 12 weeks. Should be done at Safety Follow-up Visit at 28 days (± 5 days) and at 6 months following study drug discontinuation or prior to the initiation of another anti-neoplastic therapy (whichever occurs first).
19. Performed by the treating physician as part of the evaluation for SCC. Should also be done at Safety Follow-up Visit at 28 days (± 5 days) and at 6 months following study drug discontinuation or prior to the initiation of another anti-neoplastic therapy (whichever occurs first).
20. CT of the chest for the evaluation of non-cutaneous SCC (for all patients, solid tumours and MM). For patients with solid tumours, the routinely scheduled radiographic assessment for tumour burden may be used (if available) as the chest CT for the evaluation of non-cutaneous SCC while the patient is taking vemurafenib.
21. Must be performed at this visit and 6 months following study drug discontinuation or prior to the initiation of another anti-neoplastic therapy (whichever occurs first)
22. Patients will keep a diary to record ONLY those occasions when a vemurafenib dose was missed (morning or evening, each day of treatment). The patient will bring this diary with him/her to each study visit to allow missed doses to be recorded by the Investigator.
23. See Appendix 9.
24. See Appendix 9 for further details. Bone scans to be performed every 8 weeks or as per institution standard of care, but at a minimum every 16 weeks and at the End of Treatment Visit.
25. See Appendix 10 for further details.
26. 26.Baseline tumour assessments must include CT/MRI of the chest, abdomen and pelvis (C/A/P) and any additional assessment as clinically relevant as described in Appendix 10 to define baseline extent of disease (brain MRI, cardiac MRI/echo, bone scan, ^{18}F-FDG PET). For patients with baseline measurable disease according to RECIST v1.1, the following

tumour assessments will consist of the same method(s) used at baseline to determine measurable disease (CT/MRI of [C/A/P], brain MRI, cardiac MRI). For all other patients the following tumour assessments will consist of the same method/s used at baseline that have defined the area involved by the disease (brain MRI, cardiac MRI/echo, bone scan, ^{18}F-FDG PET, CT chest/abdomen/pelvis) as described in Appendix 10.

27. For all newly enrolled patients in all cohorts, mandatory blood samples will be taken during Cycle 1 (Day 1 and Day 15) and Cycles 2 - 4 (Day 1) for PK analysis. Samples will be taken pre-dose and 2-4 hours post-dose of the morning dose on the corresponding days (see Table 9). For the day of the PK assessment, patients should be instructed not to take their morning dose, and to bring their study medication with them to their clinic visit. For all PK samples, the date and time of the last dose of vemurafenib should be recorded, along with the actual time of the PK blood draw. Approximately 2 mL of blood will be collected at each time point. The procedures for the collection, handling and shipping of samples for PK can be found in the study's Laboratory Manual.
28. Blood samples for exploratory biomarkers are optional, and can be collected from any newly enrolled patient in any cohort. All samples will be taken pre-dose of the morning dose on the corresponding days (see Table 10). In addition to the samples collected at Cycles 1 and 2, a sample will be collected at the Safety Follow-up Visit or at the time of disease progression (whichever occurs first). The procedures for the collection, handling and shipping of biomarker samples can be found in the study's Laboratory Manual.
29. All concomitant medications during the study started within 14 days prior to the screening visit and up to the Safety Follow-up Visit must be recorded.
30. During screening AEs are not recorded in the eCRF unless they are SAEs which are related to protocol-mandated procedures. ALL AEs (including SAEs) must be recorded from the time of first vemurafenib administration. After the last dose of vemurafenib any new, AEs should be reported up to 28 days after last dose. The Investigator is not required to actively monitor patients for adverse events after the end of the adverse event reporting period (defined as 28 days after the last dose of study drug). However the Sponsor should be notified if the Investigator becomes aware of any SAE that occurs after the end of the adverse event reporting period, if the event is believed to be related to prior study drug treatment. After the study site has closed, the Investigator should report adverse reactions as mandated in the protocol directly to the Local Drug Safety Affiliate.
31. Pelvic examinations for women (with special attention to cervix) and anal examinations for all patients will be performed at screening and at the Safety Follow-up Visit for evaluation of SCC. The pelvic examination should include a complete external and internal examination (internal examination of uterine cervix may include a Pap smear, which would be a decision of the investigator). The anal examination should include external examination, digital anorectal examination and anoscopy or proctoscopy. However, if in opinion of the investigator the presence of "abnormal lesions including SCC" can be excluded by the external inspection and the manual examination, this is acceptable. However, if the presence of a lesion is suspected, an anoscopy or proctoscopy are recommended.

Table 4b:
Schedule of Assessments for Cohort 3b (Colorectal Cohort with Vemurafenib and Cetuximab Study Treatment)

	Screening Period [1]	Treatment Period [2]													End of Treatment Visit [3]	Safety Follow-Up Visit [4]	Survival Follow-Up [5]
Cycle (C)		1					2				3 onwards						
Study Day	–28 to –1	1	2	8	15	22	29	36	43	50						Post treatment d/c	Every 3 months
Cycle Day		1	2	8	15	22	1	8	15	22	1	8	15	22		28 (± 5) days	
Allowed Visit Window (days)				± 1													
Informed consent [6]	X																
Documentation of BRAF V600 mutation via local test; sample taken for retrospective confirmation [7]	X																
Medical history and demographics	X																
Physical examination [8]	X	X		X	X	X	X	X	X	X	X		X		X		
Vital signs [9]	X	X		X	X	X	X	X	X	X	X		X		X		
12-lead ECG [10]	X						X				X + C4 and C5 (then Q12 weeks)				X	X	

	Screening Period [1]	Treatment Period [2]													End of Treatment Visit [3]	Safety Follow-Up Visit [4]	Survival Follow-Up [5]
Cycle (C)		**1**					**2**				**3 onwards**						
Study Day	**–28 to –1**	**1**	**2**	**8**	**15**	**22**	**29**	**36**	**43**	**50**						**Post treatment d/c**	**Every 3 months**
Cycle Day		**1**	**2**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**		**28 (± 5) days**	
Allowed Visit Window (days)				**± 1**													
ECOG performance status	X	X		X	X	X	X	X	X	X	X		X		X		
Haematology [11]	X	X[12]		X	X	X	X	X	X	X	X		X		X		
Biochemistry [13]	X	X[12]		X	X	X	X	X	X	X	X		X		X		
Serum pregnancy test [14]	X																
Tumour assessments (CT/MRI) [15]	X										X (Q8 weeks)				X		
Dermatology evaluation [16]	X						X				C5 (then Q12 weeks)				X	X[17]	At 6 months
Head and neck assessment for SCC [18]	X										C4 (then Q12 weeks)				X	X[17]	At 6 months
Chest CT for evaluation of SCC [19]	X										C7 (then Q6 months)					X[17]	At 6 months

	Screening Period [1]	Treatment Period [2]													End of Treatment Visit [3]	Safety Follow-Up Visit [4]	Survival Follow-Up [5]
Cycle (C)		**1**					**2**				**3 onwards**						
Study Day	**–28 to –1**	**1**	**2**	**8**	**15**	**22**	**29**	**36**	**43**	**50**						**Post treatment d/c**	**Every 3 months**
Cycle Day		**1**	**2**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**		**28 (± 5) days**	
Allowed Visit Window (days)				**± 1**													
Vemurafenib dispensation (**Part 1**)			X[20]				X		X		X (Q4 weeks)						
Vemurafenib dispensation (**Part 2**)		X					X		X		X (Q4 weeks)						
Vemurafenib accountability							X		X		X (Q4 weeks)				X		
Vemurafenib Dosing Exception Diary [21]				X	X	X	X	X	X	X	X (Q4 weeks)				X		
DLTs [22]				X	X	X	X										
Concomitant medications [23]	X		X												X	X	
AEs / SAEs [24]	X		X												X	X	
Cetuximab administration		X		X	X	X	X	X	X	X	X	X	X	X			

	Screening Period [1]	Treatment Period [2]													End of Treatment Visit [3]	Safety Follow-Up Visit [4]	Survival Follow-Up [5]
Cycle (C)		1					2				3 onwards						
Study Day	–28 to –1	1	2	8	15	22	29	36	43	50						Post treatment d/c	Every 3 months
Cycle Day		1	2	8	15	22	1	8	15	22	1	8	15	22		28 (± 5) days	
Allowed Visit Window (days)				± 1													
Follow-up for disease progression																	X
Survival status [5]																X	X
Next anticancer therapy																	X
Anal and pelvic exam [25]	X															X	

Notes Day 1 = first dose of study drug

1. Apart from obtaining written informed consent, no screening procedure may be performed before the patient has been confirmed to be positive for the BRAF V600 mutation (see footnote 7).
2. Visits during the Treatment Period are to be completed on Day 1, Day 8, Day 15, Day 22, Day 29 and every 14 days thereafter until study drug discontinuation. A visit window of ± 1 day will apply starting on Day 8 of Cycle 1 and onwards.
3. The End of Treatment Visit will be performed when the patient discontinues study medication regardless of when it occurs.
4. The Safety Follow-Up Visit will be performed after 28 (± 5) days from discontinuation of study medication
5. The Survival Follow-Up period will last for a minimum of 12 months after the last patient has been enrolled or until all patients have died, withdrawn consent or are lost to follow-up (whichever occurs first). The head and neck exam and chest CT for evaluation of SCC, and the dermatology evaluation should be done either 6 months following study drug discontinuation or prior to the initiation of another anti-neoplastic therapy, whichever occurs first.
6. Informed consent must be obtained prior to performing any study procedure including Screening assessments. The date of signature on the informed consent form signifies the beginning of the 28-day Screening Period.

7. Patients with BRAF V600 mutation-positive cancers will be identified through mutation analysis assays, as routinely performed at each participating site. BRAF V600 mutation and test used for the detection of the BRAF mutation assay will be recorded in the eCRFs. Note: for the patient to be eligible, they must be able to provide a tumour sample (preferably tissue; alternatively DNA) for retrospective confirmation of the BRAF mutation by a central laboratory. This tumour sample (formalin-fixed paraffin-embedded tumour tissue [FFPET] or 3-5 serially cut unstained 5-µm sections from one FFPET block) should preferably be from the original specimen used to detect the BRAF mutation. The original tumour block will be returned to the site. If archival samples are not available, the patient should be biopsied in order to obtain adequate tissue. Exceptions may be considered upon discussion with the Sponsor (e.g. ≥ 250 ng of DNA may be sent instead of tissue samples).
8. Includes the evaluation of the head, eyes, ears, nose, and throat (HEENT); cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal and neurological systems examination; and height (cm) and weight (kg). Height will only be measured during screening.
9. Includes blood pressure, heart rate, temperature and respiratory rate.
10. Includes heart rate, PR interval, QRS duration, QT and QTc intervals and ECG findings.
11. Includes haemoglobin, haematocrit, platelet count, white blood cell count (WBC) and absolute neutrophil count (ANC)
12. Haematology and biochemistry assessments must be done on Day 1, prior to cetuximab administration.
13. Includes amylase, lipase, glucose, blood urea nitrogen [BUN], creatinine or creatinine clearance, sodium, potassium, calcium, magnesium, bicarbonate ([if routinely performed on venous blood samples],), total bilirubin with fractionation into direct and indirect (if total bilirubin elevated during the study; if one component is available, the other component can be calculated), alkaline phosphatase, AST ([SGOT]], ALT ([SGPT]]
14. Serum pregnancy test to be performed within 7 days prior to first vemurafenib administration for women with childbearing potential.
15. CT/MRI of the chest, abdomen and pelvis [C/A/P]). The same imaging technique (CT or MRI) should be used for these patients throughout the study. In addition, CT/MRI of the brain may also be performed as per standard of care.
16. Performed by a dermatologist. For patients who develop any suspicious new skin lesion during treatment with study medication. Further confirmation by a designated central pathology laboratory. Only required at the End of Treatment Visit if not performed in the previous 12 weeks. Should be done at Safety Follow-up Visit at 28 days (± 5 days) and at 6 months following study drug discontinuation or prior to the initiation of another anti-neoplastic therapy (whichever occurs first).
17. Must be performed at this visit and 6 months following study drug discontinuation or prior to the initiation of another anti-neoplastic therapy (whichever occurs first).
18. Performed by the treating physician as part of the evaluation for SCC. Should be done at Safety Follow-up Visit at 28 days (± 5 days) and at 6 months following study drug discontinuation or prior to the initiation of another anti-neoplastic therapy (whichever occurs first).
19. CT of the chest for the evaluation of non-cutaneous SCC. The routinely scheduled radiographic assessment for tumour burden may be used (if available) as the chest CT for the evaluation of non-cutaneous SCC while the patient is taking study medication.
20. For patients in Part I of Cohort 3b, vemurafenib will start on Day 2 of Cycle 1 (administered while in hospital).
21. Patients will keep a diary to record ONLY those occasions when a vemurafenib dose was missed (morning or evening, each day of treatment). The patient will bring this diary with him/her to each study visit to allow missed doses to be recorded by the Investigator.
22. Only for patients enrolled in the Part 1 of Cohort 3b (the dose-escalation part of the study)
23. All concomitant medications during the study started within 14 days prior to the screening visit and up to the Safety Follow-up Visit must be recorded.
24. During screening AEs are not recorded in the eCRF unless they are SAEs which are related to protocol-mandated procedures. ALL AEs (including SAEs) must be recorded from the time of first study drug administration. After the last dose of study medication any new AEs should be reported up to 28 days after last dose. The Investigator is not required to actively

monitor patients for adverse events after the end of the adverse event reporting period (defined as 28 days after the last dose of study drug). However the Sponsor should be notified if the Investigator becomes aware of any SAE that occurs after the end of the adverse event reporting period, if the event is believed to be related to prior study drug treatment. After the study site has closed, the Investigator should report adverse reactions as mandated in the protocol directly to the Local Drug Safety Affiliate.

25. Pelvic examinations for women (with special attention to cervix) and anal examinations for all patients will be performed at screening and at the Safety Follow-up Visit for evaluation of SCC. The pelvic examination should include a complete external and internal examination (internal examination of uterine cervix may include a Pap smear, which would be a decision of the investigator). The anal examination should include external examination, digital anorectal examination and anoscopy or proctoscopy. However, if in opinion of the investigator the presence of “abnormal lesions including SCC” can be excluded by the external inspection and the manual examination, this is acceptable. However, if the presence of a lesion is suspected, an anoscopy or proctoscopy are recommended.

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GLOSSARY OF ABBREVIATIONS

^{18}F-FDG PET	fluorodeoxyglucose positron emission tomography
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALP	alkaline phosphatase
ALT (SGPT)	alanine aminotransferase
ANC	absolute neutrophil count
AST (SGOT)	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
b.i.d.	twice daily
BCC	basal cell carcinoma
BOR	best overall response
BRAF	v-raf murine sarcoma viral oncogene homolog B1
BUN	blood urea nitrogen
°C	degrees Celsius
C/A/P	chest, abdomen and pelvis
CHF	congestive heart failure
CI	confidence interval
C_{max}	maximum plasma concentration
CMML	chronic myelomonocytic leukaemia
CR	complete response(s)
CRC	colorectal cancer
CrCl	creatinine clearance
CRF	Case Report Form(s)
CMR	complete metabolic response
CT	computer tomography
cSCC	cutaneous squamous cell carcinoma
cm	centimetres
CNS	central nervous system
CoDx	Companion Diagnostic
COSMIC	Catalogue of Somatic Mutations in Cancer
CRP	C-reactive protein
CRPC	castrate resistant prostate cancer
dL	decilitre
DLT	dose-limiting toxicity
DOR	duration of response

DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms syndrome
ECD	Erdheim-Chester disease
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
EGFR	epidermal growth factor receptor
ERK	extracellular signal-regulated kinase
EMA	European Medicines Agency
ER	oestrogen receptor
ESF	eligibility screening form
EU	European Union
FDA	(United States) Food and Drug Administration
FFPET	formalin-fixed paraffin-embedded tumour tissue
FLX	free light chain
G	gram
G-CSF	granulocyte colony-stimulating factor
GCP	Good Clinical Practice
GDP	guanosine diphosphate
GGT	γ-glutamyltransferase
GMP	Good Manufacturing Practice
GTP	guanosine triphosphate
H_0	null hypothesis
H_1	alternative hypothesis
HEENT	head, eyes, ears, nose and throat
hERG	human ether-à-go-go related gene
HR	heart rate
HPV	human papillomavirus
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IRC	Independent Review Committee

ITT	intent to treat
IV	intravenous
IWC	International Workshop Criteria
IxRS	Interactive Voice/Web Response System
KA	Keratoacanthoma
L	Litre
LCH	Langerhans cell histiocytosis
LFT	liver function test
LHRH	luteinizing hormone-releasing hormone
MAP	mitogen-activated protein
MBP	micro-precipitated bulk powder
MedDRA	Medical Dictionary for Regulatory Activities
MEK1	mitogen-activated protein kinase 1
mg	milligram
ml	millilitre
MGUS	monoclonal gammopathy of undetermined significance
MM	multiple myeloma
MRI	magnetic resonance imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NCI-CTC	National Cancer Institute-Common Toxicity Criteria
NCI-CTCAE	National Cancer Institute-Common Toxicity Criteria for Adverse Events
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
OR	objective response(s)
ORR	objective response rate
OS	overall survival
PCWG2	Prostate Cancer Clinical Trials Working Group
PD	progressive disease
PERCIST	Positron Emission Response Criteria in Solid Tumors
PFS	progression-free survival
plTTP	previous line of treatment's TTP
PMD	progressive metabolic disease
PMR	partial metabolic response
PS	Performance Status
PSA	prostate specific antigens

PK	pharmacokinetic
p.o.	*per* os (oral administration)
PP	per protocol
PR	partial response(s)
PRC	PET Response Criteria
RNA	ribonucleic acid
RR	response rate
ROI	Region of interest
QTc	corrected QT interval
RAS	RAt Sarcoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SCC	squamous cell carcinoma
sCR	stringent complete response
SD	stable disease or standard deviation
SMD	stable metabolic disease
SOC	Systems Organ Class
SP	safety population
SPC	Summary of Product Characteristics
SPF	Sun Protection Factor
siRNA	silencing RNA
SPEP	serum protein electrophoresis
SUL	standardized uptake value normalized to lean body mass
SUV	standardized uptake value
$T_{1/2}$	half-life
T_{MAX}	time to maximum plasma concentration
TLG	total lesion glycolysis
TTP	time to tumour progression
UCI	upper confidence interval
ULN	upper limit of normal
UPEP	urine protein electrophoresis
US	United States
VGPR	very good partial response
WBC	white blood cell
WHO	World Health Organization

PART I: STUDY DESIGN AND CONDUCT

1. BACKGROUND AND RATIONALE

1.1 THE RAS-MAP-KINASE SIGNALLING PATHWAY

The RAS-MAP-kinase signalling pathway is a highly conserved enzymatic pathway that transduces extracellular signals into long-term changes in intracellular biochemistry and gene expression (1). Because the pathway, in its different forms, is critically involved in cell-cycle control and development, mutations in genes that affect the system—in particular, in genes that encode the RAS-MAP-kinase signalling proteins themselves, their intracellular regulators, or their cognate membrane receptors—are among the most common mutations found in cancer cells (see below). Consequently, the RAS-MAP-kinase pathway has been the subject of intense pharmacologic analysis, as any agent that specifically targets this pathway could have important clinical utility in a variety of cancers.

The core of the RAS-MAP-kinase signal transduction system consists of a membrane-associated RAS protein and 3 serine/threonine protein kinases.

1.1.1 RAS

The RAS proteins belong to the large RAS superfamily of monomeric GTPases (1). Like other GTP-binding proteins, RAS functions as a switch, cycling between two distinct conformational states: active when GTP is bound and inactive when GDP is bound. Two classes of signalling proteins regulate RAS activity by influencing its transition between active and inactive states. Guanine nucleotide exchange factors (GEFs) promote the exchange of bound nucleotide by stimulating the dissociation of GDP and the subsequent uptake of GTP from the cytosol, thereby activating RAS. GTPase-activating proteins (GAPs) increase the rate of hydrolysis of bound GTP by RAS, thereby inactivating RAS.

Three RAS proteins (H-RAS, K-RAS and N-RAS) are implicated in human cancer. Mutations in genes encoding these three proteins can produce hyperactive variants that are resistant to GAP-mediated GTPase stimulation. These mutational alterations lock the proteins permanently into their GTP-bound active states, which may ultimately promote dysregulated growth and cancer. Activated RAS mutations are particularly common in cancer. Mutations in K-RAS, for instance, have been identified in 58% of pancreatic, 34% of large intestine, 29% of biliary tract, 20% of small intestine, 17% of lung, 15% of endometrial, and 14% of ovarian cancer samples sequenced to date (2, 3).

1.1.2 MAP-Kinase

Once activated (either by binding GTP in normal cells or as a result of mutational alterations in cancer cells), RAS activates a downstream serine/threonine phosphorylation cascade composed of 3 mitogen-activated protein (MAP) kinases (1). The pathway activated by RAS begins with a MAP-kinase-kinase-kinase called RAF, which activates the MAP-kinase-kinase MEK. MEK, in turn, activates a MAP-kinase called ERK.

The MAP-kinase ERK then relays the signal further downstream by phosphorylating various proteins in the cell, including gene regulatory proteins and other protein kinases. Among the genes activated by this pathway are those required for cell proliferation, such as the genes

encoding G1 cyclins. Consequently, constitutive activation of the phosphorylation cascade can result in inappropriate mitotic drive, resulting in the unregulated growth that characterizes cancer cells.

1.2 ONCOGENIC BRAF KINASE MUTATIONS IN VARIOUS CANCERS

The MAP-kinase-kinase-kinase RAF acts at the intersection between the initial part of the signalling pathway, comprised of a receptor tyrosine kinase and RAS, and the subsequent phosphorylation cascade that transduces the extracellular signal to the nucleus. To date, mutations in three different RAF proteins (ARAF, BRAF, and CRAF) have been implicated in human cancer (2, 3). Among these, mutations in BRAF are the most common, particularly in melanoma, where BRAF mutations have been identified in 67% of primary melanoma tumours and 80% of melanoma short-term cultures (4). BRAF mutations have also been identified in 38% of thyroid, 12% of large intestine, 12% of genital tract, 11% of ovarian, 11% of eye, and 10% of biliary tract cancer cell line isolates sequenced to date and described in the Catalogue of Somatic Mutations in Cancer (COSMIC) database (2, 3).

1.2.1 Melanoma

Activating mutations in BRAF have been identified at high frequency in melanoma primary tumours, occurring in up to 67% of sequenced melanoma samples (4). These mutations typically fall within the kinase domain of the protein, with a single substitution (V600E) accounting for 90% of the sequenced mutants. Mutated BRAF proteins isolated from these tumours have elevated kinase activity and have the capacity on their own to transform NIH3T3 cells. Moreover, depletion of mRNA for oncogenic BRAF via silencing RNAs has been shown to induce a variety of phenotypic changes in cultured melanoma cells, including lower proliferation rates, reduced anchorage-independent growth, and apoptosis (5, 6). Other uncommon BRAF variants, including V600K, V600R and V600D, have been observed, and nonclinical data indicate that these variant mutations also result in constitutive activation of the BRAF kinase (7).

Recently, it has been demonstrated that therapeutic inhibition of the activating BRAF V600E mutation with vemurafenib, a new selective BRAF kinase inhibitor, has significant anticancer activity in melanoma patients. These results will be described in more detail below (Section 1.3).

1.2.2 Colorectal Cancer

Colorectal cancer (CRC) develops slowly over several years and progresses through cytologically distinct benign and malignant stages of growth, ranging from single crypt lesions through adenoma to, finally, malignant carcinoma with the potential for invasion and metastasis (8-10). This progression occurs in parallel with widespread genomic instability that leads to successive accumulation of mutations in genes controlling epithelial cell growth and differentiation (11).

Among these multiple genomic alterations, activating mutations in BRAF were found in published studies to occur in 5% to 15% of CRC cases, 80% of which induced a V600E transition in the kinase domain (12-14). In the COSMIC database, BRAF mutations were observed in 13% (1357 of 10,828 unique samples) of cancers originating in the colon and rectum, 99% of which were the V600E transition (2, 3). The most common mutations in CRC occur in three proteins, the p53 tumour suppressor (52% of sequenced samples), K-Ras (34%), and APC (29%).

An increasing number of studies have shown that the presence of activating BRAF mutations in CRC tumours is associated with significantly shorter OS (15-21). Thus, in one recent study (16),

the median OS was 8.6 months among CRC patients with mutated BRAF tumours compared with 20.8 months among those with wild type BRAF tumours (P<0.0010). The impact of BRAF mutations on PFS, however, appears to be more complex, with half of the studies showing a significant decrease in PFS (19-21), and half showing no effect (16-18).

In addition to the effects on OS and, possibly, PFS, another clinically important feature of BRAF mutations is that patients whose tumours bear activating BRAF mutations do not experience significant benefit from either cetuximab or panitumumab treatment, therapeutic antibodies directed against EGFR that are used in CRC therapy (22). This is consistent with the fact that BRAF activity functions downstream of the receptor and, hence, activated BRAF mutations can suppress the growth inhibition normally induced by the therapeutic antibody.

A phase I study assessed the efficacy and safety of the selective BRAF kinase inhibitor vemurafenib in 21 CRC patients harbouring BRAF V600E mutations (23). Among 19 patients who were evaluable for response, 1 had a confirmed PR and 4 had minor responses (≥ 10% shrinkage). Five patients showed a mixed response pattern (i.e., with both regressing and progressing lesions). Although the observed activity in this small CRC study was less than in melanoma, it is important to note that all of the patients in the trial had received at least 3 lines of prior therapy and the pharmacokinetic (PK) distribution of study drug appeared to be 20% lower than expected. Despite these caveats, though, anticancer activity in CRC was observed. This further encourages exploration of the efficacy of vemurafenib in CRC tumours harbouring activated BRAF V600 mutations.

Prahallad et al (72) have investigated the mechanisms of the limited therapeutic effect observed with vemurafenib in BRAF V600 positive CRC patients. BRAF inhibition causes a feedback activation of the epidermal growth factor receptor (EGFR) which is responsible for the continued proliferation in the presence of BRAF inhibition. Expression of EGFR is low in melanoma cells and therefore melanoma cells are not subject to this feedback activation. Interestingly, ectopic expression of EGFR in melanoma cells caused resistance to vemurafenib. When vemurafenib was combined with an EGFR inhibitor (cetuximab or gefitinib or erlotinib) in mutant CRC, there was a strong synergic effect both *in vitro* and *in vivo*. Immunodeficient mice xenografted with human WiDr and VACO432 CRC tumours received vehicle, cetuximab or erlotinib, PLX4720 (highly related to vemurafenib but formulated for *in vitro* use), or the combination of EGFR inhibitor plus PLX4720 after development of tumours. EGFR inhibitor alone and PLX4720 alone resulted in minimal tumour growth inhibition. In contrast, the combination of EGFR inhibitor plus BRAF inhibitor yielded a potent growth inhibition of WiDR and VACO432 CRC tumours.

These data provide a strong rationale for a clinical trial investigating the combination of vemurafenib and cetuximab in BRAF-mutated colorectal cancer patients, who have a poor clinical outcome and for whom there are no effective treatment options after failure of standard chemotherapy.

1.2.3 NSCLC

BRAF mutations have been detected in patients with non–small-cell lung cancer (NSCLC), although at a significantly lower frequency than in melanoma patients (4, 24). In the COSMIC database, for instance, BRAF mutations were observed in 1% of NSCLCs (7 of 1372 unique samples) (2, 3). By comparison, mutations in p53, epidermal growth factor receptor, K-Ras kinase, and cyclin-dependent kinase inhibitor 2A occurred at frequencies of 26%, 22%, 15%, and 14%, respectively. Intriguingly, of the 7 BRAF mutations identified in NSCLCs, only one occurred

in amino acid 600 (V600E transition); the remaining 6 occurred in amino acids 466 (n=2), 469 (n=2), and 597 (n=2). The mutations at 466 and 469 are thought to alter residues important in AKT-mediated BRAF phosphorylation, which has led to the speculation that BRAF mutations may be qualitatively different in NSCLCs and melanomas, specifically in that they may affect AKT, rather than RAS, signalling in the former (24).

However, a more recent study, which does not appear to have been included in the COSMIC database yet, suggests that the V600E mutation may occur more frequently and may have important clinical relevance (25). In this study, 1046 surgically resected NSCLCs, comprising 739 adenocarcinomas and 307 squamous cell carcinomas, were subjected to sequencing analysis. BRAF mutations were found to be present in 36 adenocarcinomas (4.9%) and one SCC (0.3%). Twenty-one of the mutations (56.8%) were V600E, and 16 (43.2%) were non-V600E. Importantly, V600E-mutated tumours showed an aggressive histotype characterized by micropapillary features in 80% of patients and were significantly associated with shorter disease-free survival (15.2 vs. 52.1 months; p<0.001) and OS (29.3 vs. 72.4 months; p<0.001). By contrast, all non-V600E mutations were associated with neither clinicopathologic parameters nor prognosis. Thus, BRAF V600E mutations in human lung cancers may identify a subset of tumours sensitive to targeted therapy.

1.2.4 Breast Cancer

According to the COSMIC database (2, 3), the most common mutations identified to date in breast cancer cells occur in three proteins: the catalytic subunit of phosphoinositide-3-kinase (26% of sequenced samples), the p53 tumour suppressor (23%), and cadherin-1 (16%).

In the same database, mutations in BRAF were found in 2% of breast cancer cell lines (14 of 599 unique samples), of which 10 contained the BRAF V600E mutation. These values are similar to those observed in other published studies, although BRAF mutations were observed to occur at a frequency as high as 10% in some series. In one study on 31 breast cancer cell lines, for instance, 3 carried mutations in BRAF (26). A second study found BRAF mutations in 4 of 36 breast cancer cell lines (2 of the 4 carried V600E mutations) (27). A third study that used high-resolution DNA melting to identify somatic mutations identified one mutation in exon 15 of the BRAF gene out of 60 samples (28), whereas another study found no BRAF mutations in 12 sequenced breast cancer cell lines (29). Whether BRAF mutations (and mutations in other RAS-MAP kinase pathway genes) may be found in combination with phosphoinositide-3-kinase pathway mutations remains controversial (27, 30).

Intriguingly, recent evidence suggests that BRAF mutations may be associated with distinct clinical breast cancer pathologies. In an extensive molecular characterization of 41 human breast cancer cell lines (31), 146 oncogenic mutations were identified among 27 well-known cancer genes (3.6 mutations per cell line). Mutations in genes from the p53, RB and PI3K tumour suppressor pathways were widespread among all breast cancer cell lines. However, two gene mutation profiles specifically associated with luminal-type and basal-type breast cancer cell lines. The luminal mutation profile involved E-cadherin and MAP2K4 gene mutations and amplifications of Cyclin D1, ERBB2 and HDM2. The basal mutation profile involved BRCA1, RB1, RAS and BRAF gene mutations and deletions of p16 and p14ARF. The authors suggested that these subtype-specific gene mutation profiles may constitute a genetic basis for the heterogeneity observed among human breast cancers. To date, though, the effect of activated BRAF alleles on outcomes and patient management in breast cancer patients has not been examined.

1.2.5 Ovarian Cancer

Ovarian carcinomas are a heterogeneous group of neoplasms, but are usually classified into 4 major histopathologic subtypes: serous, endometrioid, mucinous, or clear cell (32). Each of the 4 types appears to be characterized by distinct genetic abnormalities. Of these, the low-grade serous carcinomas characteristically have mutations in KRAS or BRAF, which are critical to tumour growth (33, 34). In the COSMIC database (2, 3), 17 (39%) of 44 unique samples of serous micropapillary carcinoma had BRAF mutations, all of which were the V600E allele. BRAF mutations are much rarer in high-grade serous carcinomas (35, 36) and in other histopathological subtypes of ovarian cancer (32).

These preceding data have led to the hypothesis that two separate and distinct pathways lead to low-grade vs. high-grade serous carcinomas in ovarian cancer. Low-grade carcinomas are thought to develop from serous borderline tumours and progress in a stepwise fashion. They are slow-growing, indolent tumours that have a relatively good prognosis compared with high-grade carcinomas. Molecular genetic analysis has shown that serous borderline tumours and low-grade serous carcinomas typically display sequence mutations in KRAS or BRAF, but with infrequent mutations in TP53 (35, 36). By contrast, high-grade serous carcinomas often present in advanced stages (stages III and IV) and rarely harbour mutations in KRAS or BRAF. Instead, > 75% of these high-grade tumours, which grow rapidly and are highly aggressive, harbour TP53 mutations (37-41).

From the preceding considerations, ovarian cancer patients with low-grade serous carcinomas may be particularly attractive candidates for treatment with the specific activated BRAF kinase inhibitor vemurafenib. However, despite the fact that activated BRAF mutations appear to be found primarily in low-grade serous carcinoma (35, 36), BRAF mutations have been found at a frequency of 4% in higher grade serous carcinomas, where their presence can augment the activity of the MEK inhibitor CI-1040 (33). Furthermore, poor survival has been shown to associate with a specific single-nucleotide polymorphism in BRAF in patients with invasive epithelial ovarian cancer (42), suggesting a potential role for BRAF kinase in higher grade disease. Finally, borderline evidence of an association between single-nucleotide polymorphisms in BRAF and susceptibility to mucionous ovarian cancer has also been observed (43). To date, however, the effect of activated BRAF alleles on clinicopathologic feature, outcomes, and patient management in ovarian cancer patients has yet to be fully examined.

1.2.6 Multiple Myeloma

Multiple myeloma (MM) is a clonal late B-cell disorder in which malignant plasma cells expand and accumulate in the bone marrow, leading to cytopenias, bone resorption, and the production of the monoclonal protein (44). The disease appears to evolve heterogeneously in different patients. In some with new diagnosis MM, the disease may exhibit a slow progressive evolution from monoclonal gammopathy of undetermined significance (MGUS) (for example, evolving anaemia over several months), whereas in others it may be associated with features of high clonal aggressiveness (for example, plasma cell leukaemia or extramedullary plasmacytomas) (45, 46).

Consistent with the primary function of plasma cells, i.e., immunoglobulin gene rearrangements, many of the causative genetic changes in MM arise as a result of aberrant chromosomal translocations, deletions, and other abnormalities (45, 46). Nonetheless, point mutations in RAS mutations are also observed, consistent with an important role for the RAS-MAP-kinase pathway, as well. The prevalence of activating N- or K-RAS mutations is about 30 to 40% in newly

diagnosed MM tumours, with only a small increase occurring during tumour progression (47, 48). Activating BRAF mutations also occur in MM, but at apparently lower frequency (49). In the COSMIC database, 4 (2%) of 180 unique MM samples contained BRAF mutations, of which 3 contained the V600E allele (2, 3). Similarly, among 38 tumour genomes subjected to massive parallel sequencing, 4% contained activating BRAF mutations (50).

Although no studies have been published on BRAF inhibition in MM patients, it is intriguing to note that MEK inhibition was cytotoxic for the majority of tumour cells tested from patients with relapsed and refractory MM (84%), regardless of mutational status of RAS or BRAF genes (51). However, the effect of activated BRAF alleles on clinicopathologic feature, outcomes, and patient management in MM remains unknown.

1.2.7 Cholangiocarcinoma / Cancers of the Biliary Tract

Biliary tract cancers include a spectrum of invasive adenocarcinomas encompassing both cholangiocarcinoma, i.e., cancers arising in the intrahepatic, perihilar, or distal biliary tree, and carcinoma arising from the gallbladder. The role of BRAF mutations in this genetically diverse collection of cancers remains enigmatic (52, 53). Two European collections of biliary tract cancers, including both gall bladder carcinomas and intrahepatic cholangiocarcinomas, were found to contain BRAF mutations at a frequency of approximately 20% (54-56). However, no mutations were identified in a similar collection from North America and Chile, despite the use of three methods to detect mutations (57).

Not surprisingly, given the rarity of this group of cancers, very little is also known about the association between activating BRAF mutations and the clinicopathology, patient management, and outcomes of cholangiocarcinoma and other cancers of the biliary tract. One study on the European collection did show that activating BRAF mutations were significantly more likely in cholangiocarcinomas than hepatocellular carcinomas (56), suggesting a potential specificity for the former tumour type. However, further research in this area is required.

1.3 VEMURAFENIB

1.3.1 Vemurafenib Background

Vemurafenib (also known as RO5185426, PLX4032, or RG7204) is a low molecular weight, orally available inhibitor of the activated form of the BRAF serine-threonine kinase enzyme, which is commonly found in melanoma. Vemurafenib selectively inhibits oncogenic BRAF kinase. The rationale for identifying such a compound was first provided in 2002, when the high prevalence of activating mutations in the BRAF gene was identified in a variety of cancers, including melanoma (58). The high level of selectivity of vemurafenib has been demonstrated in biochemical, cell-based, and *in vivo* assays.

In vitro biochemical and cell-based assays have confirmed a high degree of selectivity of vemurafenib for the oncogenic BRAF V600E kinase (59). The 50% inhibitory concentration (IC_{50}) of vemurafenib for V600E BRAF is 44 nM. It is equipotent against CRAF (44 nM) and 3-fold less potent against BRAF wild type (110 nM). In a panel of 58 kinases, vemurafenib had an IC_{50} <1 µM for only 1 kinase (BRK kinase) outside the BRAF family. Vemurafenib was also screened against 63 receptors in 8 different families. At 10 µM, vemurafenib showed marginal activity (20–24% inhibition) against 4 receptors and was inactive against the other 59 targets.

In several mouse xenograft models of BRAF V600E-expressing melanoma, vemurafenib treatment caused partial or complete tumour regression and improved animal survival in a dose-dependent manner (60).

In preclinical models, vemurafenib exhibited potent kinase inhibitory activity against BRAF V600K, BRAF V600D, and BRAF V600R, with IC_{50} ranging from 3 nM to 110 nM. Vemurafenib also exhibited potent inhibitory effects on the RAF/MEK signalling pathway, i.e., MEK and ERK phosphorylation and cellular proliferation (7, 60). In melanoma cell lines that expressed other BRAF mutations than V600E, such as BRAF V600K, BRAF V600D, and BRAF V600R, inhibitory activity for vemurafenib was also observed (7, 60).

Please refer to the vemurafenib Investigator's Brochure (IB) for further details on the *in vitro* and *in vivo* pharmacology.

1.3.2 Vemurafenib Clinical Development Program

Following are key clinical trials in the vemurafenib clinical development program for melanoma:

1.3.2.1 Phase I dose-finding study (PLX 06-02)

The dose of vemurafenib was established in a multicentre, phase I, dose-escalation study with a total of 55 patients, 49 of whom had a diagnosis of melanoma.

1.3.2.2 Two phase I extension cohorts

Once the recommended phase II dose of 960 mg per os (p.o.) twice daily (b.i.d.) had been identified, a cohort of 32 additional patients with metastatic melanoma and prospectively identified BRAF V600 mutations were enrolled in the extension phase of this study (61). A different cohort of 21 patients with metastatic colorectal cancer and identified BRAF V600 mutations were treated in the extension phase with the established dose of 960 mg b.i.d. (61). The primary objective of these extension cohorts was to determine clinical response rate (RR). Secondary objectives were safety and additional PK and pharmacodynamic evaluations.

1.3.2.3 Phase II single-arm study (NP22657/BRIM-2)

Study NP22657 (BRIM 2) was an open label, single-arm, multicentre phase II study in previously treated patients with metastatic melanoma harbouring the BRAF V600 mutation. In this study 132 patients were enrolled and treated with oral vemurafenib 960 mg b.i.d. The tumour BRAF mutation status was assessed by the Roche Companion Diagnostic (CoDx) cobas® 4800 BRAF V600 Test. The primary objective of this study was to evaluate the efficacy of vemurafenib using best overall response rate (BOR) as assessed by an independent review committee (RECIST, version 1.1). Secondary objectives included BOR assessed by the Investigator, duration of response, PFS, OS, safety/toxicity, effect on QT interval, quality of life using FACT-M (Version 4), validation of the Roche CoDx cobas 4800 BRAF V600 Test, and pharmacodynamic parameters.

1.3.2.4 Phase III randomized controlled study (NO25026/BRIM-3)

This randomized, open-label, multicentre, phase III study examined patients with treatment-naïve metastatic melanoma confirmed by histopathology (unresectable stage IIIC or stage IV) and with a BRAF V600 mutation by the Roche CoDx cobas 4800 BRAF V600 Test (62). Patients were randomly assigned to be treated with either vemurafenib 960 mg p.o. b.i.d. every day or intravenous dacarbazine 1000 mg/m^2 on day 1 every 3 weeks. Within this trial, OS and PFS were

defined as co-primary endpoints (NO25026 protocol version C). Major secondary study objectives included comparisons of BOR, time to response, DOR, time to treatment failure, and tolerability/safety. Further assessments of the PK profile of vemurafenib, validation of the Roche CoDx cobas 4800 BRAF V600 Test, evaluation of QoL, and additional pharmacodynamic analyses were planned. The final analysis was planned to occur after 196 deaths, and an interim analysis was planned after 50% of the projected deaths (n=98). The final analysis of PFS was to occur at the interim analysis of OS.

1.3.3 Phase I Dose-Finding and Pharmacokinetics

A total of 55 patients were enrolled in the dose escalation phase of study PLX06-02, including patients with metastatic melanoma (n=50), thyroid cancer (n=3), rectal carcinoma (n=1) and ovarian cancer (n=1). Several different capsule strengths and formulations were evaluated in this part of the study. Twenty-six patients received doses of vemurafenib ranging from 160 mg to 1120 mg b.i.d using the optimized drug formulation (referred to as micro-precipitated bulk powder [MBP] formulation) with greater bioavailability. With this optimized formulation, minimum efficacious exposures above the exposure identified in the preclinical models (≥ 400μM·h) were achieved at 240 mg b.i.d. Vemurafenib MBP formulation has shown dose proportional increases in exposure across all cohorts, particularly from 240 to 960 mg b.i.d. Mean steady state exposure levels of vemurafenib (area under the plasma concentration-time curve, $AUC_{0\text{-}24h}$) in these dose cohorts ranged from 467.1 μM·h to 1324.6 μM·h. The 960 mg b.i.d dose of vemurafenib achieved mean steady state exposure levels of 69.6 μM and 1324.6 μM·h, for maximum plasma concentration (C_{max}) and $AUC_{0\text{-}24h}$, respectively.

An apparent mean half-life of ~90 hours (range, 30 to 145 hours) following multiple doses in patients receiving 960 mg bid in the melanoma extension cohort was determined based on the mean accumulation ratio of vemurafenib exposure between Day 1 and Day 15. With the twice-daily dosing regimen, all patients were exposed to relatively constant daily levels of the drug at steady state.

Dose-limiting toxic effects were not observed until a dose of 720 mg b.i.d. At the next highest dose given to one group of patients, 1120 mg b.i.d, four of six patients developed non-life threatening dose-limiting toxicity (DLT): three patients with Grade 3 rash (two of whom also had Grade 3 fatigue) and one patient with Grade 3 arthralgia. All events resolved with temporary drug interruption. In all cases, patients resumed treatment at lower doses of 720 mg b.i.d. One DLT, Grade 4 pancytopenia, was observed at 720 mg b.i.d. Upon resolution of the pancytopenia after 9 days of study drug interruption, the patient was rechallenged with vemurafenib at a lower dose of 360 mg b.i.d without recurrence of the pancytopenia. No new occurrence of pancytopenia was observed in the 1120 mg b.i.d dose cohort or since in the extension cohort.

The dose of 960 mg b.i.d orally was determined to be tolerated in the first six patients given the dose. This dose level of 960 mg b.i.d was established as the recommended phase II dose for the extension cohort (these 6 patients were included as the first six patients in the extension cohort) and for future phase II and III studies.

1.3.4 Clinical Efficacy in Melanoma

Note: Efficacy and safety data on vemurafenib, which are summarized in this and the following section (Section 1.3.5), have been obtained primarily from studies on patients with metastatic

melanoma. Examining the reproducibility of these data in other indications is a primary goal of the present study.

1.3.4.1 PLX06-02

Of the patients enrolled in the dose-escalation portion of the melanoma study PLX 06-02 who received doses of 240 mg b.i.d. or more, 16 presented with tumours that harboured the V600 BRAF mutation. Among these 16 patients, a PR or CR was seen in one patient receiving 240 mg b.i.d., two of the four patients receiving 320 or 360 mg b.i.d., four of the six patients receiving 720 mg b.i.d., and four of the five patients receiving 1120 mg b.i.d. The overall RR (including either confirmed or unconfirmed responses) was 69% (11 of 16 patients), with 10 PR and one CR. Responses were seen at all sites of metastatic disease, including liver, small bowel, and bone. The DOR ranged from two to more than 18 months.

Five patients with metastatic melanoma without BRAF mutation received vemurafenib doses of at least 240 mg b.i.d. None had evidence of tumour regression during the study. Four developed progressive disease (PD) within the first two months of treatment (61).

All 32 patients enrolled in the extension cohort of study PLX 06-02 had metastatic melanoma with BRAF V600E mutation. All were treated with vemurafenib at the recommended phase II dose of 960 mg p.o. b.i.d. Thirteen patients (41%) required a dose reduction during therapy (to 720 mg b.i.d. in 10 patients, to 600 mg b.i.d. in one patient, and to 480 mg b.i.d. in two patients). Among the 32 evaluable patients in the melanoma extension cohort, the unconfirmed response rate was 81.3%; 3 patients had a CR and 24 patients had a PR. The confirmed response rate (CR + PR) was 56.3%.

Responses were observed in visceral organs and bone metastases, as well as lungs and lymph nodes. Responses were also observed in patients with increased concentrations of serum lactate dehydrogenase (10 PR among the 13 patients). Responses were observed in patients who had received no previous therapy (six of seven patients responded with vemurafenib in first-line treatment) and in patients who received one or more prior systemic therapies (nine of nine patients in second-line, four of four patients in third-line and seven of 12 patients beyond third-line). The median OS is 16 months with a 2-year survival rate of 44% (71).

1.3.4.2 NP22657/BRIM-2

A total of 132 patients were enrolled into study NP22657/BRIM-2 between October 2009 and March 2010 (63, 64). Of these, 122 (92.5%) harboured the BRAF V600E mutation and 10 (7.5%) the BRAF V600K mutation.

At the data cut off of July 1, 2011 the median follow-up was 12.9 months (range, 0.6 to 20.1). In total, 8 CR, 62 PR, 38 SD, and 18 PD have been confirmed by an Independent Review Committee (IRC), resulting in an IRC-assessed ORR of 53% (primary endpoint). Investigator-assessed ORR and RR (the latter includes unconfirmed responses) were 57% and 69%, respectively. Median duration of response was 6.7 months (95% CI, 5.6–9.8 months; range 1.3–12.7 months). Median PFS was 6.8 months (95% CI, 5.6-8.1 months), with a six-month PFS rate of 56% (95% CI, 47%-64%). The median overall survival was 15.9 months (95% CI, 11.6 to 18.3). The overall survival rate at 6 months was 77% (95% CI, 70-85), 58% at 12 months (95% CI, 49 to 67) (73).

Of note, of the 10 patients harbouring the V600K allele, 4 exhibited PRs.

1.3.4.3 NO25026/BRIM-3

A total of 675 patients with previously untreated, metastatic melanoma harbouring the BRAF V600E mutation were randomly assigned to receive either vemurafenib or dacarbazine in the global, randomized phase III study NO25026/BRIM-3 between January 2010 and December 2010 (62). In the interim analysis for OS and final analysis for PFS (see Section 1.3.2.4), vemurafenib was associated with a relative reduction of 63% in the risk of death and of 74% in the risk of either death or disease progression, as compared with dacarbazine (P<0.001 for both comparisons). The survival benefit in the vemurafenib group was observed in each pre-specified subgroup, according to age, sex, ECOG performance status, tumour stage, lactate dehydrogenase level, and geographic region. After review of the interim analysis by an independent data and safety monitoring board, crossover from dacarbazine to vemurafenib was recommended.

In the vemurafenib group, most patients had a detectable decrease in tumour size and 106 of 219 patients (48%; 95% CI, 42%–55%) had a confirmed objective response (including 2 patients with a CR and 104 with a PR). Median time to response was 1.45 months. Ten patients in the vemurafenib group were later found to have BRAF V600K mutations; of these, 4 had a PR (40%). In the dacarbazine group, a minority of patients had a detectable decrease in tumour size and only 12 of 220 patients (5%; 95% CI, 3%–9%) met the criteria for a confirmed response (all partial responses). Median time to response was 2.7 months. The difference in confirmed RR between the two study groups (48% vs. 5%) was highly significant (P<0.001).

In a recent post hoc analysis (data cut 1 February, 2012) the median overall survival was 13.6 for the vemurafenib treatment arm and 9.7 months for the dacarbazine treatment arm (Hazard ratio 0.70 (95% CI: 0.57–0.87) p<0.001). The median PFS was 6.9 months with vemurafenib treatment compared to 1.6 months with dacarbazine treatment (Hazard ratio 0.38 (95% CI: 0.32–0.46) p<0.001) (74).

1.3.5 Clinical Safety in Melanoma

Safety data from the clinical trials with vemurafenib include arthralgia, fatigue, rash, photosensitivity reaction, nausea, alopecia and pruritus Vemurafenib also has been associated with reports of cSCC most of which are keratoacanthoma (KA) sub-type, or with some features of KA (incompletely expressed or with some features unusual in KA). AEs with vemurafenib have been predominantly mild in severity and transient, even with continuous dosing (over 15 months of treatment in 1 patient). At the recommended phase II and phase III dose of 960 mg b.i.d., AEs have been consistent with the safety profile observed in the phase I setting. Treatment-related Grade 3 AEs and DLTs have been successfully managed by a temporary discontinuation of study drug and/or a reduction in dose. Further details of cSCC findings across all vemurafenib melanoma clinical trials can be found in the latest vemurafenib IB (current version 11).

Two cases of SCC of the head and neck have been reported in 2 patients treated with vemurafenib in excess of 300 days while enrolled in clinical trials (NO25026/BRIM-3 and NP25163 a PK/pharmacodynamic study of vemurafenib). A pathology examination of both tumours (both arising in the tonsilar area) revealed the presence of invasive SCC. Of note, one patient's medical history was significant for risk factors for head and neck cancer, and the tumour tissue tested positive for human papillomavirus (HPV). The patient in the second case did not have any risk factors for head and neck cancer, and the tumour tissue preliminarily did not reveal the presence of HPV. Detailed accounts of these events are provided as an addendum to the current vemurafenib IB.

Two cases of adenomatous colonic polyps have been reported in patients who were receiving vemurafenib for over 2 years. The first patient developed an upper gastrointestinal bleed, and on a work up, was found to have duodenal ulceration (non-malignant), hyperplastic gastric polyps, and five colonic polyps (three adenomatous). A previous colonoscopy, performed in 2008 at time of a jejunal resection for recurrent melanoma, documented no prior evidence of colonic polyps. All polyps have been resected, and the patient has subsequently resumed vemurafenib therapy. The second patient was found to have seven colonic polyps (five adenomatous) during elective colonoscopy, and all were detected and removed. There is no information at this time as to the findings on a previous colonoscopy or whether one was performed. The patient has continued treatment with vemurafenib without interruption. Detailed accounts of these events are provided as an addendum to the current vemurafenib IB (75).

Eight skin lesions in seven vemurafenib-treated patients were reported as new primary malignant melanomas in Study NO25026. No cases were reported in patients treated with dacarbazine. Cases were managed with excision and patients continued treatment without dose adjustment.

As based on mechanism of action, vemurafenib may cause progression of cancers associated with RAS mutations, vemurafenib should be used with caution in patients with prior or concurrent cancers associated with RAS mutation.

Surveillance measures to monitor for the occurrence of new primary melanomas, cSCC, SCCs (cutaneous and non-cutaneous), and any new primary malignancies are outlined in Section 5.3.8.4.

An analysis of liver-related adverse events reported with vemurafenib use showed that 63 cases (out of estimated exposure of approximately 20,000 patients) of medically confirmed serious adverse events were consistent with drug-induced liver injury based on clinical chemistry criteria from the DILI Expert Working Group (76). Of these 63 cases, two were assessed as severe, both reported as hepatic failure. There were no reported deaths among the 63 cases of liver injury; the outcome of one case of severe liver injury was reported as completely resolved with vemurafenib discontinuation, while information on the outcome of the second case of severe liver injury is not available at this time. The median time to onset of the adverse events was 44 days after initial dose. The median ALT to ALP ratio was calculated as 1.5, suggesting a trend towards a cholestatic pattern of liver injury. The analysis did not reveal any risk factors or populations at risk.

A review of the Roche safety database found neutropenia to be an uncommon (6 cases per 1000 person-years, 0.6%) adverse drug reaction associated with the use of vemurafenib, typically occurring during the first 6-12 weeks of treatment. It appeared to be reversible usually within 2 weeks, with either temporary interruption, dose reduction or discontinuation of vemurafenib, and in some cases was managed with granulocyte colony-stimulating factor (G-CSF).

One case of progression of NRAS-mutated chronic myelomonocytic leukaemia (CMML) occurred in a male patient with metastatic melanoma treated with vemurafenib for less than two weeks (77). After the first dose of vemurafenib, laboratory results showed a marked leucocytosis and monocytosis and vemurafenib treatment was subsequently stopped. There was a temporal relationship between vemurafenib treatment and increase in white blood cell (WBC) and absolute monocyte counts, through multiple cycles of de-challenge and re-challenge. *In vitro* studies demonstrated proliferation of the leukemic cell population, an effect that was reversed upon drug withdrawal. Further, the cells exhibited dose-dependent and reversible activation of ERK in the NRAS-mutated leukemic clone. On the basis of its mechanism of action, vemurafenib may cause

progression of cancers associated with RAS mutations. Vemurafenib should be used with caution in patients with a prior or concurrent cancer associated with RAS mutation. Full details are provided in the vemurafenib IB (version 11).

As of March 31st 2013, 12 cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome have been observed with vemurafenib treatment. No cases have been reported to result in death. The time to onset was 7 to 25 days. In the majority of patients (7 patients), vemurafenib was discontinued. Five patients were treated with systemic steroids with corresponding improvement or resolution of symptoms. In addition, two patients with Grade 3 rash, who were treated with vemurafenib after ipilimumab, had biopsies that showed pathology consistent with drug hypersensitivity reaction (78). Full details are provided in the vemurafenib IB (version 11).

As of May 23rd 2014, an adverse drug reaction of pancreatitis has been identified in patients being treated with vemurafenib. Seventeen cases of pancreatitis with no strong risk factors or alternative explanations were reported. Eight of the 17 cases were assessed as likely associated with vemurafenib use based on event onset latency and re-challenge/de-challenge information. The clinical presentation including mild to moderate severity was consistent with the clinical picture of drug-induced pancreatitis (81).

1.3.5.1 PLX 06-02

Among patients enrolled in the phase I study PLX 06-02, the most common vemurafenib-related Grade 2 or 3 toxicities observed were arthralgia, rash, nausea, photosensitivity, fatigue, cutaneous SCC, pruritus, and palmar-plantar dysesthesia (Table 5). In total, 89% of the toxicities were Grade 1 or 2. Rashes were evenly distributed among face/neck, trunk, and extremities. Four patients had a Grade 4 AE: two had elevated γ-glutamyltransferase (GGT) levels; one had fatigue; and one had reversible pancytopenia of uncertain attribution. Thirteen patients out of 32 total (41%) in the extension cohort required a dose reduction (10 patients to 720 mg b.i.d., one patient to 600 mg b.i.d., and two patients to 480 mg b.i.d.) (61).

Table 5:
PLX 06-02: Vemurafenib-Related Adverse Events ≥ Grade 2 in > 5% of Patients

	< 240 mg (N=30) [b]	240 mg (N=4) [a]	320/360 mg (N=8)	720 mg (N=7)	960 mg (N=32)	1120 mg (N=6)	Overall (N=87)
Arthralgia							
Grade 2	0	1 (25%)	2 (25%)	0	10 (31%)	1 (17%)	14 (16%)
Grade 3	0	0	0	0	1 (3%)	1 (17%)	2 (2%)
Rash							
Grade 2	1 (3%)	0	0	1 (14%)	7 (22%)	1 (17%)	10 (12%)
Grade 3	0	0	0	0	1 (3%)	2 (33%)	3 (3%)
Cutaneous squamous cell carcinoma							
Grade 2	0	0	0	0	0	0	0
Grade 3	1 (3%)	2 (50%)	3 (38%)	0	10 (31%)	2 (33%)	18 (21%)
Nausea							
Grade 2	1 (3%)	0	1 (13%)	1 (14%)	4 (13%)	1 (17%)	8 (9%)
Grade 3	0	0	0	0	1 (3%)	0	1 (1%)
Fatigue							
Grade 2	0	0	0	0	2 (6%)	1 (17%)	3 (3%)
Grade 3	0	0	0	0	2 (6%)	2 (33%)	4 (5%)
Photosensitivity reaction							
Grade 2	0	0	0	1 (14%)	4 (13%)	1 (17%)	6 (7%)
Grade 3	0	0	0	0	1 (3%)	0	1 (1%)
Palmar-plantar dysesthesia							
Grade 2	0	0	0	0	2 (6%)	1 (17%)	3 (3%)
Grade 3	0	0	0	0	2 (6%)	0	2 (2.3%)
Pruritus							
Grade 2	0	0	0	0	4 (13%)	0	4(5%)
Grade 3	0	0	0	0	0	1 (17%)	1 (1%)
Lymphopenia							
Grade 2	0	0	2 (25%)	0	2 (6%)	0	4 (5%)
Grade 3	0	0	0	0	0	1 (17%)	1 (1%)

c. Initial dose escalation utilized a crystalline formulation with inadequate bioavailability; the MBP formulation was used for doses > 320 mg/day.

1.3.5.2 NP22657/BRIM-2

Treatment-related AEs reported in more than 5% of patients in BRIM-2 are shown in Table 6.

Table 6:
BRIM-2: Treatment-Related Adverse Events ≥ Grade 2 in ≥ 20 Patients

	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Overall	130 (99)	79 (60)	5 (4) [a]
Arthralgia	78 (59)	8 (6)	0 (0)
Rash	69 (52)	9 (7)	0 (0)
Photosensitivity reaction	69 (52)	4 (3)	0 (0)
Fatigue	56 (42)	2 (2)	0 (0)
Alopecia	48 (36)	0 (0)	0 (0)
Pruritus	38 (29)	3 (2)	0 (0)
Skin papilloma	38 (29)	0 (0)	0 (0)
Cutaneous SCC / KA [b]	34 (26)	34 (26)	0 (0)
Nausea	30 (23)	2 (2)	0 (0)
Elevated liver enzymes	23 (17)	8 (6) [c]	4 (3) [d]

SCC, squamous cell carcinoma; KA, keratoacanthoma.

a. One patient had 2 Grade 4 AEs.
b. Cases of cutaneous SCC / KA were generally managed with simple excision and did not generally require dose modification.
c. Managed with dose reduction; one removed from study.
d. Led to discontinuation of therapy.

The median average daily dose of vemurafenib was 1740 mg per day. A total of 59 patients (45%) had their vemurafenib doses reduced: 37 (28%) to 720 mg b.i.d.; 21 (16%) to 480 mg b.i.d.; and 1 to less than 480 mg b.i.d. Eighty-five patients (64%) had their dosing interrupted during the course of the trial. Common AEs that led to dose reduction and interruptions were rash, arthralgia, liver function test abnormalities (GGT elevation), and photosensitivity. Four patients discontinued vemurafenib due to an AE: retinal vein occlusion (n=1); jaundice, blood bilirubin increased, fatigue, AST, and ALT (1); delirium (1); and cellulitis (1).

Grade 3 cutaneous SCCs / keratoacanthomas occurred in 34 patients (26%). Median time to first occurrence was 8 weeks (range, 2–36 weeks), and the median number per patient was 1 (range, 1–7).

1.3.5.3 NO25026/BRIM-3

A total of 618 patients (92%) underwent at least one assessment as of the clinical cutoff date (December 2010) and were evaluated for toxic effects. AEs of Grade 2 or more that were reported in more than 5% of patients in either study group are shown in Table 7.

Table 7:
BRIM-3: Adverse Events ≥ Grade 2 in > 5% of Patients in Either Study Group (N=618)

Adverse event, n (%)	Vemurafenib (N=336) [a]	Dacarbazine (N=282)
Arthralgia		
Grade 2	60 (18)	1 (< 1)
Grade 3	11 (3)	2 (< 1)
Rash		
Grade 2	33 (10)	0 (0)
Grade 3	28 (8)	0 (0)
Fatigue		
Grade 2	38 (11)	33 (12)
Grade 3	6 (2)	5 (2)
Cutaneous squamous cell carcinoma [b]		
Grade 3	40 (12)	1 (< 1)
Keratoacanthoma [c]		
Grade 2	7 (2)	0 (0)
Grade 3	20 (6)	0 (0)
Nausea		
Grade 2	25 (7)	32 (11)
Grade 3	4 (1)	5 (2)
Alopecia		
Grade 2	26 (8) [d]	0 (0)
Pruritus		
Grade 2	19 (6)	0 (0)
Grade 3	5 (1)	0 (0)
Hyperkeratosis		
Grade 2	17 (5)	0 (0)
Grade 3	4 (1)	0 (0)
Diarrhoea		
Grade 2	16 (5)	4 (1)
Grade 3	2 (< 1)	1 (< 1)
Headache		
Grade 2	15 (4)	5 (2)
Grade 3	2 (< 1)	0 (0)
Vomiting		
Grade 2	9 (3)	14 (5)

Adverse event, n (%)	Vemurafenib (N=336) [a]	Dacarbazine (N=282)
Grade 3	4 (1)	3 (1)
Neutropenia		
Grade 2	1 (< 1)	4 (1)
Grade 3	0 (0)	15 (5)
Grade 4	1 (< 1)	8 (3)
Grade 5	0 (0)	1 (< 1)

a. One patient in the dacarbazine group who was treated with vemurafenib in error was included in the vemurafenib group for the assessment of AEs.

b. The criteria for the diagnosis of cutaneous SCC were defined in the protocol and were reported as Grade 3, according to the NCI-CTCAE, v4.0. These events were evaluated by the Investigators as Grade 1 in one patient and as Grade 2 in one patient.

c. Three patients with keratoacanthomas that were assessed by the Investigator as Grade 1 are included among the Grade 2 keratoacanthomas.

d. In one patient, alopecia that was scored as Grade 3 by the investigator was rescored as Grade 2, since the NCI-CTCAE, v4.0 does not include Grade 3 alopecia.

The most common AEs in the vemurafenib group were cutaneous events, arthralgia, and fatigue; photosensitivity skin reactions of Grade 2 or 3 were seen in 12% of the patients, with Grade 3 reactions characterized by blistering that often could be prevented with sunblock. AEs led to dose modification or interruption in 129 of 336 patients (38%) in the vemurafenib group.

In the vemurafenib group, a cutaneous SCC, keratoacanthoma, or both developed in 61 patients (18%). All lesions were treated by simple excision. Pathological analyses of skin-biopsy specimens from these patients are currently being performed by an independent dermatology working group.

1.3.5.4 Cardiac effects in NP2265/BRIM-2

The effects of single and multiple doses of vemurafenib 960 mg bid on ECG measurement, including the QT interval, were evaluated in 132 adult patients with metastatic melanoma in the phase 2 study, NP22657. Centralized measurement of ECG intervals and T/U wave morphology was conducted by the core ECG laboratory on the robust schedule of serial time matched 12-lead ECGs obtained for up to 16 cycles. For each of the time points, the means from the available triplicate assessments were used as a single observation for the numeric ECG parameter. The T-wave and U-wave morphology and the ECG normality were assessed on each ECG from a triplicate.

Vemurafenib treatment at 960 mg bid did not appear to have a clinically meaningful effect on heart rate (HR). The study population-specific correction (QTcP) had eliminated most of the bias from the QT-RR relationship and was therefore used for the primary statistical analyses of variables related to the QTc interval.

Ninety-one patients (68.9%) exhibited normal ECG values (n=25) or developed new abnormal yet clinically insignificant ECG changes (n = 66). However, 41 patients (31.1%) exhibited new ECG changes considered to be abnormal and potentially significant. No patients developed new abnormal U waves, and 19 patients (14.4%) had new abnormal T-waves. Vemurafenib did not

cause a meaningful change from the time-matched baseline in either the QRS or the PR (PQ) interval.

Two patients (1.5%) developed treatment-emergent absolute QTcP values > 500 ms (CTC Grade 3), while 49 (37.1%) and 6 (4.5%) patients exhibited QTcP values > 450 ms and > 480 ms, respectively. No patients had treatment-emergent QT (uncorrected) values > 500 ms. Maximum treatment-emergent individual QTcP changes from baseline of > 30 ms were observed in 58 (43.9%) of patients, but only one patient (0.8%) exhibited a QTcP change from baseline of > 60 ms.

In the central tendency analysis, the largest mean QTcP prolongation (dQTcP) after the first vemurafenib dose on Day 1 was 3.3 ms with the upper bound of the 1-sided 95% CI (UCI) of 5.0 ms, constituting a small QTc effect below the threshold of clinical interest. However, the mean QTc prolongation increased with repeated vemurafenib dosing towards the expected steady-state on Day 15, which corresponded with vemurafenib accumulation in plasma. The largest dQTcP on Day 15 was 12.8 ms (UCI 14.9 ms), and appeared to remain sustained at a similar level in subsequent cycles. The pattern of increasing vemurafenib concentration from Day 1 to 15 and the constant exposure in the later cycles appeared to correlate with the increased mean QTcP change from Day 1 to 15 and the subsequent maintenance of this effect. The relationship between vemurafenib exposure and the QTc interval is being pursued further.

AEs in the study that were possibly attributable to QTc prolongation were as follows: one event of intermittent dizziness in a patient with a maximal QTc of 456 msec, and 2 cases of pericardial effusion in patients with maximal QTc values of 469 msec and 456 msec. The maximal QTc values reported in these patients did not necessarily occur at the same time as the AEs in question. Pericardial effusion is not a consequence of electrocardiographic changes and is not known to affect the QT interval.

1.4 CETUXIMAB

For full details on the background, clinical safety and efficacy of cetuximab in CRC refer to cetuximab Summary of Product Characteristics (SPC) (79).

1.5 RATIONALE FOR THE STUDY

As described in Section 1.2 (Oncogenic BRAF Kinase Mutations in Various Cancers), mutations in the BRAF gene, in particular mutations resulting in a V600E mutant kinase, may play significant roles in the pathogenesis of a variety of clinically significant cancers. Moreover, the presence of BRAF mutations is known to attenuate the activity of other anticancer agents, most notably EGFR therapeutic antibodies. Therefore, the identification of new therapies that specifically target BRAF mutations in cancer cells is of significant interest.

Vemurafenib has reproducibly demonstrated high anticancer activity in a number of phase I, II and phase III trials in metastatic melanoma. Based on this prior activity, as well as the evidence that activated BRAF kinase may play a highly conserved role in dysregulated cell growth across multiple cancer types, it is reasonable to posit that this new drug may be effective in non-melanoma cancers harbouring BRAF V600 mutations, as well. Indeed, preliminary evidence suggested that vemurafenib may have some activity in CRC (66). This further encourages exploration of the efficacy of vemurafenib in CRC and other non-melanoma tumours harbouring activated BRAF V600 mutations.

As described in Section 1.2.2 (Colorectal Cancer) there is preclinical evidence that BRAF inhibition causes a feedback activation of EGFR which is responsible for the continued proliferation in the presence of BRAF inhibition in CRC cell lines. The combination of vemurafenib and EGFR inhibitors demonstrated a strong synergic effect both *in vitro* and *in vivo*. These data provide a strong rationale for a clinical trial investigating the combination of vemurafenib and cetuximab in BRAF-mutated colorectal cancer patients, who have a poor clinical outcome and for whom there are no effective treatment options after failure of standard chemotherapy as per Cohort 3b.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of this trial is to evaluate the efficacy of vemurafenib in patients with cancers harbouring BRAF V600 mutations as response rate (RR) at Week 8 determined by the Investigator using Response Evaluation Criteria In Solid Tumors, Version 1.1 (RECIST, v1.1)* or International Myeloma Working Group (IMWG) uniform response criteria and to identify tumour types for further development

*For prostate cancer, ECD and/or LCH specific response criteria see Appendix 9 and Appendix 10, respectively.

2.2 SECONDARY OBJECTIVES

- To evaluate the safety and tolerability of vemurafenib in this patient population.
- To evaluate in solid tumours and multiple myeloma (MM):
  - overall response rate (ORR)
  - clinical benefit rate (CR (or sCR), PR (or VGPR)) and stable disease (SD) of vemurafenib
  - duration of response (DOR)
  - time to response
  - time to tumour progression (TTP)
  - PFS
  - overall survival (OS)
  - To determine the maximum tolerated dose (MTD) and recommended dose for stage I/II of the combination of vemurafenib and cetuximab in BRAF V600-positive metastatic CRC patients (Cohort 3b only)
  - To investigate the safety, tolerability, efficacy of the combination of vemurafenib and cetuximab in BRAF V600-positive metastatic CRC patients (Cohort 3b only)
  - To evaluate tumour assessment scans by an IRC for Cohort 1 (NSCLC) and other cohorts that demonstrate clinically meaningful efficacy per investigator assessment.

2.3 EXPLORATORY OBJECTIVES

- To perform concordance testing for the detection of BRAF V600 mutation in tumour samples via either the Roche CoDx cobas 4800 BRAF V600 Test or other standard methodology.

- To examine the previous line of treatment's TTP (plTTP) in relation to the TTP achieved during study treatment
- For all newly enrolled patients in all cohorts:
    - To explore the PK characteristics of vemurafenib
    - To assess the correlation of BRAF V600 mutation between tissue samples and plasma samples

3. STUDY DESIGN

3.1 OVERVIEW OF STUDY DESIGN

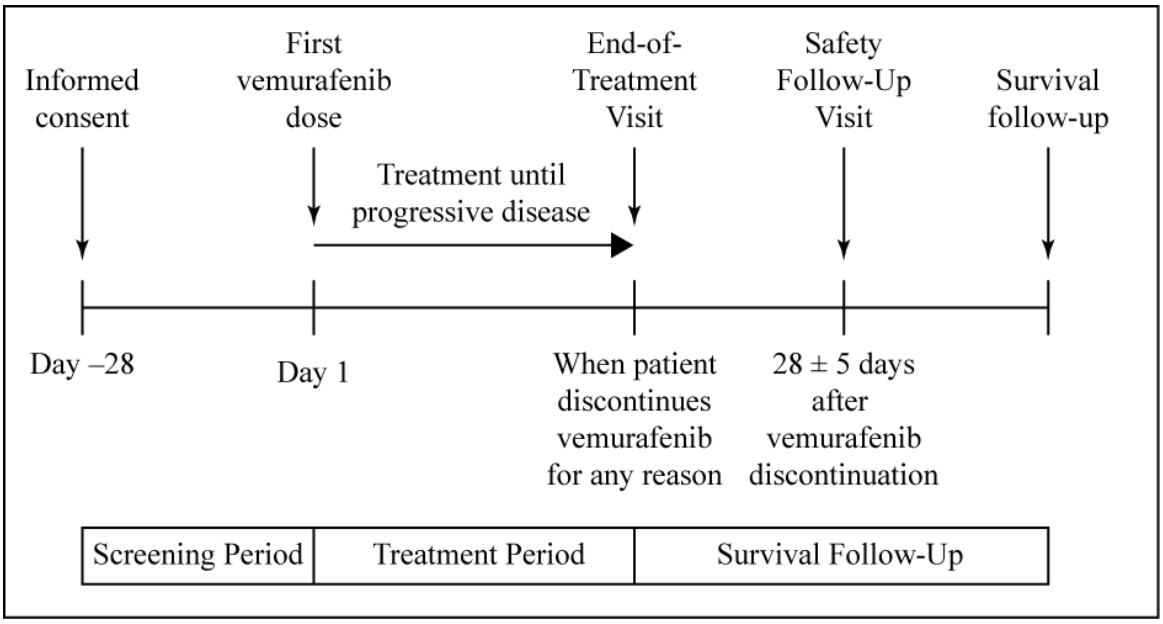
This is an open-label, multicentre, multinational, phase II study exploring the efficacy and safety of vemurafenib in a diverse population of patients with cancers (excluding melanoma and papillary thyroid cancer) known to harbour BRAF V600 mutations and for whom vemurafenib is deemed the best treatment option in the opinion of the Investigator.

In the population of colorectal cancer patients, the safety and efficacy of vemurafenib in combination with cetuximab will also be explored in addition to vemurafenib monotherapy.

Patients with BRAF V600 mutation-positive cancers will be identified through mutation analysis assays as routinely performed at each participating site according to their local procedure. The BRAF V600 mutation identified at the site, as well as the specific BRAF mutation assay that was performed, will be recorded in the electronic case report form (eCRF). The presence of BRAF V600 mutations will be retrospectively confirmed by the Roche CoDx cobas 4800 BRAF V600 Test or other standard methodology.

The trial will consist of a Screening Period (Day –28 to −1), a Treatment Period, an End of Treatment Visit occurring when study medication is discontinued for any reason, a Safety Follow-Up Visit occurring 28 days (± 5 days) after the last dose of study medication and a Survival Follow-Up Period lasting for a minimum of 12 months after the last patient has been enrolled or until all patients have died, withdrawn consent or are lost to follow-up (whichever occurs first) to monitor survival status. Day 1 of the study (baseline) will be defined as the first day a patient receives study medication. One cycle of therapy will be defined as 28 days of treatment. Patients will be asked to attend clinic visits at regular intervals during the study for safety and efficacy assessments.

Figure 1: Study Design



The study will include 7 cohorts of patients with the following cancers:

Cohort 1: Non-small cell lung cancer (NSCLC)

Cohort 2: Ovarian cancer

Cohort 3: Colorectal cancer

Cohort 3a: Vemurafenib only

Cohort 3b: Combination therapy with vemurafenib and cetuximab

Cohort 4: Cholangiocarcinoma / cancer of the biliary tract

Cohort 5: Breast cancer

Cohort 6: Multiple myeloma (MM)

Cohort 7: Solid tumours other than the above

Colorectal cancer patients with BRAF V600 mutation-positive cancers will receive vemurafenib as a single agent (Cohort 3a) or the combination of vemurafenib and cetuximab (Cohort 3b).

The Cohort 3b is designed to investigate the safety, tolerability, efficacy and to determine the MTD and the recommended dose for stage I/II of the combination of vemurafenib and cetuximab. Cohort 3b has two parts:

- Part 1 is a dose finding phase of vemurafenib in combination with cetuximab (based on a classical 3+3 design)
- Part 2 is investigating the efficacy and safety of the recommended dose for stage I/II of the combination of vemurafenib and cetuximab and will be the same Stage I/II design as the other cohorts will be used

The decision to carry on enrolment of CRC patients into Cohort 3a (vemurafenib monotherapy) and/or enrol patients into Cohort 3b (combination of vemurafenib and cetuximab) will be based on the stage I analysis for Cohort 3a (vemurafenib monotherapy). This will be decided by the Sponsor in discussion with study Steering Committee. The decision to continue enrolment in Cohort 3b after the Part I dose escalation phase will be decided by the Sponsor in discussion with study Steering Committee.

Recruitment/enrolment in any of the above cohorts may present some challenges due to the low frequency of BRAF V600 mutations in the specific disease settings. Therefore the following rule on cohort closure (permanent enrolment stop) will be applied: if no patients are enrolled in the remaining cohorts one year after any of the cohorts has completed enrolment, then enrolment in those remaining cohorts will be stopped. Cohort 7 (Other solid tumours) will be closed to enrolment when all other cohorts are closed, regardless of the number of patients recruited at that time. This cohort is quite heterogeneous and will be examined primarily to seek efficacy signals in the relatively rare BRAF V600 mutation-positive tumours.

Enrolled patients will receive:

- Cohorts 1 – 7 (except patients in the Cohort 3b): continuous oral dosing of vemurafenib at 960 mg twice daily (b.i.d)
- Cohort 3b: Part 1 vemurafenib and cetuximab at the doses allocated for dose escalation (see Section 6.3.1) or Part 2 at the dose recommended for stage I/II of vemurafenib and cetuximab

Treatment will continue until the development of progressive disease (as per Investigator assessment), unacceptable toxicity, withdrawal of consent, protocol violation endangering the patient's safety, death, reasons deemed critical by the treating physician, or study termination by the Sponsor.

Patients who develop disease progression but, in the opinion of the Investigator, would still benefit from continuing study treatment may continue treatment with study treatment after discussion with the Sponsor.

Patients with ECD/LCH have the option of discontinuing vemurafenib treatment after one year, if the investigator considers it to be in the best interest of the patient. Patients can then resume vemurafenib treatment if they become symptomatic or if their scans show worsening of their disease.

Recruitment into any cohort/indication can be expanded up to a total of 70 patients if a response rate has been demonstrated in Stage II of that cohort as per stopping rules defined in the protocol or a clear clinical benefit for patients is observed. This will be decided by the Sponsor in discussion with study Steering Committee.

3.1.1 Rationale for Study Design

The multi-cohort design will allow for the examination of 7 separate cohorts of different cancers with enough statistical power to determine whether further examination may be warranted in the individual indications. The open-label, uncontrolled design is appropriate since the trial will only enrol patients with BRAF V600 mutation positive cancers, who in the opinion of the Investigator, have vemurafenib as their best treatment option, i.e., no other obvious comparator is available.

The Cohort 3b is designed to investigate the safety, tolerability, efficacy and determine the maximum tolerated dose (MTD) and recommended dose for stage I/II of the combination of vemurafenib and cetuximab in BRAF V600 positive CRC.

Recruitment into any cohort/indication can be expanded up to a total of 70 patients if a response rate has been demonstrated in Stage II of that cohort as per stopping rules defined in the protocol or a clear clinical benefit for patients is observed. This will be decided by the Sponsor in discussion with study Steering Committee. The data from these additional patients will help further characterize the safety and efficacy of vemurafenib in the specific indication.

3.1.2 Rationale for Dose Selection

3.1.2.1 Rationale for the starting doses of vemurafenib (Cohort 1-7, excluding Cohort 3b)

The dose of vemurafenib at 960 mg b.i.d was identified in the phase I dose-finding study PLX 06-02 and is established as the recommended dosage for phase II and III trials (see Section 1.2.4) for the treatment of melanoma. It is presumed that a similar dosage would be effective in other types of cancers harbouring the same BRAF V600 mutations.

3.1.2.2 Rationale for the starting doses of vemurafenib and cetuximab in combination (Cohort 3b)

The loading dose of cetuximab will be 300 mg/m^2 given intravenously (IV) followed by a weekly IV dose of 200 mg/m^2 (see Appendix 1 for body surface area calculation). These doses are respectively 75% and 80% of the registered doses as single agent in second or third line for advanced CRC.

Vemurafenib: the starting dose will be 720 mg b.i.d. This is 75% of the registered dose in melanoma when given as single agent.

These starting reduced doses will be explored for safety reasons as vemurafenib and cetuximab will be administered concomitantly.

Doses will be escalated according to a standard 3+3 dose-escalation design (see Section 6.3.1).

3.1.3 End of Study

The end of study will occur when all patients have been followed for survival for a minimum period of 12 months after the last patient has been enrolled or until all patients have died, withdrawn consent or are lost to follow up, whichever occurs first.

At this time, the trial will end and no further data will be collected on the clinical database for this study. The end of the MO28072 study is defined as the last patient last visit at the end of the follow-up period.

3.2 NUMBER OF PATIENTS / ASSIGNMENT TO TREATMENT GROUPS

It is estimated that up to 170 patients with solid tumours or multiple myeloma will be enrolled in this study for the Stage I/II analysis. Approximately 13–37 patients per indication (cohort) will be included. The number of patients in a cohort can be less than 13 if a cohort is closed earlier as a result of stopping rules for the cohort.

Recruitment into any cohort/indication can be expanded up to a total of 70 patients if a response rate has been demonstrated in Stage II of that cohort as per stopping rules defined in the protocol or a clear clinical benefit for patients is observed. This will be decided by the Sponsor in discussion with study Steering Committee. The maximum number of patients in this study is therefore 490 (7 cohorts up to 70 patients each).

3.3 CENTRES

This study is a multinational, multicentre study conducted in 6 countries and approximately 30 sites.

4. STUDY POPULATION

4.1 OVERVIEW

The target population will include adult patients with BRAF V600 mutation-positive cancers (excluding melanoma and papillary thyroid cancer). BRAF V600 mutations will be identified by mutation analysis assays as routinely performed at each individual participating site according to their local procedures. See Sections 4.2 and 4.3 for further Inclusion and Exclusion Criteria.

4.2 INCLUSION CRITERIA

Inclusion Criteria:

For solid tumours only*

1. Histologically confirmed cancers (excluding melanoma and papillary thyroid cancer) that harbour a BRAF V600 mutation and are refractory to standard therapy or for which standard or curative therapy does not exist or is not considered appropriate by the Investigator

   Note: for the patient to be eligible, they must be able to provide a tumour sample (preferably tissue; alternatively DNA) for retrospective confirmation of the BRAF mutation by a central laboratory. This tumour sample should preferably be from the original specimen used to detect the BRAF mutation. If archival samples are not available, the patient should be biopsied in order to obtain adequate tissue. Exceptions may be considered upon discussion with the Sponsor (e.g. ≥ 250 ng of DNA may be sent instead of tissue samples).
2. Measurable disease according to RECIST, v1.1
3. Adequate hematologic function, as defined by the following laboratory values; test performed within 7 days prior to the first dose of vemurafenib:
   a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
   b. Platelet count ≥ 100 x 10^9/L

For multiple myeloma only:

4. Patients with a confirmed diagnosis of MM harbouring a BRAF V600 mutation

   Note: for the patient to be eligible, they must be able to provide a tumour sample (preferably tissue; alternatively DNA) for retrospective confirmation of the BRAF mutation by a central laboratory. This tumour sample should preferably be from the original specimen used to detect the BRAF mutation. If archival samples are not available, the patient should be biopsied in

order to obtain adequate tissue. Exceptions may be considered upon discussion with the Sponsor (e.g. ≥ 250 ng of DNA may be sent instead of tissue samples).

5. Patients must have received at least one line of prior systemic therapy for the treatment of MM. A line of treatment is sequential treatment without interruption for response and subsequent progression
6. Patients treated with local radiotherapy (with or without concomitant exposure to steroids for pain control or management of cord/nerve root compression); two weeks must have elapsed since the last date of radiotherapy, which is recommended to be a limited field. Patients who require concurrent radiotherapy should have entry into the Study deferred until the radiotherapy is completed and two weeks have passed since the last date of therapy
7. Patients must have relapsed and/or refractory MM with measurable disease, defined as disease that can be measured either by serum or urinary evaluation of the monoclonal component or by serum assay of free light chain (FLC) of at least one of the following three parameters:
   - Serum M-protein > 0.5 g/dL
   - Urine M-protein > 200 mg per 24 hours
   - Involved FLC level > 10 mg/dL (> 100 mg/L) provided serum FLC ratio is abnormal
8. Adequate hematologic function as defined by the following laboratory values performed within 7 days prior to the first dose of vemurafenib:
   - Absolute neutrophil count (ANC) ≥ 1.0 x 10^9/L
   - Platelets count ≥ 50 x 10^9/L

<u>For all patients (solid tumours and MM):</u>

9. Signed written informed consent approved by the relevant Independent Ethics Committee (IEC) / Institutional Review Board (IRB) must be obtained prior to performing any study-related procedures
10. Male or female ≥ 16 years of age
11. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2
12. Must have recovered from all side effects of their most recent systemic or local treatment
13. Able to swallow pills
14. Adequate hematologic, renal and liver function as defined by the following laboratory values; tests performed within 7 days prior to the first dose of vemurafenib:
    - Haemoglobin ≥ 9 g/dL
    - Serum creatinine ≤ 1.5 times upper limit of normal (ULN) or creatinine clearance (CrCl) > 50 mL/min by Cockroft–Gault formula (Protocol Appendix 1)
    - Aspartate aminotransferase (AST [SGOT]) and alanine aminotransferase (ALT [SGPT]) ≤ 2.5 times ULN (≤ 5 times ULN if considered due to primary or metastatic liver involvement)
    - Serum bilirubin ≤ 1.5 times ULN
    - Alkaline phosphatase ≤ 2.5 times ULN (≤ 5 times ULN if considered due to tumour)
15. Negative serum pregnancy test within 7 days prior to commencement of dosing in premenopausal women. Women of non-childbearing potential may be included without serum pregnancy test if they are either surgically sterile or have been postmenopausal for ≥ 1 year

16. Fertile men and women must use an effective method of contraception during treatment and for at least 6 months after completion of treatment as directed by their physician. Effective methods of contraception are defined as those which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly (for example implants, injectables, combined oral contraception or intra-uterine devices). At the discretion of the Investigator, acceptable methods of contraception may include total abstinence in cases where the lifestyle of the patient ensures compliance. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)
17. Absence of any psychological, familial, sociological, or geographical conditions potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before trial entry

*For prostate cancer, ECD and/or LCH specific eligibility criteria as part of Cohort 7, see Appendix 9 and Appendix 10, respectively.

4.3 EXCLUSION CRITERIA

Exclusion Criteria:*

1. Melanoma, papillary thyroid cancer or haematological malignancies (with the exception of multiple myeloma).
2. Uncontrolled concurrent malignancy (early stage or chronic disease is allowed if not requiring active therapy or intervention and is under control)
3. For MM, solitary bone or solitary extramedullary plasmacytoma as the only evidence of plasma cell dyscrasia
4. Active or untreated CNS metastases.
   - Patients with brain metastasis are eligible if asymptomatic, off corticosteroid therapy, and without evidence of disease progression in brain for ≥ 2 months.
   - Patients with incidentally found brain metastases that are asymptomatic and for which no treatment is planned are also eligible.
5. History of or known carcinomatous meningitis
6. Concurrent administration of any anti-cancer therapies (e.g., chemotherapy, other targeted therapy, experimental drug, etc.) other than those administered in this study
7. Known hypersensitivity to vemurafenib or another BRAF inhibitor. In addition, for Cohort 3b only: known hypersensitivity to cetuximab
8. Prior treatment with a BRAF or MEK inhibitor (prior sorafenib is allowed)
9. Pregnant or lactating women
10. Refractory nausea and vomiting, malabsorption, external biliary shunt or significant bowel resection that would preclude adequate absorption.
11. Any of the following within the 6 months prior to first vemurafenib administration:
    - Myocardial infarction, severe/unstable angina, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack
12. Pulmonary embolism within 30 days prior to first study medication administration

13. Hypertension not adequately controlled by current medications within 30 days prior to first study medication administration
14. History or presence of clinically significant ventricular or atrial dysrhythmias ≥ Grade 2 (National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 [NCI CTCAE, v4.0])
15. Corrected QT (QTc) interval ≥ 450 msec at baseline or history of congenital long QT syndrome or uncorrectable electrolyte abnormalities
16. Uncontrolled medical illness (such as infection requiring treatment with intravenous [IV] antibiotics)
17. Other severe, acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study medication administration or may interfere with the interpretation of study results which, in the judgment of the Investigator, would make the patient inappropriate for entry into this study
18. Unwillingness to practice effective birth control
19. Inability to comply with other requirements of the protocol

*For prostate cancer or ECD/LCH specific eligibility criteria as part of Cohort 7, see Appendix 9 and Appendix 10, respectively

4.4 CONCOMITANT THERAPY

At study initiation, patients should continue with their concomitant medications, as directed by their physician, with the exception of study precluded medications (see below and Section 4.3 above). All concomitant medication must be fully recorded on the eCRF. Additionally, any diagnostic, therapeutic, or surgical procedure performed during the study period should be recorded including the date, indication, description of the procedure(s) and any clinical findings.

Due to the underlying illness and the frequency of co-existent medical conditions in this patient population, all concomitant medication or treatment required by the patient will be at the discretion of the treating physician. In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the patient are allowed, provided their use is documented in the patient records and on the eCRF.

For Cohort 3b only, prior to the first infusion of cetuximab, patients must receive premedication with an antihistamine and a corticosteroid. This premedication is recommended prior to all subsequent infusions. See cetuximab SPC for further details (79).

See Appendix 9 for more details for prostate cancer patients.

4.4.1 Excluded Therapy and Potential Interactions with Concomitant Drugs

4.4.1.1 Excluded therapy

The following medications and treatments are not allowed while the patient is on the study:

- other anti-cancer therapies (except cetuximab for patients in Cohort 3b)
- concomitant alternative therapies and herbal preparations
- radiotherapy for the treatment of disease during the study; the exception will be limited field radiotherapy for palliative bone pain due to pre-existing bone metastasis if not considered a target lesion for RECIST assessments

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

Appendix 2 includes a non-exhaustive list of typical examples of CYP1A2 and CYP3A4 substrates and CYP3A4 inducers and inhibitors.

4.4.1.2 Potential interactions with concomitant drugs

Overall, < 10% of vemurafenib was observed to be metabolized in melanoma patients in an ADME (absorption, distribution, metabolism, and excretion) study (NP25158). Preclinical studies suggest that CYP3A4 metabolism and subsequent glucuronidation are responsible for the metabolism of vemurafenib that is observed to occur in patients.

Further details on potential vemurafenib drug-drug interactions mediated via cytochrome P450 enzymes are presented below. Also presented is a brief section on potential interactions between vemurafenib and drugs that may cause QTc interval prolongation and cardiac arrhythmia.

4.4.1.2.1 CYP3A4 substrates

In the CYP450 probe study NP22676, vemurafenib induced CYP3A4 activity in melanoma patients by approximately 2-fold, as evidenced by a parent-to-metabolite AUC ratio of 2.2 for midazolam in the presence vs. the absence of vemurafenib. This interaction was statistically significantly outside the customary no-effect boundary (0.8–1.25). Thus, medications predominantly metabolized via CYP3A4 may have decreased exposure when administered concomitantly with vemurafenib.

The clinical significance of this observation depends on the therapeutic index of the specific CYP3A4 substrate administered concomitantly with vemurafenib. If CYP3A4 substrates must be co-administered with vemurafenib, the Investigator should monitor the signs of reduced benefit of CYP3A4 drugs due to potential decrease in their plasma concentration. Doses of the concomitant CYP3A4 drug, but not the dose of vemurafenib, may be adjusted as necessary to alleviate the impact of drug interaction.

Appendix 2 includes a non-exhaustive list of CYP3A4 substrates.

4.4.1.2.2 CYP1A2 substrates

In the CYP450 probe study NP22676, vemurafenib inhibited CYP1A2 in metastatic melanoma patients by approximately 3-fold, as evidenced by a parent-to-metabolite AUC ratio of 0.32 for xanthine in the presence vs. the absence of vemurafenib. This interaction was statistically significantly outside the customary no-effect boundary (0.8–1.25). Similarly, other PK assessments have demonstrated drug-drug interactions between vemurafenib and caffeine that are consistent with CYP1A2 inhibition. **Thus, medications predominantly metabolized via CYP1A2 may have increased exposure when administered concomitantly with vemurafenib.**

The clinical significance of these observations depends on the therapeutic index of the specific CYP1A2 substrate administered with vemurafenib. The Investigator should assess the safety risk associated with a potential increase in plasma concentrations of any concomitantly administered, CYP1A2 metabolized drug. If there is a concern, doses of the concomitant CYP1A2 drug, but not the dose of vemurafenib, may be adjusted as necessary to alleviate the impact of drug interaction.

Appendix 2 includes a non-exhaustive list of CYP1A2 substrates.

4.4.1.2.3 CYP2C9 substrates

Vemurafenib exhibited a strong signal for CYP2C9 inhibition *in vitro* in human hepatic microsomes (IC50, 5.9 µM). This *in vitro* inhibition did not appear to be as significant, however, in melanoma patients. Thus, in the NP22676 study, vemurafenib increased exposure to warfarin, a CYP2C9 substrate, by approximately 20%, which was within the statistical no-effect boundary.

It should be noted, though, that some increase in warfarin exposure and a decrease in clearance were noted in NP22676. Warfarin has a narrow therapeutic index, and the potential increase in warfarin exposure, the *in vitro* evidence of CYP2C9 inhibition, and the inherent propensity for coagulation disorders in patients with malignant disease urge caution when vemurafenib is co-administered with warfarin. The same considerations are true of other medications with narrow therapeutic indices that are metabolized primarily by CYP2C9.

Appendix 2 includes a non-exhaustive list of CYP2C9 substrates.

4.4.1.2.4 CYP2C19 and CYP2D6 substrates

No drug-drug interactions have been observed between with omeprazole (a CYP2C19 substrate) and dextromethorphan (a CYP2D6 substrate).

4.4.1.2.5 Drugs that may cause QTc prolongation or cardiac arrhythmia

In a Good Laboratory Practice patch clamp assay, the IC_{50} for inhibition of the human Ether-à-go-go Related Gene (hERG) channel in serum-free conditions was 1.24 µM. Due to a potential preclinical signal for hERG ion channel blockade by vemurafenib *in vitro* and clinical evidence that vemurafenib may prolong QTc interval, caution should be taken when vemurafenib is co-administered with drugs that cause QTc prolongation or cardiac arrhythmia, or when they have a pre-exiting cardiac disease or ECG abnormality that may predispose them to cardiac dysrhythmia.

Investigators should closely monitor patients who are on medications and/or supplements that may affect QT interval prolongation. Such agents include, but are not limited to, terfenadine, quinidine, procainamide, disopyramide, sotalol, probucol, bepridil, haloperidol, risperidone, indapamide, and other drugs with dysrhythmic potential. Alternative treatment options for medications known to affect QT interval should be discussed with each patient prior to their inclusion into this study. Please refer to QT Drug List by Risk Groups (http://www.azcert.org/) for additional information and Appendix 3.

4.5 CRITERIA FOR PREMATURE WITHDRAWAL

Patients have the right to withdraw from the study at any time for any reason. Patients who discontinue the study will be asked to return to the clinic for an End of Treatment Visit and a Safety Follow-Up Visit 28 (± 5) days after the last dose of vemurafenib.

If lost to follow-up, the Investigator should make all possible efforts to contact the patient or a responsible relative by telephone followed by registered mail or through a personal visit to establish as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made with an explanation of why the patient is withdrawing from the study.

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

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

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

4.6 REPLACEMENT POLICY (ENSURING ADEQUATE NUMBERS OF EVALUABLE PATIENTS)

4.6.1 For Patients

The following patients will be replaced:

- patients who never received study treatment as per protocol
- patients who did not have measurable disease at baseline

4.6.2 For Centres

A centre may be replaced for the following administrative reasons:

- Excessively slow recruitment
- Poor protocol adherence

5. SCHEDULE OF ASSESSMENTS AND PROCEDURES

Table 8a:
Schedule of Assessments for Cohorts 1, 2, 3a, 4 – 7 (Cohorts with Vemurafenib Study Treatment Only)

	Screening Period [1]	Treatment Period [2]										End of Treatment Visit [3]	Safety Follow-Up Visit [4]	Survival Follow-Up [5]
Cycle		**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9 onwards**		**Post treatment d/c**	**Every 3 months**
Day	**–28 to –1**	**1**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**Every 28 Days**		**28 (± 5) days**	
Allowed Visit Window (days)			**± 2**	**± 5**										
Informed consent [6]	X													
Documentation of BRAF V600 mutation via local test; sample taken for retrospective confirmation [7]	X													
Medical history and demographics	X													
Physical examination [8]	X	X	X	X	X	X	X	X	X	X	X	X		
Vital signs [9]	X	X	X	X	X	X	X	X	X	X	X (Q8 weeks)	X		
12-lead ECG [10]	X			X	X	X	X			X	C11 (then Q12 weeks)	X	X	
ECOG performance status	X	X	X	X	X	X	X	X	X	X	X (Q8 weeks)	X		

	Screening Period [1]	Treatment Period [2]										End of Treatment Visit [3]	Safety Follow-Up Visit [4]	Survival Follow-Up [5]
Cycle		**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9 onwards**		**Post treatment d/c**	**Every 3 months**
Day	**–28 to –1**	**1**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**Every 28 Days**		**28 (± 5) days**	
Allowed Visit Window (days)			**± 2**	**± 5**										
Haematology [11]	X	X[12]	X	X	X	X	X	X	X	X	X	X		
Biochemistry [13]	X	X[12]	X	X	X	X	X	X	X	X	X	X		
Serum pregnancy test [14]	X													
Solid tumour assessments (CT/MRI) [15]	X				X		X		X		X (Q8 weeks)	X		
Assessments for Multiple Myeloma [16]	X				X[17]	X[17]	X[17]	X[17]	X[17]	X[17]	X[17]	X[17]		
Dermatology evaluation [18]	X			X			X			X	C11 (then Q12 weeks)	X	X[19]	At 6 months
Head and neck assessment for SCC [20]	X					X			X		C10 (then Q12 weeks)	X	X[19]	At 6 months
Chest CT for evaluation of SCC [21]	X								X		C13 (then Q6 months)		X[19]	At 6 months
Drug dispensation		X		X	X	X	X	X	X	X	X			
Drug accountability				X	X	X	X	X	X	X	X	X		

	Screening Period [1]	Treatment Period [2]										End of Treatment Visit [3]	Safety Follow-Up Visit [4]	Survival Follow-Up [5]
Cycle		**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9 onwards**		**Post treatment d/c**	**Every 3 months**
Day	**–28 to –1**	**1**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**Every 28 Days**		**28 (± 5) days**	
Allowed Visit Window (days)			**± 2**	**± 5**										
Drug Dosing Exception Diary [22]				X	X	X	X	X	X	X	X	X		
Prostate Cancer patients only – PSA Assessment [23]	X				X		X		X		X (Q8 weeks)	X		
Prostate Cancer patients only – Bone Scans [24]	X				X		X		X		X (Q8 weeks)	X		
ECD/LCH patients only – C-reactive protein[25]		X		X	X		X		X		X (Q8 weeks)	X		
ECD/LCH patients only – additional tumour assessments [26]	X				X		X		X		X (Q8 weeks)	X		
Mandatory PK sampling (all newly enrolled patients) [27]		X	X	X	X	X								
Biomarker assessment (optional) [28]		X		X	at time of PD, if applicable								X (if no PD)	
Concomitant medications [29]	X	X										X	X	
AEs / SAEs [30]	X	X										X	X	
Vemurafenib administration		X												

	Screening Period [1]	Treatment Period [2]										End of Treatment Visit [3]	Safety Follow-Up Visit [4]	Survival Follow-Up [5]
Cycle		**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9 onwards**		**Post treatment d/c**	**Every 3 months**
Day	**–28 to –1**	**1**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**Every 28 Days**		**28 (± 5) days**	
Allowed Visit Window (days)			**± 2**	**± 5**										
Follow-up for disease progression														X
Survival status [5]													X	X
Next anticancer therapy														X
Anal and pelvic exam [31]	**X**												X	

Notes Day 1 = first dose of study drug (vemurafenib)

1. Apart from obtaining written informed consent, no screening procedure may be performed before the patient has been confirmed to be positive for the BRAF V600 mutation (see footnote 7).
2. Visits during the Treatment Period are to be completed on Day 1, Day 15, Day 29 and every 28 days thereafter until study drug discontinuation. A window of ± 2 days will apply for Cycle 1 / Day 15, and ± 5 days is allowed for each visit from Cycle 2 onwards (28-day cycle).
3. The End of Treatment Visit will be performed when the patient discontinues vemurafenib regardless of when it occurs.
4. The Safety Follow-Up Visit will be performed after 28 (± 5) days from discontinuation of vemurafenib.
5. The Survival Follow-Up period will last for a minimum of 12 months after the last patient has been enrolled or until all patients have died, withdrawn consent or are lost to follow-up (whichever occurs first). The head and neck exam and chest CT for evaluation of SCC, and the dermatology evaluation should be done either 6 months following study drug discontinuation or prior to the initiation of another anti-neoplastic therapy, whichever occurs first.
6. Informed consent must be obtained prior to performing any study procedure including Screening assessments. The date of signature on the informed consent form signifies the beginning of the 28-day Screening Period.
7. Patients with BRAF V600 mutation-positive cancers will be identified through mutation analysis assays, as routinely performed at each participating site. BRAF V600 mutation and test used for the detection of the BRAF mutation assay will be recorded in the eCRFs. Note: for the patient to be eligible, they must be able to provide a tumour sample (preferably tissue; alternatively DNA) for retrospective confirmation of the BRAF mutation by a central laboratory. This tumour sample (formalin-fixed paraffin-embedded tumour tissue [FFPET] or 3-5 serially cut unstained 5-µm sections from one FFPET block) should preferably be from the original specimen used to detect the BRAF mutation. The original tumour block will

be returned to the site. If archival samples are not available, the patient should be biopsied in order to obtain adequate tissue. Exceptions may be considered upon discussion with the Sponsor (e.g. ≥ 250 ng of DNA may be sent instead of tissue samples).

8. Includes the evaluation of the head, eyes, ears, nose, and throat (HEENT); cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal and neurological systems examination; and height (cm) and weight (kg). Height will only be measured during screening.
9. Includes blood pressure, heart rate, temperature and respiratory rate.
10. Includes heart rate, PR interval, QRS duration, QT and QTc intervals and ECG findings.
11. Includes haemoglobin, haematocrit, platelet count, white blood cell count (WBC) and absolute neutrophil count (ANC)
12. Haematology and biochemistry assessments do not need to be repeated on Day 1 if performed within 7 days of first vemurafenib administration. NB: if it is necessary to repeat these blood tests, the results must be known before the patient receives first dose of vemurafenib to ensure that the inclusion and exclusion criteria related to these tests are met.
13. Includes amylase, lipase, glucose, blood urea nitrogen [BUN], creatinine or creatinine clearance, sodium, potassium, calcium, magnesium, bicarbonate ([if routinely performed on venous blood samples],), total bilirubin with fractionation into direct and indirect (if total bilirubin elevated during the study; if one component is available, the other component can be calculated), alkaline phosphatase, AST ([SGOT]], ALT ([SGPT]],
14. Serum pregnancy test to be performed within 7 days prior to first vemurafenib administration for women with childbearing potential.
15. Includes for solid tumour patients only: CT/MRI of the chest, abdomen and pelvis [C/A/P]). The same imaging technique (CT or MRI) should be used for these patients throughout the study. Exception: for patients with a confirmed primary brain tumour, the CT/MRI of C/A/P may be omitted. In addition, CT/MRI of the brain may also be performed as per standard of care. For all patients in Cohort 1, the CT scans during the patient's last therapy prior to this study, as well as CT scans made during this study, will be collected and reviewed retrospectively by an IRC. The collection of scans and IRC review may also be considered for confirmation of efficacy assessments for other cohorts where clinically meaningful efficacy is demonstrated with Investigator assessment.
16. Serum protein electrophoresis (SPEP), Urine protein electrophoresis (UPEP), Serum free light chains, 24 hour urine proteins, Bone marrow for histology, cytogenetics and FISH, and flow cytometry with or without biopsy, Beta 2 microglobulin, albumin and lactate dehydrogenase (LDH). A skeletal survey is done during Screening only; thereafter it should be done as per routine clinical practice.
17. Bone marrow assessment only to be done to confirm complete remission after two consecutive immunofluorescence analyses are negative.
18. Performed by a dermatologist. For patients who develop any suspicious new skin lesion during treatment with vemurafenib. Further confirmation by a designated central pathology laboratory. Only required at the End of Treatment Visit if not performed in the previous 12 weeks. Should be done at Safety Follow-up Visit at 28 days (± 5 days) and at 6 months following study drug discontinuation or prior to the initiation of another anti-neoplastic therapy (whichever occurs first).
19. Performed by the treating physician as part of the evaluation for SCC. Should also be done at Safety Follow-up Visit at 28 days (± 5 days) and at 6 months following study drug discontinuation or prior to the initiation of another anti-neoplastic therapy (whichever occurs first).
20. CT of the chest for the evaluation of non-cutaneous SCC (for all patients, solid tumours and MM). For patients with solid tumours, the routinely scheduled radiographic assessment for tumour burden may be used (if available) as the chest CT for the evaluation of non-cutaneous SCC while the patient is taking vemurafenib.
21. Must be performed at this visit and 6 months following study drug discontinuation or prior to the initiation of another anti-neoplastic therapy (whichever occurs first).
22. Patients will keep a diary to record ONLY those occasions when a vemurafenib dose was missed (morning or evening, each day of treatment). The patient will bring this diary with him/her to each study visit to allow missed doses to be recorded by the Investigator.
23. See Appendix 9.

24. See Appendix 9 for further details. Bone scans to be performed every 8 weeks or as per institution standard of care, but at a minimum every 16 weeks and at the End of Treatment Visit.
25. See Appendix 10 for further details.
26. Baseline tumour assessments must include CT/MRI of the chest, abdomen and pelvis (C/A/P) and any additional assessment as clinically relevant as described in Appendix 10 to define baseline extent of disease (brain MRI, cardiac MRI/echo, bone scan, ^{18}F-FDG PET). For patients with baseline measurable disease according to RECIST v1.1, the following tumour assessments will consist of the same method(s) used at baseline to determine measurable disease (CT/MRI of [C/A/P], brain MRI, cardiac MRI). For all other patients the following tumour assessments will consist of the same method/s used at baseline that have defined the area involved by the disease (brain MRI, cardiac MRI/echo, bone scan, ^{18}F-FDG PET, CT chest/abdomen/pelvis) as described in Appendix 10.
27. For all newly enrolled patients in all cohorts, mandatory blood samples will be taken during Cycle 1 (Day 1 and Day 15) and Cycles 2 - 4 (Day 1) for PK analysis. Samples will be taken pre-dose and 2-4 hours post-dose of the morning dose on the corresponding days (see Table 9). For the day of the PK assessment, patients should be instructed not to take their morning dose, and to bring their study medication with them to their clinic visit. For all PK samples, the date and time of the last dose of vemurafenib should be recorded, along with the actual time of the PK blood draw. Approximately 2 mL of blood will be collected at each time point. The procedures for the collection, handling and shipping of samples for PK can be found in the study's Laboratory Manual.
28. Blood samples for exploratory biomarkers are optional, and can be collected from any newly enrolled patient in any cohort. All samples will be taken pre-dose of the morning dose on the corresponding days (see Table 10). In addition to the samples collected at Cycles 1 and 2, a sample will be collected at the Safety Follow-up Visit or at the time of disease progression (whichever occurs first). The procedures for the collection, handling and shipping of biomarker samples can be found in the study's Laboratory Manual.
29. All concomitant medications during the study started within 14 days prior to the screening visit and up to the Safety Follow-up Visit must be recorded.
30. During screening AEs are not recorded in the eCRF unless they are SAEs which are related to protocol-mandated procedures. ALL AEs (including SAEs) must be recorded from the time of first vemurafenib administration. After the last dose of vemurafenib any new, AEs should be reported up to 28 days after last dose. The Investigator is not required to actively monitor patients for adverse events after the end of the adverse event reporting period (defined as 28 days after the last dose of study drug). However the Sponsor should be notified if the Investigator becomes aware of any SAE that occurs after the end of the adverse event reporting period, if the event is believed to be related to prior study drug treatment. After the study site has closed, the Investigator should report adverse reactions as mandated in the protocol directly to the Local Drug Safety Affiliate.
31. Pelvic examinations for women (with special attention to cervix) and anal examinations for all patients will be performed at screening and at the Safety Follow-up Visit for evaluation of SCC. The pelvic examination should include a complete external and internal examination (internal examination of uterine cervix may include a Pap smear, which would be a decision of the investigator). The anal examination should include external examination, digital anorectal examination and anoscopy or proctoscopy. However, if in opinion of the investigator the presence of "abnormal lesions including SCC" can be excluded by the external inspection and the manual examination, this is acceptable. However, if the presence of a lesion is suspected, an anoscopy or proctoscopy are recommended.

Table 8b:
Schedule of Assessments for Cohort 3b (Colorectal Cohort with Vemurafenib and Cetuximab Study Treatment)

	Screening Period [1]	Treatment Period [2]													End of Treatment Visit [3]	Safety Follow-Up Visit [4]	Survival Follow-Up [5]
Cycle (C)		1					2				3 onwards						
Study Day	–28 to –1	1	2	8	15	22	29	36	43	50						Post treatment d/c	Every 3 months
Cycle Day		1	2	8	15	22	1	8	15	22	1	8	15	22		28 (± 5) days	
Allowed Visit Window (days)				± 1													
Informed consent [6]	X																
Documentation of BRAF V600 mutation via local test; sample taken for retrospective confirmation [7]	X																
Medical history and demographics	X																
Physical examination [8]	X	X		X	X	X	X	X	X	X	X		X		X		
Vital signs [9]	X	X		X	X	X	X	X	X	X	X		X		X		
12-lead ECG [10]	X						X				X + C4 and C5 (then Q12 weeks)				X	X	

	Screening Period [1]	Treatment Period [2]													End of Treatment Visit [3]	Safety Follow-Up Visit [4]	Survival Follow-Up [5]
Cycle (C)		**1**					**2**				**3 onwards**						
Study Day	**–28 to –1**	**1**	**2**	**8**	**15**	**22**	**29**	**36**	**43**	**50**						**Post treatment d/c**	**Every 3 months**
Cycle Day		**1**	**2**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**		**28 (± 5) days**	
Allowed Visit Window (days)				**± 1**													
ECOG performance status	X	X		X	X	X	X	X	X	X	X		X		X		
Haematology [11]	X	X[12]		X	X	X	X	X	X	X	X		X		X		
Biochemistry [13]	X	X[12]		X	X	X	X	X	X	X	X		X		X		
Serum pregnancy test [14]	X																
Tumour assessments (CT/MRI) [15]	X										X (Q8 weeks)				X		
Dermatology evaluation [16]	X						X				C5 (then Q12 weeks)				X	X[17]	At 6 months
Head and neck assessment for SCC [18]	X										C4 (then Q12 weeks)				X	X[17]	At 6 months
Chest CT for evaluation of SCC [19]	X										C7 (then Q6 months)					X[17]	At 6 months

	Screening Period [1]	Treatment Period [2]													End of Treatment Visit [3]	Safety Follow-Up Visit [4]	Survival Follow-Up [5]
Cycle (C)		**1**					**2**				**3 onwards**						
Study Day	**–28 to –1**	**1**	**2**	**8**	**15**	**22**	**29**	**36**	**43**	**50**						**Post treatment d/c**	**Every 3 months**
Cycle Day		**1**	**2**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**		**28 (± 5) days**	
Allowed Visit Window (days)				**± 1**													
Vemurafenib dispensation (**Part 1**)			X[20]				X		X		X (Q4 weeks)						
Vemurafenib dispensation (**Part 2**)		X					X		X		X (Q4 weeks)						
Vemurafenib accountability							X		X		X (Q4 weeks)				X		
Vemurafenib Dosing Exception Diary [21]				X	X	X	X	X	X	X	X (Q4 weeks)				X		
DLTs [22]				X	X	X	X										
Concomitant medications [23]	X		X												X	X	
AEs / SAEs [24]	X		X												X	X	
Cetuximab administration		X		X	X	X	X	X	X	X	X	X	X	X			

	Screening Period [1]	Treatment Period [2]													End of Treatment Visit [3]	Safety Follow-Up Visit [4]	Survival Follow-Up [5]
Cycle (C)		1					2				3 onwards						
Study Day	–28 to –1	1	2	8	15	22	29	36	43	50						Post treatment d/c	Every 3 months
Cycle Day		1	2	8	15	22	1	8	15	22	1	8	15	22		28 (± 5) days	
Allowed Visit Window (days)				± 1													
Follow-up for disease progression																	X
Survival status [5]																X	X
Next anticancer therapy																	X
Anal and pelvic exam [25]	X															X	

Notes Day 1 = first dose of study drug

1. Apart from obtaining written informed consent, no screening procedure may be performed before the patient has been confirmed to be positive for the BRAF V600 mutation (see footnote 7).
2. Visits during the Treatment Period are to be completed on Day 1, Day 8, Day 15, Day 22, Day 29 and every 14 days thereafter until study drug discontinuation. A visit window of ± 1 day will apply starting on Day 8 of Cycle 1 and onwards.
3. The End of Treatment Visit will be performed when the patient discontinues study medication regardless of when it occurs.
4. The Safety Follow-Up Visit will be performed after 28 (± 5) days from discontinuation of study medication
5. The Survival Follow-Up period will last for a minimum of 12 months after the last patient has been enrolled or until all patients have died, withdrawn consent or are lost to follow-up (whichever occurs first). The head and neck exam and chest CT for evaluation of SCC, and the dermatology evaluation should be done either 6 months following study drug discontinuation or prior to the initiation of another anti-neoplastic therapy, whichever occurs first.
6. Informed consent must be obtained prior to performing any study procedure including Screening assessments. The date of signature on the informed consent form signifies the beginning of the 28-day Screening Period.

7. Patients with BRAF V600 mutation-positive cancers will be identified through mutation analysis assays, as routinely performed at each participating site. BRAF V600 mutation and test used for the detection of the BRAF mutation assay will be recorded in the eCRFs. Note: for the patient to be eligible, they must be able to provide a tumour sample (preferably tissue; alternatively DNA) for retrospective confirmation of the BRAF mutation by a central laboratory. This tumour sample (formalin-fixed paraffin-embedded tumour tissue [FFPET] or 3-5 serially cut unstained 5-µm sections from one FFPET block) should preferably be from the original specimen used to detect the BRAF mutation. The original tumour block will be returned to the site. If archival samples are not available, the patient should be biopsied in order to obtain adequate tissue. Exceptions may be considered upon discussion with the Sponsor (e.g. ≥ 250 ng of DNA may be sent instead of tissue samples).
8. Includes the evaluation of the head, eyes, ears, nose, and throat (HEENT); cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal and neurological systems examination; and height (cm) and weight (kg). Height will only be measured during screening.
9. Includes blood pressure, heart rate, temperature and respiratory rate.
10. Includes heart rate, PR interval, QRS duration, QT and QTc intervals and ECG findings.
11. Includes haemoglobin, haematocrit, platelet count, white blood cell count (WBC) and absolute neutrophil count (ANC)
12. Haematology and biochemistry assessments must be done on Day 1, prior to cetuximab administration.
13. Includes amylase, lipase, glucose, blood urea nitrogen [BUN], creatinine or creatinine clearance, sodium, potassium, calcium, magnesium, bicarbonate ([if routinely performed on venous blood samples],), total bilirubin with fractionation into direct and indirect (if total bilirubin elevated during the study; if one component is available, the other component can be calculated), alkaline phosphatase, AST ([SGOT]], ALT ([SGPT]]
14. Serum pregnancy test to be performed within 7 days prior to first vemurafenib administration for women with childbearing potential.
15. CT/MRI of the chest, abdomen and pelvis [C/A/P]). The same imaging technique (CT or MRI) should be used for these patients throughout the study. In addition, CT/MRI of the brain may also be performed as per standard of care.
16. Performed by a dermatologist. For patients who develop any suspicious new skin lesion during treatment with study medication. Further confirmation by a designated central pathology laboratory. Only required at the End of Treatment Visit if not performed in the previous 12 weeks. Should be done at Safety Follow-up Visit at 28 days (± 5 days) and at 6 months following study drug discontinuation or prior to the initiation of another anti-neoplastic therapy (whichever occurs first).
17. Must be performed at this visit and 6 months following study drug discontinuation or prior to the initiation of another anti-neoplastic therapy (whichever occurs first).
18. Performed by the treating physician as part of the evaluation for SCC. Should be done at Safety Follow-up Visit at 28 days (± 5 days) and at 6 months following study drug discontinuation or prior to the initiation of another anti-neoplastic therapy (whichever occurs first).
19. CT of the chest for the evaluation of non-cutaneous SCC. The routinely scheduled radiographic assessment for tumour burden may be used (if available) as the chest CT for the evaluation of non-cutaneous SCC while the patient is taking study medication.
20. For patients in Part I of Cohort 3b, vemurafenib will start on Day 2 of Cycle 1 (administered while in hospital).
21. Patients will keep a diary to record ONLY those occasions when a vemurafenib dose was missed (morning or evening, each day of treatment). The patient will bring this diary with him/her to each study visit to allow missed doses to be recorded by the Investigator.
22. Only for patients enrolled in the Part 1 of Cohort 3b (the dose-escalation part of the study)
23. All concomitant medications during the study started within 14 days prior to the screening visit and up to the Safety Follow-up Visit must be recorded.
24. During screening AEs are not recorded in the eCRF unless they are SAEs which are related to protocol-mandated procedures. ALL AEs (including SAEs) must be recorded from the time of first study drug administration. After the last dose of study medication any new AEs should be reported up to 28 days after last dose. The Investigator is not required to actively

monitor patients for adverse events after the end of the adverse event reporting period (defined as 28 days after the last dose of study drug). However the Sponsor should be notified if the Investigator becomes aware of any SAE that occurs after the end of the adverse event reporting period, if the event is believed to be related to prior study drug treatment. After the study site has closed, the Investigator should report adverse reactions as mandated in the protocol directly to the Local Drug Safety Affiliate.

25. Pelvic examinations for women (with special attention to cervix) and anal examinations for all patients will be performed at screening and at the Safety Follow-up Visit for evaluation of SCC. The pelvic examination should include a complete external and internal examination (internal examination of uterine cervix may include a Pap smear, which would be a decision of the investigator). The anal examination should include external examination, digital anorectal examination and anoscopy or proctoscopy. However, if in opinion of the investigator the presence of “abnormal lesions including SCC” can be excluded by the external inspection and the manual examination, this is acceptable. However, if the presence of a lesion is suspected, an anoscopy or proctoscopy are recommended.

All screening assessments as outlined in Table 8a and Table 8b - Schedule of Assessments must be performed within 28 days prior to the first administration of study medication on Day 1.

Results of tests or examinations performed as standard of care before obtaining informed consent and within the 28 days prior to commencing study medication may be used.

Eligibility for the study will be determined by the Investigator from the mandatory screening assessments performed during the Screening Period and according to the study inclusion/exclusion criteria. First dosing of study medication will be determined by the patient's eligibility and the laboratory assessments done on Day 1 prior to dosing on Day 1.

The Investigator/Designee will collect and document in the eCRFs whether the patient has progressed or not.

Patients who discontinue vemurafenib (vemurafenib and cetuximab in the Cohort 3b) for any reason (disease progression, AEs, etc.) other than consent withdrawal will continue to be followed for survival and new anti-cancer therapy every 3 months after last dose until death or for a minimum of 12 months after the last patient has been enrolled or until all patients have died, withdrawn consent or are lost to follow-up (whichever occurs first).

5.1 SCREENING EXAMINATION AND ELIGIBILITY SCREENING FORM

All patients must provide written informed consent before any study specific assessments or procedures are performed. The patient who has provided a written informed consent will be allocated a patient number by the IxRS system which has been established for the purpose of this study. Each identifying number will be unique to the patient for whom it is issued.

All screening evaluations must be performed between Day –28 and Day –1. Patients who fulfil all the inclusion and none of the exclusion criteria will be accepted into the study.

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

A log must be maintained by the Investigator of all patients who fail screening. For consented patients who fail to meet the inclusion and exclusion criteria, only the Screening Log pages, demographics, and reason for screening failure will be collected.

5.1.1 Procedures for Screening Patients for the BRAF V600 Mutation

Patients with BRAF V600 mutation-positive cancers will be identified through mutation analysis assays as routinely performed at each participating site (the BRAF V600 mutation and the assay used for its detection will be recorded in the eCRFs).

5.2 PROCEDURES FOR ENROLMENT OF ELIGIBLE PATIENTS

A patient who has fulfilled the entry criteria will attend on the morning of Day 1. The same patient number allocated to the patient during screening will be used throughout the study. A patient number will not be re-used if the patient leaves the study.

Under no circumstances will patients who enrol in this study and have completed treatment as specified be permitted to re-enrol in the study.

A Patient Enrolment and Identification Code List must be maintained by the Investigator.

5.3 CLINICAL ASSESSMENTS AND PROCEDURES

The following clinical assessments and procedures must be completed for all patients enrolled in this study.

Please refer to Table 8a and Table 8b - Schedule of Assessments for specific details and time points related to the clinical assessments and procedures outlined below:

5.3.1 Screening Period*

The following assessments should be performed within 28 days before the first administration of study medication on Day 1 (unless they have already been conducted during this time period as part of the patient's routine clinical care):

- Signed written informed consent approved by the relevant Independent Ethics Committee (IEC) / Institutional Review Board (IRB) must be obtained prior to performing any study-related procedures
- Documentation of BRAF V600 mutation and test used for the identification of the mutation.
- Sites must submit a tumour sample for retrospective confirmation in a central laboratory of the BRAF mutation using the Roche CoDx cobas 4800 BRAF V600 Test or other standard methodology. This tumour sample should preferably be from the original specimen used to detect the BRAF mutation. The original tumour block will be returned back to the site. If archival samples are not available, the patient should be biopsied in order to obtain adequate tissue. Exceptions may be considered upon discussion with the Sponsor (e.g. ≥ 250 ng DNA may be sent instead of tissue samples).
- Medical history (including demographics)
- Physical examination, including the evaluation of the head, eyes, ears, nose, and throat (HEENT); cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and a neurological systems examination; height and weight (height will only be measured during screening)
- Vital signs (blood pressure, heart rate, temperature, respiratory rate)
- 12-lead ECG, including heart rate, PR interval, QRS duration, QT and QTc intervals and ECG findings
- ECOG Performance Status
- Haematology, including haemoglobin, haematocrit, platelet count, white blood cell count (WBC) and absolute neutrophil count (ANC)
- Biochemistry (including amylase, lipase, glucose, blood urea nitrogen ([BUN]], creatinine or creatinine clearance, sodium, potassium, calcium, magnesium, bicarbonate ([if routinely performed on venous blood samples]), total bilirubin with fractionation into direct and indirect (if total bilirubin elevated during the study; if one component is available, the other component can be calculated), alkaline phosphatase, AST ([SGOT]], ALT [(SGPT)].
- Serum pregnancy test within 7 days prior to commencement of dosing for women of child-bearing potential. Women surgically sterile or postmenopausal for ≥ 1 year are not to be considered for a pregnancy test.
- Tumour assessments for patients with solid tumours (CT/MRI of the chest, abdomen and pelvis [C/A/P]). Exception: for patients with a confirmed primary brain tumour, the CT/MRI of

C/A/P may be omitted. In addition, CT/MRI of the brain may also be performed as per standard of care

- For all patients in Cohort 1, the CT scans during the patient's last therapy prior to this study will be collected and reviewed retrospectively by an IRC. The collection of scans and IRC review may also be considered for confirmation of efficacy assessments for other cohorts where clinically meaningful efficacy is demonstrated with Investigator assessment.
- Assessments for multiple myeloma (Skeletal survey, Serum protein electrophoresis (SPEP) with quantitation of M-protein by immunofixation, Urine protein electrophoresis (UPEP) using 24 hours urine protein electrophoresis, Serum free light chains, Bone marrow for histology, cytogenetics and FISH, and flow cytometry with or without biopsy, Beta 2 microglobulin albumin and lactate dehydrogenase (LDH)
- Dermatology evaluation by a dermatologist.
- Head and neck examination (as part of the evaluation for SCC) performed by the treating physician
- CT of chest for evaluation of non-cutaneous SCC (for all patients, solid tumours and MM. For solid tumours, the routinely performed chest CT for tumour assessment may be used as chest CT for the evaluation of non-cutaneous SCC while the patient is taking vemurafenib)
- Concomitant medications
- AEs (including SAEs) related to study-mandated procedures from time ICF is signed
- Pelvic examinations for women (with special attention to cervix) and anal examinations for all patients for evaluation of SCC

*For patients included in Cohort 7 with Prostate cancer or ECD/LCH, see Appendix 9 and Appendix 10, respectively, for additional assessments.

5.3.2 Treatment Period*

Visits during the treatment period are to be completed on Day 1, Day 15, Day 29, and every 28 days thereafter. A window of ± 2 days will apply for Cycle 1 / Day 15, and ± 5 days is allowed for each visit from Cycle 2 onwards (28-day cycle).

For the patients included in Cohort 3b only, the visits will be weekly throughout the treatment period, and a visit window of ± 1 days will apply starting on Day 8 of Cycle 1 and onwards.

The following assessments should be performed during the Treatment Period:

- Physical examination (as described previously) on Day 1, Day 15, Day 29 and every 28 days thereafter until study drug discontinuation. For Cohort 3b only, physical examination assessments will be done weekly for the first 8 weeks, and then every 2 weeks thereafter from Day 57.
- Vital signs (as described previously) on Day 1, Day 15, Day 29 and every 28 days for the first 8 cycles and then every 8 weeks until study drug discontinuation. For Cohort 3b only, vital sign assessments will be done weekly for the first 8 weeks, and then every 2 weeks thereafter from Day 57.
- 12-lead ECG (as described previously) on Day 29, every 28 days for the following 3 months and every 12 weeks thereafter until study drug discontinuation

- ECOG performance status on Day 1, Day 15, Day 29 and every 28 days for the first 8 cycles and then every 8 weeks thereafter until study drug discontinuation. For Cohort 3b only, ECOG performance status assessments will be done weekly for the first 8 weeks, and then every 2 weeks thereafter from Day 57.
- Haematology (as described previously) on Day 1, Day 15, Day 29 and every 28 days thereafter until study drug discontinuation. For Cohort 3b only, haematology assessments will be done weekly for the first 8 weeks, and then every 2 weeks thereafter from Day 57.
  - Haematology assessments do not need to be repeated on Day 1 if performed within 7 days prior to the first vemurafenib administration (this does not apply to Cohort 3b, where haematology must be done on Day 1 prior to cetuximab administration)
- Biochemistry (as described previously) on Day 1, Day 15, Day 29 and every 28 days thereafter until study drug discontinuation. For Cohort 3b only, biochemistry assessments will be done weekly for the first 8 weeks, and then every 2 weeks thereafter from Day 57.
  - Biochemistry assessments do not need to be repeated on Day 1 if performed within 7 days prior to the first vemurafenib administration (this does not apply to Cohort 3b, where biochemistry must be done on Day 1 prior to cetuximab administration)
- The following tumour assessments are to be performed for all patients with solid tumours;
  - CT/MRI of the chest/abdomen/pelvis (C/A/P) every 8 weeks after starting study drug. The same imaging technique (CT or MRI) should be used for each patient throughout the study. Exception: for patients with a confirmed primary brain tumour, the CT/MRI of C/A/P may be omitted.
  - In addition, CT/MRI of the brain as per standard care
- For all patients in Cohort 1, the CT scans made during this study will be collected and reviewed retrospectively by an IRC. The collection of scans and IRC review may also be considered for confirmation of efficacy assessments for other cohorts where clinically meaningful efficacy is demonstrated with Investigator assessment.
- The following assessments are to be performed for patients with MM 8 weeks after starting vemurafenib and every 4 weeks thereafter;
  - Serum protein electrophoresis (SPEP) with quantitation of M-protein level by immunofixation, urine protein electrophoresis (UPEP) using 24-hour urine protein electrophoresis, Serum free light chains , LDH, and beta 2 microglobulin. Bone marrow analysis only to be done only to confirm complete remission after two consecutive immunofixation analyses are negative.
- Dermatology evaluation by a dermatologist 28 days after starting study drug and every 12 weeks thereafter until study drug discontinuation
- Head and neck examination (as part of the evaluation for SCC) performed by the treating physician every 12 weeks after starting study drug
- Chest CT for evaluation of SCC every 6 months after starting study drug (for all patients with solid tumours and MM)
- Vemurafenib dispensation on Day 1 and every 28 days thereafter until study drug discontinuation
- Vemurafenib accountability every 28 days after starting vemurafenib until study drug discontinuation

- Review of the vemurafenib Dosing Exception Diary every 28 days after starting vemurafenib until study drug discontinuation.
- Concomitant medications throughout the Treatment Period.
- AEs (including SAEs) throughout the Treatment Period.
- Assessment of dose-limiting toxicities on Day 8, Day 15, Day 22 and Day 29 in the first cycle for patients who are participating in the dose escalation phase of Cohort 3b Part 1 (see Section 6.3.2.2)
- For all newly enrolled patients in all cohorts, mandatory blood samples will be taken during Cycle 1 (Day 1 and Day 15) and Cycles 2 – 4 (Day 1) for PK analysis. Samples will be taken pre-dose and 2-4 hours post-dose of the morning dose on the corresponding days. For all PK samples, the date and time of the last dose of vemurafenib should be recorded, along with the actual time of PK blood draw. See Section 5.4.2.
- For newly enrolled patients in any cohort, blood samples for exploratory biomarkers are optional. Samples will be taken pre-dose during Cycle 1 (Day 1) and Cycle 2 (Day 1), as well as at the End of Treatment Visit or at time of disease progression (whichever occurs first). See Section 5.4.3.
- Vemurafenib administration throughout the Treatment Period. Note that for patients in Part I of Cohort 3b, vemurafenib will start on Day 2 of Cycle 1 (administered while in hospital).
- Weekly administration of cetuximab throughout the Treatment Period for all patients included in Cohort 3b.

* Patients included in Cohort 7 with Prostate cancer or ECD/LCH, see Appendix 9 and Appendix 10, respectively, for additional assessments.

5.3.3 End of Treatment Visit

The End of Treatment Visit will occur when the patient discontinues vemurafenib for any reason, unless the patient withdraws consent and refuses, or is lost to follow-up. The following assessments will be conducted at the End of Treatment Visit:

- Physical examination (as described previously)
- Vital signs (as described previously)
- 12-lead ECG (as described previously)
- ECOG Performance Status
- Haematology (as described previously)
- Biochemistry (as described previously)
- Tumour assessments (as described previously) if not done within the last 8 weeks
- Response assessments for multiple myeloma if not done within the last 28 days
- Dermatology evaluation by a dermatologist if not done within the previous 12 weeks
- Head and neck examination (as part of the evaluation for SCC) performed by the treating physician every 12 weeks after starting vemurafenib Drug accountability
- Review of the Drug Dosing Exception Diary
- Concomitant medications
- AEs (including SAEs)

- For newly enrolled patients in any cohort, blood samples for exploratory biomarkers are optional. Samples will be taken at the Safety Follow-up Visit or at time of disease progression (whichever occurs first). See Section 5.4.3.

5.3.4 Safety Follow-Up Visit

The Safety Follow-Up Visit will occur 28 (± 5) days after discontinuation of study drug. The following assessments will be conducted at the Safety Follow-Up Visit:

- 12-lead ECG (as previously described)
- Dermatology evaluation by a dermatologist
- Head and neck examination (as part of the evaluation for SCC) performed by the treating physician
- CT of the chest, dermatology evaluation by a dermatologist and head and neck examination for evaluation of SCC must be performed at this visit and in all patients (both solid tumour and MM) 6 months following study drug discontinuation or prior to the initiation of another anti-neoplastic therapy (whichever occurs first)
- Concomitant therapy
- AEs (including SAEs)
- Follow up for disease progression for those patients who have discontinued study drug for any reason (i.e., AEs, etc.) other than disease progression
- Survival status
- Pelvic examinations for women (with special attention to cervix) and anal examinations for all patients for evaluation of SCC
- For newly enrolled patients in any cohort, blood samples for exploratory biomarkers are optional. Samples will be taken at the Safety Follow-up Visit or at time of disease progression (whichever occurs first). See Section 5.4.3.

5.3.5 Survival Follow-Up

The following assessments will be conducted during the Survival Follow-Up Period:

- Survival status every 3 months after the last dose until death or for a minimum of 12 months after the last patient has been enrolled or until all patients have died, withdrawn consent or are lost to follow-up (whichever occurs first).
- Furthermore, new anticancer therapy will be documented.

5.3.6 Response Criteria

5.3.6.1 Solid tumours

Response of measurable solid tumours to study treatment will be evaluated by the Investigator according to RECIST, v1.1 criteria (Appendix 4) (67). See Appendix 9 for prostate, Appendix 10 for ECD and/or LCH specific response criteria.

Tumour evaluations will occur once during the Screening Period (Days –28 and –1), every 8 weeks after starting vemurafenib during the Treatment Period, and at the End of Treatment Visit. A window of ± 5 days of scheduled visit is allowed to complete the tumour assessments at the required intervals.

Radiological tumour assessments to measure extent of disease will be carried out by CT/MRI of the chest/abdomen/pelvis (C/A/P) for all patients. In addition, CT/MRI of the brain can be performed if clinically indicated and as per standard care.

Patients should be assessed at the designated time points using a consistent imaging modality. The same imaging technique must be used for a patient throughout the study. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. If more than one method of assessment is used at baseline, the most accurate method according to RECIST should be selected when recording data; in addition, this method should be performed in all subsequent evaluations. Tumour measurements should be made by the same Investigator/radiologist for each patient during the study to the extent that this is feasible.

For solid tumours to be assigned a status of partial response (PR) or complete response (CR) (i.e., a responder), changes in tumour measurements must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met, i.e., patients need to have two consecutive assessments of PR or CR to be a responder.

Symptomatic deterioration may indicate progressive disease (PD). However, radiological confirmation of PD is strongly recommended.

For all patients in Cohort 1, the CT scans during the patient's last therapy prior to this study, as well as CT scans made during this study, will be collected and reviewed retrospectively by an IRC. Scans from the prior therapy will be used to establish plTTP, and this may be examined in relation to the TTP achieved from study treatment. During the study, the investigator-assessed response rate will remain as the primary efficacy endpoint and the IRC assessment will be a supportive secondary endpoint. The concordance tables between Investigator and IRC assessment will be produced. The collection of scans and IRC review may also be considered for confirmation of efficacy assessments for other cohorts where clinically meaningful efficacy is demonstrated with Investigator assessment.

5.3.6.2 Multiple myeloma

Response of MM to study treatment will be evaluated according to IMWG uniform response criteria (Appendix 5) (68, 69).

Evaluations will occur once during the Screening Period (Days –28 and –1), 8 weeks after starting vemurafenib, every 28 days thereafter during the Treatment Period, and at the End of Treatment Visit.

Serum M-protein level will be quantitated using densitometry on serum protein electrophoresis (SPEP) by immunofixation.

Urine M-protein measurement will be estimated using 24-hour urine protein electrophoresis (UPEP) only. Random or 24-hour urine tests measuring kappa and lambda light chain levels are not reliable and are not recommended. For oligosecretory and light chain myeloma patients, serum free light chains will be measured.

Patients will need to have two consecutive assessments of CR, sCR, VGPR or PR to be considered a responder.

5.3.7 ECOG Performance Status

Performance Status will be measured using the Eastern Cooperative Oncology Group (ECOG) Performance Status Scale (Appendix 6) at each visit.

It is recommended that the same person assess a patient's performance status throughout the study, whenever possible.

5.3.8 Clinical Safety Assessments

The National Cancer Institute's Cancer Toxicity Criteria for Adverse Events, Version 4.0 (NCI-CTCAE, v4.0) will be used to quantify the intensity of AEs occurring during treatment in this study (Appendix 7).

Patients will be assessed for AEs at each clinic visit and as necessary throughout the study. Incidence, type, and severity of AEs, serious adverse events (SAEs), incidence of AEs and SAEs leading to study drug interruption or discontinuation, and cause of death will be reported.

All other safety monitoring will occur by the reporting of AEs, by the assessment of routine laboratory values (blood counts and differential and serum chemistries), vital signs, electrocardiograms (ECGs), dermatology, and head & neck evaluations for cutaneous squamous cell carcinoma (cSCC) and non-cutaneous SCC, respectively, chest CT scans for non-cutaneous SCC surveillance, and findings on physical examinations.

In addition during the dose escalation of vemurafenib and cetuximab in Part 1 of Cohort 3b, dose-limiting toxicities will be assessed at Days 8, 15, 22 and 29.

The schedule for safety assessments is presented in Table 8a and Table 8b - Schedule of Assessments**.** Individual assessments are described further below:

5.3.8.1 Medical history and demographics

As part of the physical exam, a medical history will be collected, including demographics, relevant medical history, previous and current diseases, prior therapies including surgeries and relative responses, prior skin cancer history, therapies and procedures, all medications started within 14 days prior to screening visit, and measurements for weight (kilograms, kg) and height (cm, screening visit only). Mutation and/or receptor status as applicable per tumour type (e.g. KRAS and EGFR expression for CRC).

5.3.8.2 Physical examination

The initial (Screening) complete physical examination should include the evaluation of the head, eyes, ears, nose, and throat (HEENT) and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Subsequent physical examinations during the study for safety assessment may be restricted to evaluation of specific systems or areas of interest, including those with previously abnormal findings or associated with symptomatic or laboratory evidence of toxicity. A skin examination by the treating physician should, however, be performed at each visit.

5.3.8.3 Vital signs

Vital signs will be recorded for all patients and will include blood pressure, temperature (degrees Celsius, °C), heart rate, and respiratory rate.

5.3.8.4 Squamous cell carcinoma assessments

5.3.8.4.1 Cutaneous SCC

Cutaneous squamous cell carcinoma (cSCC) is defined as an event requiring close monitoring. With the exception of events of actinic keratosis, these events must always be designated as SAEs in order to ensure their reporting to the Health Authorities in an appropriate and timely manner. Patients are required to have ongoing full skin examinations by a dermatologist to screen and monitor for SCC, basal cell carcinoma (BCC), actinic keratosis, and keratoacanthoma (KA). Dermatology evaluation will be performed at Screening/Baseline (anytime up to 28 days prior to Day 1), approximately 28 days on therapy, every 12 weeks thereafter while the patient is on the study, when the patient discontinues vemurafenib unless done within the prior 12 weeks, and at the Safety Follow-Up Visit 28 (± 5) days after discontinuing study drug and at 6 months following study drug discontinuation or prior to the initiation of another anti-neoplastic therapy (whichever occurs first). Patients should report to their physician any new skin lesion or change, including rash and photosensitivity, while on study treatment, and any suspicious lesions should be referred to a dermatologist for further evaluation as required.

The initial examination by the dermatologist should include a complete dermatological history of prior medications, and cutaneous SCC risk factors (i.e., radiation therapy, sun exposure, immunosuppression, prior SCC, use of tanning beds, precursor lesions and photochemotherapy for psoriasis).

Any lesion suspected of representing a new SCC, BCC, actinic keratosis, or keratoacanthoma identified by the dermatologist should be treated as per local standard of care. Skin biopsies of any suspicious lesions identified at baseline and during the study must be biopsied/excised and sent for pathological examination. Available blocks/sections from any suspicious lesion should also be sent to a designated central pathology laboratory for confirmation of diagnosis.

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

5.3.8.4.2 Non-cutaneous SCC

A head and neck examination must be performed by the treating physician or other qualified physician at baseline and during the study for all patients enrolled. The head and neck examination will consist of at least a visual inspection of the oral mucosa and lymph node palpation. This will be done at Screening/Baseline (anytime up to 28 days prior to Day 1), every 12 weeks while the patient is on study, when the patient discontinues vemurafenib unless done within the prior 12 weeks, and at the Safety Follow-Up Visit 28 (± 5) days after discontinuing study drug and at 6 months following study drug discontinuation or prior to the initiation of another anti-neoplastic therapy (whichever occurs first). Any suspicious findings will be referred to an appropriate specialist.

A CT scan of the chest is required for non-cutaneous SCC screening and surveillance for all patients. MRI may be used if a CT scan is contra-indicated for the patient. Because radiologic assessments for tumour burden are a standard requirement for patients with solid tumours, it is not necessary to perform a separate chest CT/MRI. Instead, the same (routine tumour assessment CT/MRI) should suffice for monitoring of non-cutaneous SCC as well for solid tumour patients only. However, chest CT for the evaluation of SCC are required at a minimum of every

6 months for each patient and at 6 months following study drug discontinuation or prior to the initiation of another anti-neoplastic therapy (whichever occurs first).

Pelvic examinations for women (with special attention to cervix) and anal examinations for all patients will be performed at baseline and the end of the study. The pelvic examination should include a complete external and internal examination (internal examination of uterine cervix may include a Pap smear, which would be a decision of the investigator). The anal examination should include external examination, digital anorectal examination and anoscopy or proctoscopy. However, if in opinion of the investigator the presence of "abnormal lesions including SCC" can be excluded by the external inspection and the manual examination, this is acceptable. However, if the presence of a lesion is suspected, an anoscopy or proctoscopy are recommended.

5.3.8.5 Electrocardiographic assessments

Prolongation of the corrected QT (QTc) interval (change from baseline) has been reported in vemurafenib clinical trials. As a result of these findings, mandatory ECG assessments, with a focus on QTc interval, will be conducted during the Screening Period, 4 weeks after starting vemurafenib treatment, every 4 weeks for the next 3 months, every 12 weeks thereafter during the Treatment Period, at the End of Treatment Visit, and at the Safety Follow-Up Visit. The following parameters will be collected: heart rate, PR interval, QRS duration, QT and QTc intervals, and ECG findings.

Please refer to Section 6.2.1 and 6.3.3 for dose modifications guidelines (for vemurafenib monotherapy and the combination of vemurafenib and cetuximab) to minimize the risk of ventricular arrhythmia in patients with metastatic melanoma treated with vemurafenib.

5.3.8.6 Photosensitivity

Photosensitivity has been reported in patients treated with vemurafenib in clinical trials. The majority of cases were mild or moderate in severity. All patients should be advised to avoid sun exposure and/or wear protective clothing with sun block and lip balm (minimum of SPF 30, re-applied every 2 to 3 hours) during vemurafenib treatment and for at least 5 to 10 days after study drug discontinuation.

5.3.8.7 Pancreatitis

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

5.4 LABORATORY ASSESSMENTS

Samples for haematology, serum biochemistry, and pregnancy will be analysed at the study site's local laboratory as part of regular safety assessments. Protection of patient confidentiality (See Section 16) will extend to any data generated from the assaying of these samples.

Normal ranges for the study laboratory parameters must be supplied to Roche before the study starts. Changes to the normal ranges during the course of the study should be notified to Roche as soon as possible.

Laboratory assessments will be performed at screening/baseline, at each every 28-Day visit and at the end of the study visit.

5.4.1 Safety Laboratory Assessments

Haematology and biochemistry will be done as part of regular safety assessments. Specifically:

- Haematology: Haemoglobin, haematocrit, white blood cell count (WBC), absolute neutrophil count (ANC), and platelet count
- Biochemistry: amylase, lipase, glucose, blood urea nitrogen (BUN), creatinine or creatinine clearance (CrCl), sodium, potassium, calcium, magnesium, bicarbonate (if routinely performed on venous blood samples), total bilirubin with fractionation into direct and indirect bilirubin (if total bilirubin is elevated; if one component is available, the other component can be calculated), alkaline phosphatase, and AST (SGOT), ALT (SGPT)
- Serum pregnancy test in all women of child-bearing potential at screening (within 7 days prior to first administration of vemurafenib.

5.4.2 Pharmacokinetic Assessments

For all newly enrolled patients in all cohorts, mandatory blood samples will be taken during Cycle 1 (Day 1 and Day 15) and Cycles 2 – 4 (Day 1) to explore the PK characteristics of vemurafenib. Samples will be taken pre-dose and 2-4 hours post-dose of the morning dose on the corresponding days (see Table 9). For the day of the PK assessment, patients should be instructed not to take their morning dose, and to bring their study medication with them to their clinic visit.

Table 9:
PK Blood Draws

Cycle	Day	Timing	Blood Volume Required per Sample
1	1	pre-dose	2 mL
		2-4 hrs post-dose	
	15	pre-dose	
		2-4 hrs post-dose	
2	1	pre-dose	
		2-4 hrs post-dose	
3	1	pre-dose	
		2-4 hrs post-dose	
4	1	pre-dose	
		2-4 hrs post-dose	

For all PK samples, the date and time of the last dose of vemurafenib should be recorded, along with the actual time of the PK blood draw. The procedures for the collection, handling and shipping of samples for PK can be found in the study's Laboratory Manual.

Collected samples will be destroyed no later than five years after the end of the study.

5.4.3 Exploratory Biomarkers

Optional blood samples for exploratory biomarkers can be collected from any newly enrolled patient in any cohort. Blood samples will be taken at pre-dose of the morning dose of Cycle 1 (Day 1) and Cycle 2 (Day 1), as well as at the Safety Follow-up Visit or at time of disease progression (whichever occurs first), with approximately 10 mL blood being required at each time point (see Table 10). Any collected samples will be destroyed no later than five years after the end of the study.

For these patients, BRAF V600 mutations in tissue may be correlated to BRAF V600 mutations in plasma and assessed in relation to clinical parameters and clinical outcome. Further exploratory analysis may include, but are not limited to, markers relevant in the pathogenesis, course and outcome of vemurafenib treatment, such as genetic alterations and candidate biomarkers.

Table 10:
Biomarker Samples (Optional)

Cycle	Day	Timing	Blood Volume Required
1	1	pre-dose	10 mL
2	1	pre-dose	
Safety Follow-up Visit or at time of disease progression (which ever happens first)		pre-dose (if applicable)	

The procedures for the collection, handling and shipping of biomarker samples can be found in the study's Laboratory Manual.

6. INVESTIGATIONAL MEDICINAL PRODUCT

6.1 VEMURAFENIB

The formulated drug product vemurafenib is provided as 240-mg film-coated tablets packed in bottles for oral administration. For additional batch-specific instructions and information, vemurafenib will be labelled in compliance with Good Manufacturing Procedures (GMP). The drug label will include the contents, protocol number, batch number, and storage conditions, as well as any required statements that the drug is: "For Clinical Trial Use Only." Patients will be requested to store the vemurafenib at the recommended storage conditions noted on the label out of the reach of children or other cohabitants. For further details, please see the vemurafenib IB.

6.2 DOSE AND SCHEDULE OF VEMURAFENIB

Patients will receive continuous oral doses of vemurafenib 960 mg b.i.d. without scheduled dose interruption starting on Day 1 (except for Part I of Cohort 3b where vemurafenib starts on Day 2 (administered while in hospital), see Section 6.3) of the Treatment Period until the development of progressive disease, unacceptable toxicity, consent withdrawal, protocol violation endangering the patient's safety, death, reasons deemed by the Investigator, or study termination by the Sponsor.

Vemurafenib is supplied in 240 mg film-coated tablets packed in bottles for oral administration. Patients should be instructed to take four tablets in the morning and four tablets approximately 12 hours later in the evening (total daily dose of 1920 mg [960 mg b.i.d.]) (except for Cohort 3b where vemurafenib dose will be determined by the dose finding phase, see Section 6.3). Each dose should always be taken in the same manner i.e. either with or without a meal.

If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. However if a patient forgets to take a dose, it can be taken up to 4 hours prior to the next dose.

If a patient misses a dose (e.g., due to emesis), he or she should be instructed not to take or make up that dose and to resume dosing with the next scheduled dose. Missed doses will not be made up. Patients will be instructed to bring all unused tablets to each study visit for assessment of compliance.

Patients who develop disease progression but, in the opinion of the Investigator, would still benefit from continuing study treatment may continue treatment with study treatment after discussion with the Sponsor.

Patients will be given a dosing exception diary to record the time and date of *missed* study medication doses. Any such data provided by the patient will be transcribed from the diary to the eCRF by the study coordinators.

A 6-week supply of study medication (three 120-tablet bottles) will be given to the patient on Day 1 of the first cycle. From Cycle 2 onwards a 4-week supply of study medication (two 120-tablet bottles) will be given to the patient on Day 1 of each dosing cycle. Patients will be instructed not to open a new bottle until the previous bottle has been finished and to bring their study medication and bottles (used or unused) back to the clinic at the next study visit for reconciliation.

If recruitment is expanded in any cohort (due to promising efficacy seen in Stage II), patients who are part of this expansion will receive the same treatment as patients who were treated in Stage II of that cohort.

6.2.1 Dose Modifications, Interruptions, and Delays for Vemurafenib

Management of symptomatic adverse drug reactions (e.g., arthralgia, fatigue, rash) may require temporary interruption and/or dose reduction of vemurafenib treatment. When needed, dose reduction in 240-mg b.i.d. increments is recommended based on individual safety and tolerability. Up to two dose reductions of vemurafenib will be allowed, i.e., to 720 mg p.o. b.i.d., and then to 480 mg p.o. b.i.d. There will be no dosage reductions or interruptions for skin cancer.

Dose escalation after dose reduction is generally not recommended unless under special circumstances, i.e., increased likelihood of clinical benefit for the dose increase and no safety concerns. This should only be done after discussion with the Sponsor. Dose increases above 960 mg b.i.d. are NOT allowed.

Patients with ECD/LCH have the option of discontinuing vemurafenib treatment after one year, if the investigator considers it to be in the best interest of the patient. Patients can then resume vemurafenib treatment if they become symptomatic or if their scans show worsening of their disease.

Dosage modification criteria should occur as follows (also see Table 11):

Table 11:
Dose Interruption/Modification Criteria for Vemurafenib

Toxicity Grade (CTCAE, v4.0)[a]	Vemurafenib dose changes during current treatment period	Dose adjustments for resumption of treatment
Grade 1	100% of starting dosage	100% of starting dosage
Tolerable Grade 2	100% of starting dosage	100% of starting dosage
Intolerable Grade 2		
First appearance	Interrupt until resolved to Grade 0 – 1	Reduce by 240 mg b.i.d.
Second appearance	Interrupt until resolved to Grade 0 – 1	Reduce by 240 mg b.i.d.
Third appearance	Discontinue permanently	
Grade 3 [b]		
First appearance	Interrupt until resolved to Grade 0 – 1	Reduce by 240 mg b.i.d.
Second appearance	Interrupt until resolved to Grade 0 – 1	Reduce by 240 mg b.i.d.
Third appearance	Discontinue permanently	–
Grade 4		
First appearance	Discontinue permanently or interrupt until resolved to Grade 0 – 1[c]	Reduce to 50% of starting dosage or reduce to 480 mg b.i.d. if starting dose is 720 mg b.i.d.
Second appearance	Discontinue permanently	–

a. Common Terminology Criteria for Adverse Events, Version 4.0.
b. Treatment interruptions or and/or dose reductions for Grade 3 haematology test abnormalities, except for neutropenia and thrombocytopenia, will be at investigator's discretion.
c. Discontinue permanently if starting dose is 480 mg b.i.d.

Prolongation of the corrected QT (QTc) interval (change from baseline) was observed in a substudy of the NP22657/BRIM-2 phase II trial. As a result of these findings, the following recommendations have been developed to minimize the risk of ventricular arrhythmia in patients with metastatic melanoma treated with vemurafenib:

Avoid combination with other agents with known potential to lead to prolongation of QTc interval, if possible.

ECG monitoring, with a focus on QTc interval, should occur during the Screening/Baseline period, 28 days after starting vemurafenib, every 28 days for the following 3 months, and every 12 weeks thereafter until study drug discontinuation at the End of Treatment Visit, and at the Safety Follow-Up Visit.

If QTc interval exceeds 500 ms or the change from baseline is > 60 ms, vemurafenib treatment should be temporarily interrupted. The Investigator should check electrolytes (K+, Mg++, and Ca++) with a focus on hypokalaemia, correct any electrolyte abnormalities prior to reinstitution of therapy, recheck concomitant medications to insure that none has been implicated in QTc prolongation, and rule out or control other cardiac risk factors (i.e., ischemia). ECG should be monitored weekly until QTc decreases to less than 500 ms, at which point treatment should be reinitiated at one reduced dose level, i.e., from 960 mg b.i.d. to 720 mg b.i.d. If a subsequent

increase in QTc to > 500 ms or change from baseline is > 60 ms is observed, vemurafenib may be reduced to 480 mg b.i.d.

Vemurafenib should be permanently discontinued if a QTc increase meets both criteria of > 500 ms and > 60 ms change from pre-treatment values or if QTc > 500 ms or change from baseline > 60 ms is observed on two separate prior occasions.

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

For patients required to have tumour surgery, radiotherapy or other procedures, treatment with vemurafenib must be interrupted prior to these procedures. The treating physician must contact the Sponsor for guidelines as when study drug is to be stopped and re-started after the procedure.

6.3 DOSE AND SCHEDULE OF VEMURAFENIB AND CETUXIMAB COMBINATION (COHORT 3B ONLY)

Cohort 3b has two parts;

Part 1 vemurafenib and cetuximab combination dose levels will be escalated as per Section 6.3.1 sequentially in a classical 3+3 design.

Part 2 the vemurafenib and cetuximab doses will be at the recommended dose for stage I/II as determined by Part 1.

Once assigned to specific dosages of vemurafenib and cetuximab in combination, each patient will continue to be dosed at these dosages, without interruption throughout the study unless dose modification or interruption is indicated. Refer to Section 6.3.3 for dose modifications guidelines for the combination of vemurafenib and cetuximab.

6.3.1 Planned Dose Escalation Levels (Cohort 3b only)

For Part 1 of Cohort 3b, the dose escalation levels of vemurafenib and cetuximab combination will be as follows:

Dose Level	vemurafenib	cetuximab
1	720 mg b.i.d. starting on Day 2 of cycle 1	Cetuximab: 300 mg/m^2 loading dose and then 200 mg/m^2 weekly
2	720 mg b.i.d. starting on Day 2 of cycle 1	Cetuximab: 400 mg/m^2 loading dose and then 250 mg/m^2 weekly
3	960 mg b.i.d. starting on Day 2 of cycle 1	Cetuximab: 400 mg/m^2 loading dose and then 250 mg/m^2 weekly

If the dose levels above are not tolerated then the following provisional dose levels may be considered as alternative to any of the above dose levels after discussion between the Sponsor and study Steering Committee.

Dose Level	vemurafenib	cetuximab
1A	720 mg b.i.d. starting on Day 2 of cycle 1	Cetuximab: 200 mg/m^2 loading dose and then 125 mg/m^2 weekly
2A	720 mg b.i.d. starting on Day 2 of cycle 1	Cetuximab: 300 mg/m^2 loading dose and then 250 mg/m^2 weekly
3A	960 mg b.i.d. starting on Day 2 of cycle 1	Cetuximab: 300 mg/m^2 loading dose and then then 250 mg/m^2 weekly

Patients included in Part 2 of Cohort 3b of the study will receive vemurafenib and cetuximab at the doses recommended during the dose escalation part.

6.3.2 Recommended Dose of Vemurafenib and Cetuximab

A dose will be considered non-tolerable and dose escalation will cease if 2 or more of up to 6 evaluable patients experience a DLT at a dose level. Once the non-tolerable dose is defined the MTD will be confirmed at the previous dose-level below or a dose between the MTD and the last tolerable dose (see Section 6.3.1). Six evaluable patients are required to determine the MTD.

Expected dose levels for the dose escalation are described in Section 6.3.1. The dose escalation guidelines are summarized in Section 6.3.2.1. Decisions to escalate or de-escalate the doses will be made based on a review of all available safety data both from the study i.e. nature of the DLTs that occurred at one dose level together with all other available data including generally available data on vemurafenib and cetuximab.

The MTD is defined to be the highest dose of vemurafenib in combination with cetuximab which can be given to 6 patients such that less than 2 subjects experience DLT within 28 days (or no more than one-third if there are more than 6 treated patients).

The recommended dose for stage I/II will be based on considerations of the estimated MTD, and on an overall assessment of safety taking into consideration tolerability data from subsequent cycles at all different dose levels tested. The recommended dose for stage I/II will be determined once the MTD is determined by the Sponsor after discussion with the study Steering Committee. The decision to continue enrolment in Cohort 3b after the Part I dose escalation phase will be decided by the Sponsor in discussion with study Steering Committee.

6.3.2.1 Dose Escalation Guidelines (Cohort 3b only)

A minimum of 3 patients initially will be enrolled at the first dose level (Dose level 1 Section 6.3.1).

The first patient entered at the first dose level will be observed for at least 28 days before the next two patients receive vemurafenib and cetuximab at that dose level. For subsequent dose levels, three patients can be entered simultaneously, although close monitoring is required.

The dose escalation rules (Table 12) proceed as follows, escalating in cohorts of 3-6 patients per dose level.

Three patients are treated at the current dose level.

- If at least 2 patients are observed to have a dose-limiting toxicity (DLT) [DLTs are defined in Section 6.3.2.2] during the 28 days following the first administration of vemurafenib and cetuximab (DLT assessment period), the MTD will have been exceeded and no further patients will be enrolled at this dose level or at any higher dose level. The prior dose level is defined as the MTD (unless only 3 patients have been treated at that level, in which case it is the tentative MTD).
- If 0 of the 3 patients are observed to have DLT during the DLT assessment period, the dose level is escalated one step for the next cohort of 3 patients, and the process continues as above.
- If exactly 1 of the 3 patients treated show DLT during the DLT assessment period, 3 additional patients are treated at the current dose level.

If none of these additional 3 patients show DLT during the DLT assessment period, the dose level is escalated for the next cohort of 3 patients, and the process continues as above; otherwise, the prior dose level is defined as the MTD (unless only 3 patients have been treated at that level, in which case it is the tentative MTD).

A tentative MTD becomes final when a total of 6 patients are treated with less than 2 showing DLT.

Once the MTD is determined, the dose to be recommended for stage I/II will be confirmed by the Sponsor in discussion with the study Steering Committee.

Table 12:
Dose Escalation Guidelines

Number of Patients with a DLT at a given dose level	Escalation Decision Guidance
0 out of 3	Enter 3 patients at the next dose level
1 out of 3	Enter at least 3 more patients at this dose level and then If 0 of these 3 patients experience a DLT, proceed to the next dose level. If 1 or more of these 3 patients experience a DLT then dose escalation is stopped and this dose is declared the maximal administered dose as the MTD has been exceeded. Three additional patients will be entered at the next lower dose level if only 3 patients were treated previously at that dose, or an intermediate lower dose level will be assessed
≥ 2	Dose escalation will be stopped. This dose level is declared the maximal administered dose (highest dose administered). Three additional patients will be entered at the next lower dose level if only 3 patients were treated previously at that dose, or an intermediate lower dose level will be assessed
≤ 1 out of 6 at highest dose level below the maximal administered dose	This is the MTD.

6.3.2.2 Dose-limiting toxicities (Cohort 3b only)

DLT is defined as a clinically significant adverse event or abnormal laboratory value assessed as unrelated to disease progression, undercurrent illness, or concomitant medications and occurring during the first 4 weeks of treatment with the combination of vemurafenib and cetuximab.

For the purposes of this protocol, the following adverse events determined to be possibly, probably or definitely related to the combination of cetuximab and vemurafenib that occur during the 28 days following the first administration of the combination of vemurafenib and cetuximab at any dose level and that meet any of the following criteria are considered to be dose-limiting toxicities (DLT) that count for the determination of the MTD.

Toxicity grades are defined in the NCI CTCAE v 4.0 (80).

- Grade ≥ 3 non-haematological toxicity (other than untreated nausea, vomiting and diarrhoea and excluding alopecia)
- Grade ≥ 3 nausea, vomiting or diarrhoea refractory to appropriate treatment for at least 2 days
- Grade 4 anaemia lasting > 7 consecutive days
- Neutropenia Grade 4 lasting > 7 consecutive days
- Neutropenia Grade 3 or 4 complicated by fever and/or infection (ANC <1.0 x 10^9/L; fever ≥ 38.5 ºC
- Grade 4 thrombocytopenia lasting > 7 consecutive days
- Treatment delay >33% of the scheduled doses over 28 days due to treatment related toxicity

Skin and subcutaneous tissue toxicity is not considered a DLT unless a dose reduction of study treatment is required to permit continuous dosing.

6.3.3 Dose Modifications, Interruptions, and Delays for Vemurafenib and Cetuximab (Cohort 3b only)

For all patients in Cohort 3b when an occurring toxicity can be clearly ascribed to either cetuximab or vemurafenib, it will be considered to only dose reduce the compound responsible for the toxicity. See Table 13 for the recommended cetuximab dose interruptions/ modifications and Section 6.2.1 for vemurafenib dose reductions.

When an occurring toxicity cannot be clearly ascribed to either cetuximab or vemurafenib, both drugs will be dose reduced as per guidance in Table 11 and Table 13 for vemurafenib and cetuximab respectively.

Table 13:
Dose Interruption/Modification Criteria for Cetuximab

Toxicity Grade (CTCAE, v4.0)[a]	Cetuximab dose changes during current treatment period	Dose adjustments for resumption of treatment of weekly dose
Grade 1	100% of starting dosage	100% of starting weekly dosage
Tolerable Grade 2	100% of starting dosage	100% of starting weekly dosage
Intolerable Grade 2		
First appearance	Interrupt until resolved to Grade 0 – 1	Reduce to 75% of starting weekly dosage
Second appearance	Interrupt until resolved to Grade 0 – 1	Reduce to 75% of starting weekly dosage
Third appearance	Discontinue permanently	-
Grade 3[b]		
First appearance	Interrupt until resolved to Grade 0 – 1	Reduce to 75% of starting weekly dosage
Second appearance	Interrupt until resolved to Grade 0 – 1	Reduce to 50% of starting weekly dosage
Third appearance	Discontinue permanently	-
Grade 4		
First appearance	Discontinue permanently or interrupt until resolved to Grade 0 – 1	Reduce to 50% of starting weekly dosage
Second appearance	Discontinue permanently	–

a. Common Terminology Criteria for Adverse Events, Version 4.0.

b. Treatment interruptions or and/or dose reductions for Grade 3 haematology test abnormalities, except for neutropenia and thrombocytopenia, will be at investigator's discretion.

When an occurring toxicity can be clearly ascribed to either cetuximab or vemurafenib, it will be considered to only dose reduce the compound responsible for the toxicity (see Section 6.2.1 for vemurafenib dose reductions). When an occurring toxicity cannot be clearly ascribed to either cetuximab or vemurafenib, both drugs will be dose reduced as per guidance in Table 11 and Table 13 for vemurafenib and cetuximab respectively.

Cetuximab infusion-related reactions - Reduce the infusion rate by 50% for NCI-CTC Grade 1 or 2 and non-serious NCI-CTC Grades 3-4 infusion related reactions. Immediately and permanently discontinue cetuximab for serious infusion related reactions, requiring medical intervention and/or hospitalization. See cetuximab SPC for further details (79).

6.4 PREPARATION AND ADMINISTRATION OF STUDY DRUGS

6.4.1 Vemurafenib

Vemurafenib will be supplied as 240-mg film-coated tablets packed in bottles for oral administration. No further preparation is required.

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

Vemurafenib should be stored at room temperature < 25°C and should be protected from excessive exposure to sunlight. Patients will be requested to store vemurafenib at the recommended storage conditions noted on the label, out of the reach of children or other vulnerable persons. Under hot weather conditions storage in the refrigerator is possible to not exceed storage conditions above 25 °C.

For additional batch-specific instructions and information for vemurafenib film-coated tablets, please refer to the packaging.

Vemurafenib should be taken at approximately the same times each day, the first dose is to be taken in the morning and the second dose is to be taken approximately 12 hours later in the evening. Each dose should always be taken in the same manner i.e. either with or without a meal

If a patient misses a dose (e.g., due to emesis), he or she should be instructed not to take or make up that dose and to resume dosing with the next scheduled dose. Missed doses will not be made up.

6.4.2 Cetuximab (Cohort 3b only)

Cetuximab must be administered in hospital under the supervision of a physician experienced in the use of antineoplastic medicinal products. Close monitoring is required during the infusion and for at least 1 hour after the end of the infusion. Availability of resuscitation equipment must be ensured.

Cetuximab should all be administered at the dose level as per Section 6.3. Patients must receive adequate premedication prior to and/or after receiving cetuximab in this study (according to local institutional guidelines and approved cetuximab labelling (79)).

For further details of administration, preparation and storage, refer to the cetuximab SPC (79).

6.5 PACKAGING AND LABELLING

Study drug packaging will be overseen by the Roche clinical trial supplies department and will bear a label with the identification required by local law, the protocol number, batch number, storage conditions, drug identification, and dosage, and the statements:

For vemurafenib: “Do Not Store above 25°C” and “Keep Container Tightly Closed,” as well as any required statements that the drug is “For Clinical Trial Use Only.”

For cetuximab (Cohort 3b only): “Store in a refrigerator (2°C – 8°C)” For cetuximab (Cohort 3b only): “Store from 2° – 8°C” and “Solution for infusion” and “Use as directed in the study protocol”.

The packaging and labelling of the study medication will be in accordance with Roche standards and local regulations and in compliance with Good Manufacturing Procedures (GMP). Local packaging in some countries may be different.

Cetuximab should be store in a refrigerator (2°C – 8°C). Cetuximab does not contain any antimicrobial preservative or bacteriostatic agent. From a microbiological point of view, the product shall be used immediately after opening. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24

hours at 2 to 8 °C, unless opening has taken place in controlled and validated aseptic conditions. See cetuximab SPC (79).

6.6 BLINDING AND UNBLINDING

Not applicable, study is open label.

6.7 ACCOUNTABILITY OF IMP AND ASSESSMENT OF COMPLIANCE

6.7.1 Accountability of Vemurafenib and Cetuximab

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

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

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

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

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

All records and drug supplies must be available for inspection by the Monitor at every monitoring visit.

Patients will be asked to return all used and unused drug supply containers at the end of the treatment as a measure of compliance.

This inventory must be available for inspection by the Monitor. All supplies, including partially used or empty containers and copies of the dispensing & inventory logs, must be returned to the Monitor at the end of the study, unless alternate destruction has been authorized by Roche, or required by local or institutional regulations (Section 6.8).

6.7.2 Assessment of Compliance

Patient compliance will be assessed by maintaining adequate study drug dispensing records. The Investigator is responsible for ensuring that dosing is administered in compliance with the protocol. Delegation of this task must be clearly documented and approved by the Investigator.

6.8 DESTRUCTION OF VEMURAFENIB AND CETUXIMAB

Local or institutional regulations may require immediate destruction of used investigational medicinal product (IMP) for safety reasons e.g., cytotoxicity. In these cases, it may be acceptable for investigational site staff to destroy dispensed IMP before a monitoring inspection provided that source document verification is performed on the remaining inventory and reconciled against the

documentation of quantity shipped, dispensed, returned and destroyed. Written authorization must be obtained from the Sponsor at study start up before destruction.

Written documentation of destruction must contain the following:

- Identity (batch numbers and patient numbers) of investigational product(s) destroyed
- Quantity of investigational product(s) destroyed
- Date of destruction (date discarded in designated hazardous container for destruction)
- Method of destruction (the site must provide the Sponsor with documentation of their institutional policy and procedures for handling and disposing of hazardous drugs)
- Name and signature of responsible person who discarded the investigational product in a hazardous container for destruction

6.9 POST-TRIAL ACCESS TO VEMURAFENIB AND CETUXIMAB

The Sponsor will offer post-trial access to the study drug(s) (vemurafenib and cetuximab) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive study drug after the end of the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued study drug treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive study drug after the end of the study if any of the following conditions are met:

- The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the study drug or data suggest that the study drug is not effective for the patient’s disease
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for the patient’s disease
- Provision of study drug is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:

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

7. SAFETY INSTRUCTIONS AND GUIDANCE

7.1 WARNINGS AND PRECAUTIONS

Investigators and patients should be aware of the risks of photosensitivity reactions, SCC, and potential drug–drug interactions during treatment with vemurafenib (see Section 4.4 and Appendix 2 for advice on which concomitant treatments should be avoided while taking vemurafenib).

Mild to severe photosensitivity has been reported in patients treated with vemurafenib. All patients should be advised to avoid prolonged sun exposure while taking vemurafenib and for at least 5 days after study drug discontinuation. Patients should also be advised to use a broad spectrum sun screen of at least SPF >30 to help protect against sunburn. For acneiform rash, Investigators should consider treatment with minocycline.

Section 5.3.8.4 of this protocol outlines a detailed surveillance plan for SCC which includes a thorough skin evaluation by a dermatologist, head and neck exam, and CT scan of the chest for all patients who participate in the study. Please see Table 8a and Table 8b - Schedule of Assessments for specific details on when assessments for SCC risk management plan are to be conducted at screening and throughout study. Owing to the possible tumour biopsy requirement (for screening or evaluation of suspicious skin lesions) in this study, risks such as infection of the surgical site, excessive bleeding, or injury to adjacent tissues, should be considered for patients who undergo tumour tissue biopsies.

In addition, for Cohort 3b see cetuximab SPC (79) for special warnings and precautions for use.

As based on mechanism of action, vemurafenib may cause progression of cancers associated with RAS mutations, vemurafenib should be used with caution in patients with prior or concurrent cancers associated with RAS mutation.

7.2 ADVERSE EVENTS AND LABORATORY ABNORMALITIES

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

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 7.3.4.

7.2.1 Clinical Adverse Events

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

7.2.1.1 Intensity

Intensity of all adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events, Version 4.0 (CTCAE, v4.0) on a five-point scale (Grade 1 to 5) and reported in detail on the eCRF.

Adverse events not listed on the CTCAE v4.0 should be graded as described in Table 14.

Table 14:
Adverse Event Grading (Severity) Scale

CTC Grade	Equivalent to:	Definition
Grade 1	Mild	Discomfort noticed but no disruption of normal daily activity
Grade 2	Moderate	Discomfort sufficient to reduce or affect daily activity; no treatment or medical intervention is indicated although this could improve the overall well-being or symptoms of the patient
Grade 3	Severe	Inability to work or perform normal daily activity; treatment or medical intervention is indicated in order to improve the overall well-being or symptoms; delaying the onset of treatment is not putting the survival of the subject at direct risk.
Grade 4	Life threatening / disabling	An immediate threat to life or leading to a permanent mental or physical conditions that prevents work or performing normal daily activities; treatment or medical intervention is required in order to maintain survival.
Grade 5	Death	AE resulting in death

7.2.1.2 Drug – Adverse Event relationship

The causality relationship of study drug to the adverse event will be assessed by the Investigator as either:

Yes or No

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

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

- Reasonable temporal association with drug administration
- It may or may not have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
- Known response pattern to suspected drug
- Disappears or decreases on cessation or reduction in dose
- Reappears on rechallenge

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

- It does not follow a reasonable temporal sequence from administration of the drug.
- It may readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
- It does not follow a known pattern of response to the suspected drug.
- It does not reappear or worsen when the drug is readministered.

7.2.1.3 Serious Adverse Events (Immediately Reportable to Roche)

A serious adverse event is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any Adverse Event that at any dose fulfils at least one of the following criteria:

- is fatal (i.e., the adverse event actually causes or leads to death); (results in **death**; NOTE: death is an outcome, not an event)
- is Life-Threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

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

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

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 7.2.1.1); the event itself may be of relatively minor medical significance (such as severe headache without any further findings). Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

The study will comply with all local regulatory requirements and adhere to the full requirements of the **ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2.**

After informed consent, but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies, medication washout, or no treatment run-in). See Section 7.3.1.

7.2.1.4 Progression of Underlying Malignancy

Progression of underlying malignancy is not reported as an adverse event if it is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST criteria, or other criteria as determined by protocol. This includes also deaths solely due to underlying malignancy. An SAE with outcome death solely due to progression of the underlying malignancy does not need to be reported as an SAE. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as a serious adverse event. Clinical symptoms of progression may be reported as adverse events if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.

Symptomatic deterioration may indicate progressive disease (PD), however radiological confirmation of PD is strongly recommended. In this situation, progression is evident in the subject's clinical symptoms, but is not supported by the tumour measurements. Or, the disease progression is so evident that the Investigator may elect not to perform further disease assessments. In such cases, the determination of clinical progression is based on symptomatic deterioration. These determinations should be a rare exception as every effort should be made to document the objective progression of underlying malignancy.

If there is any uncertainty about an adverse event being due only to the disease under study, it should be reported as an AE or SAE.

7.2.1.5 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfils seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 7.3.4).

7.2.2 Treatment and Follow-up of AEs

After 28 (± 5) days from the last dose of study drug, Investigators will continue to follow up AEs as follows:

Related AEs: Follow until one of the following occurs:

- Resolved or improved to baseline
- Relationship is reassessed as unrelated
- Death
- Start of new anti-cancer regimen
- Investigator confirms that no further improvement can be expected
- Clinical or safety data will no longer be collected, or final database closure

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

- Resolved or improved to baseline
- Severity improved to Grade 2
- Death
- Start of new anti-cancer regimen
- Investigator confirms that no further improvement can be expected
- Clinical or safety data will no longer be collected, or final database closure

Unrelated Grade 1 or Grade 2 AEs: Follow until **28 days from the last dose of study drug.**

The final outcome of each adverse event must be recorded on the eCRF

7.2.3 Laboratory Test Abnormalities

Local laboratories will be used for all laboratory tests. Laboratory test results will be recorded on the laboratory results form of the eCRF.

Any laboratory result abnormality fulfilling the criteria for a serious adverse event (SAE) should be reported as such, in addition to being recorded as an AE in the eCRF.

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

- Is accompanied by clinical symptoms
- Leading to a change in study medication (e.g. dose modification, interruption or permanent discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalaemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

  Note: For oncology trials, certain abnormal values may not qualify as adverse events.

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

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

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

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 7.3.2 for details on recording persistent adverse events).

7.2.3.1 Follow-up of Abnormal Laboratory Test Values

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

7.2.4 Abnormal Vital Sign Values

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

- Is accompanied by clinical symptoms

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

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

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

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 7.3.2 for details on recording persistent adverse events).

7.2.5 Abnormal Liver Function Tests

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

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest (see Section 7.3.4).

7.3 HANDLING OF SAFETY PARAMETERS

7.3.1 Reporting of Adverse Events

After informed consent, but prior to initiation of any study medications, only SAEs caused by protocol-mandated intervention should be collected.

After initiation of study drug, SAEs and non-serious AEs of special interest will be reported until 28 days after the last dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event / Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

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

All AEs and SAEs regardless of the relationship to the trial drug will be recorded in the eCRF.

All AE reports should contain a brief description of the event, date and time of onset, date and time of resolution, intensity, treatment required, relationship to trial drug, action taken with the trial drug, outcome, and whether the AE is classified as serious.

All adverse events experienced after the patient has started study treatment must be recorded on the AE form of the eCRF, as well as all new adverse events experienced during the study and up to 28 days after the last dose of study treatment.

The Investigator is not required to actively monitor patients for adverse events after the end of the adverse event reporting period (defined as 28 days after the last dose of study drug). The Investigator is not required to actively monitor patients for adverse events after the end of the adverse event reporting period (defined as 28 days after the last dose of study drug). However the Sponsor should be notified if the Investigator becomes aware of any SAE that occurs after the end of the adverse event reporting period, if the event is believed to be related to prior study drug treatment.

A pre-existing medical condition that is present at the start of the study should be recorded on the Medical History eCRF.

AEs will be reported and graded following NCI CTCAE, v4.0. Accordingly, intensity of all AEs will be graded on a five-point scale (Grade 1 to 5) and reported in detail on the CRF. Reporting of AE based on CTCAE terms and corresponding grading are an integral part of safety/AE/SAE reporting in this study and will have to be strictly followed. The causality relationship of study 'treatment' to the adverse event will be assessed by the Investigator as either **Yes or No**.

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

The Investigator should provide his/her assessment as to whether an AE is related to the study treatment regimen.

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

- Reasonable temporal association with drug administration
- It may or may not have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient
- Known response pattern to suspected drug
- Disappears or decreases on cessation or reduction in dose
- Reappears on rechallenge

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

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

- It may readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient
- It does not follow a known pattern of response to the suspected drug
- It does not reappear or worsen when the drug is re-administered

7.3.2 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 7.3.4 for reporting instructions). The Adverse Event eCRF 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 serious adverse events.

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

7.3.3 Adverse Events in Individuals not Enrolled in the Study

If an adverse event inadvertently occurs in an individual not enrolled in the study (e.g., during administration of study drug), the Adverse Event Form provided to investigators should be completed and submitted to Roche or its designee, either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

7.3.4 Immediate Reporting Requirements from Investigator to Sponsor

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

- Serious adverse events (see Section 7.3.4.1 for further details)
- Non-serious adverse events of special interest (see Section 7.3.4.2 for further details)
- Pregnancies (see Section 7.3.4.2.3 for further details)

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

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

- Additional narrative information on the clinical course of the event

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

7.3.4.1 Reporting of Serious Adverse Events

Only SAEs caused by a protocol mandated intervention that are experienced after the patient has signed the Informed Consent form but before they have received study treatment should be reported as SAEs. Any clinical adverse event or abnormal laboratory test value that is *serious* and which occurs during the course of the study (as defined in Section 7.2.1.3 above), must be reported to Roche **within 24 hours** of the Investigator becoming aware of the event (expedited reporting).

The Investigator is not required to actively monitor patients for adverse events after the end of the adverse event reporting period (defined as 28 days after the last dose of study drug). However the Sponsor should be notified if the Investigator becomes aware of any SAE that occurs after the end of the adverse event reporting period, if the event is believed to be related to prior study drug treatment. After the study site has closed, the Investigator should report adverse reactions as mandated in the protocol directly to the Local Drug Safety Affiliate using a paper SAE form. Paper SAE forms and contact details for the Local Drug Safety Affiliate will be provided to the investigational site at close-out.

Suspected Unexpected Serious Adverse Reactions (SUSARs) are reported to Investigators at each site and associated IRB/IEC when the following conditions occur:

- The event must be a SAE.
- There must be a certain degree of probability that the event is an adverse reaction from the administered drug.
- The adverse reaction must be unexpected, that is to say, not foreseen in the Investigator's Brochure.

When all subjects at a particular site are off treatment as defined by the protocol:

- only individual SUSAR reports originating in that particular trial will be forwarded to the site and associated IRB/IEC on an expedited basis;
- individual SUSARs considered to be a significant safety issue and/or which result in Roche recommending a change to the Informed Consent Form (ICF), will be reported in an expedited manner to all Investigators and IRBs/IECs;

SUSAR reports originating from other trials using the same IMP will be provided as six monthly SUSAR Reports (SSRs) to Investigators and IRBs/IECs where long-term follow-up studies are carried out, unless they are considered significant.

All adverse events must be collected and reported during the study and for up to 28 days after the last dose of study medication.

This study adheres to the definition and reporting requirements of **ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2.** Complete information can be found in Appendix 8.

7.3.4.2 Reporting of Protocol-Defined Events of Special Interest

7.3.4.2.1 Abortion, Congenital Anomaly, and Birth Defects

Abortions, congenital anomalies, and birth defects are events of special interest and will need to be reported to the Sponsor expeditiously.

Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious (as the Sponsor considers these medically significant), recorded on an SAE eCRF page, and expeditiously reported to the Sponsor.

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to the investigational product should be recorded and reported as an SAE.

7.3.4.2.2 Cutaneous Squamous Cell Carcinoma / Keratoacanthoma & Second Primary Malignancies

Cutaneous squamous cell carcinoma (cSCC), Keratoacanthoma (KA), basal cell carcinoma (BCC) and any other second primary malignancies and its progression or recurrence are defined as events requiring close monitoring. With the exception of events of actinic keratosis, these events must always be designated as SAEs in order to ensure their reporting to the Health Authorities in an appropriate and timely manner. The treating physician is asked to perform regular (at each study visit) skin exams of the patient. A full skin examination by a dermatologist is requested during the Screening Period, after 28 days of vemurafenib treatment, every 12 weeks thereafter during the Treatment Period, at the End of Treatment Visit, and at the Safety Follow-Up Visit. Any lesion at baseline or during treatment clinically suspected of representing cutaneous, basal cell carcinoma, actinic keratosis, keratoacanthoma or other skin conditions identified by the dermatologist should be treated as per local standard of care.

If more than one SCC lesion occurs in more than one location on the skin, and the multiple lesions are detected during the same observation period (i.e., clinic visit), then these SCC lesions should be reported together as one event on the same **SAE** form and also reported as one event on the **SAE or AE** page of the eCRF. Locations of each lesion can be listed in the event term and narrative for **SAEs or AE** reporting.

If more than one SCC lesion occurs in more than one location on the skin and the lesions are detected during separate observation periods (i.e., separate clinic visits), then these SCC lesions should be reported as separate events on separate **SAE** forms and also as separate events on the **SAE or AE** page of the eCRF.

Cases in which patients rapidly develop multiple lesions within a limited time-frame (e.g., 5–10 lesions over a 2-week period) will be handled on a case by case basis in terms of reporting. Please contact the Medical Monitor when these cases occur, for additional discussion.

Skin biopsies should be performed by a dermatologist, as necessary, with histopathologic interpretation of suspected lesions. Biopsy-proven non-melanoma skin cancers should be excised. Available excised cutaneous SCC/KA as well as from any suspicious lesions specimen block/sections should be sent to a designated central dermatopathology laboratory for confirmation of diagnosis.

Details including histological findings should be reported within the eCRF (see also Section 5.3.8.4).

SCC events should be reported in any case as an SAE as follows:

(a) In the SAE form in the eCRF

- Cutaneous SCC events should be reported using the event term of “Squamous Cell Carcinoma of the skin” or “Cutaneous Squamous Cell Carcinoma”.
- The term “Squamous Cell Carcinoma” should only be used if there is a confirmed non-cutaneous squamous cell carcinoma.
- If the SCC is confirmed to be cutaneous the term “Cutaneous Squamous Cell Carcinoma” or “Squamous Cell Carcinoma of the skin” should be used. Do not report the event term of “treatment related secondary malignancy” or “Squamous Cell Carcinoma”.
- If a cSCC or SCC is suspected, an SAE with the event term “suspected cutaneous SCC” or “suspected non-cutaneous of <insert organ site>”and onset date of admission has to be submitted within 24 hours.
- If the SCC has been confirmed by the local pathology laboratory, the SAE has to be updated with the event term “cutaneous SCC” or “non-cutaneous of <insert organ site>”explaining shortly in the comments section that the diagnosis has been confirmed. The onset date would still remain at the date of admission.
- For all SCC cases, the tick box medically significant must be ticked. The onset date for an SCC SAE is always the date of when the suspicion of an SCC occurred regardless of when and if the suspected diagnosis was confirmed.
- Events of actinic keratosis do not need to be reported as SAEs under the current cSCC reporting guidelines.

(b) In the eCRF AE form

- Cutaneous SCC events should be reported using the event term of “Squamous Cell Carcinoma of the skin” or “Cutaneous Squamous Cell Carcinoma” and should be designated as Grade 3 severity.
- The term “Squamous Cell Carcinoma” should only be used if there is a confirmed non-cutaneous squamous cell carcinoma.
- SCC events should be reported as “Squamous Cell Carcinoma”.
- If the SCC is confirmed to be cutaneous the term “Cutaneous Squamous Cell Carcinoma” or “Squamous Cell Carcinoma of the skin” should be used with a Grade 3 designation

Any second primary malignancies should be reported in any case as an SAE as follows:

(a) In the SAE form in the eCRF

Second primary malignancies should be reported with the type of malignancy. Do not report the event term of “treatment related secondary malignancy”.

(b) In the eCRF AE form

Second primary malignancies should be reported with the type of malignancy and a Grade 3 designation.

7.3.4.2.3 Pregnancy

A female subject must be instructed to stop taking the test “drug” and immediately inform the investigator if she becomes pregnant during the study. The investigator should counsel the subject; discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the patient should continue until conclusion of the pregnancy. Pregnancies

occurring up to 90 days after the completion of the study medication must also be reported to the investigator.

Pregnancy occurring in the partner of a male subject participating in the study should be reported to the investigator and the Sponsor. The partner should be counselled, the risks of continuing the pregnancy discussed, as well as the possible effects on the foetus. Monitoring of the patient should continue until conclusion of the pregnancy.

NOTE: The Investigator should fill out a *Pregnancy Reporting Form* only if the pregnant partner has signed a Pregnant Partner Data Release Form.

In the event that the EDC system is unavailable, the Clinical Trial Pregnancy Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

7.4 WARNINGS AND PRECAUTIONS

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the vemurafenib IB and described in this Protocol.

8. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

8.1 PRIMARY AND SECONDARY STUDY VARIABLES

8.1.1 Primary Variable

Response rate at Week 8, as assessed by the Investigator using RECIST, v1.1* for patients with solid tumours or IMWG uniform response criteria for patients with MM, is the primary endpoint for each cohort. For patients with solid tumours, responders at Week 8 will be defined based on tumour assessment status of PR or CR at Week 8. For patients with MM, responders at Week 8 will be defined based on tumour assessment status of CR, sCR, VGPR or PR. Only patients with measurable disease at baseline will be included in the analysis of the RR. Patients without a post-baseline tumour assessment will be considered to be non-responders.

There will be 7 cohorts with different cancer types. There will be Cohort 3a and 3b with patients with colorectal cancer treated with vemurafenib or vemurafenib in combination with cetuximab, respectively.

Cohort 3b has two parts,

Part 1 is a dose finding phase for vemurafenib in combination with cetuximab (based on a classical 3+3 design)

Part 2 is investigating the efficacy and safety of the recommended dose for stage I/II of the combination of vemurafenib and cetuximab

*see Appendix 9 for prostate cancer, Appendix 10 for ECD and/or LCH response criteria

8.1.2 Secondary Efficacy Variables

Secondary endpoints for each cohort and for patients with solid tumours and MM will include:

- duration of response (DOR),
- time to response,
- time to progression,
- clinical benefit rate (CR (or sCR), PR (or VGPR)) and stable disease [SD]),
- best overall response (BOR),
- PFS,
- overall survival (OS),
- IRC assessment of response rates focussing on Week 8, Week 16 and BOR for Cohort 1 (NSCLC) and other cohorts that demonstrate clinically meaningful efficacy per investigator assessment.

PFS is defined as the time from the first day of study treatment, until the first documented progression of disease or death from any cause, whichever occurs first. Patients with no PFS events will be censored at the time of the last evaluable tumour assessment. Patients with no tumour assessment after the baseline visit will be censored at the time of the first day of study treatment plus 1 day.

Overall survival (time to death) is defined as time between the first day of study treatment and date of death of any cause. Patients for whom no death is captured on the clinical database are censored at the most recent date they were known to be alive.

Time to progression is defined as time from the first day of study treatment to the first occurrence of progressive disease. Patients who have not progressed at the time of study completion (including patients who have died before progressive disease) or who are lost to follow-up are censored at the date of the last tumour assessment.

Clinical benefit response includes patients whose best response was:

- PR (or VGPR) or
- CR (or sCR) or
- Stable disease (SD) that have lasted at least 6 weeks.

For patients with response at Week 8, duration of response (unconfirmed) is defined as the period from the date of initial PR or CR until the date of progressive disease or death from any cause. Patients with no documented progression after CR or PR will be censored at the last date at which they are known to have had the CR or PR, respectively. The method for handling censoring is the same as described for the PFS.

For patients with a response at Week 8 of CR or PR, time to response is defined as the time from the first day of study treatment to the date of first CR or PR. The censoring rules will be similar to those of the PFS.

For patients with MM, responders will be defined as patients with CR, sCR, PR and VGPR status. All other definitions for secondary endpoints for these patients will be similar to definitions above.

The best (confirmed) overall response (BOR) will be also assessed at the end of Stage II for each cohort. BOR is defined as the best response recorded from the first day of study treatment until

disease progression/recurrence or death. To be assigned a status of PR or CR (i.e., a responder), changes in tumour measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met, i.e., patients need to have two consecutive assessments of PR or CR to be a responder. Only patients with measurable disease at baseline will be included in the analysis of the BOR. Patients without a post-baseline tumour assessment will be considered to be non-responders. Duration of confirmed response is defined as the period from the date of initial PR or CR that contributed for the BOR status until the date of progressive disease or death from any cause. Patients with no documented progression after CR or PR will be censored at the last date at which they are known to have had the CR or PR, respectively. The method for handling censoring is the same as described for the PFS.

For responders in BOR, time to response is defined as the time from the first day of study treatment to the date of first CR or PR. The censoring rules will be similar to those of the PFS.

8.1.3 Safety Variables

Adverse events (AEs), all AEs, AEs Grade 3 or 4, AEs leading to treatment interruption and discontinuation, serious adverse events (SAEs), premature discontinuation from study and treatment, laboratory parameters, exposure to study medication and skin evaluation, head/neck evaluations, chest CT scan will be the primary safety variables for each cohort. Vital signs, electrocardiogram, ECOG performance status, and physical examination will be the secondary safety variables.

For Cohort 3b, patients with colorectal cancer, dose-limiting toxicities parameters as defined in Section 6.3.2.2 will be summarized by dose levels.

8.2 STUDY POPULATIONS

The main analysis population for the efficacy analysis will be the intent-to-treat (ITT) population, which will include all patients enrolled in the study irrespective of whether they have received study medication or not. ITT1 to ITT7 will correspond to the ITT population for each cohort (Cohort 1 to Cohort 7, respectively).

The per-protocol (PP) population will not be defined due to the small number of patients per cohort, but protocol deviations will be listed (including patients with non-measurable disease at baseline).

The safety populations SP1 to SP7 will correspond to the safety populations for Cohort 1 to Cohort 7, respectively, and will include, for each cohort, all patients who have received at least one dose of study medication.

Cohort 7 (patients with other solid tumours) will include patients with different tumour types and therefore different safety/ITT populations will be defined for different tumour types.

8.3 STATISTICAL AND ANALYTICAL METHODS

8.3.1 Statistical Model

The main analysis for RR will use an adaptive design based on Simon's two stage design for a single proportion (70).

Stage I will be defined as when a pre-specified number of patients (as determined in the Sample Size section) will have a minimum of 8 weeks of treatment, develop progressive disease, prematurely withdraw from the study medication, or die, whichever occurs first.

If a pre-specified minimal RR will not be achieved in certain cohorts in the first stage of the study in certain cohorts, this cohort will be closed and no further enrolment of patients will be performed for that cohort. However, if a clear clinical benefit has been observed for patients in the cohort, e.g. majority of patients recorded SD at Week 8 and no CR or PR is recorded, then enrolment into Stage II might be allowed for this cohort after discussion with the Sponsor and study Steering Committee. Otherwise, enrolment will continue into Stage II until a pre-determined number of additional patients has been reached (as explained in the Sample Size section). At the conclusion of this study, vemurafenib will be declared effective or ineffective for each indication (cohort) based on rules for Stage II.

The analysis at Stage II (for lower or higher desirable response) for each cohort will be performed when all patients enrolled in the study, as estimated in the Sample Size section, will have a minimum of 8 weeks of treatment, develop progressive disease, withdraw, or are lost to follow-up, whichever occurs first.

Recruitment into any cohort/indication can be expanded up to a total of 70 patients if a response rate has been demonstrated in Stage II of that cohort as per stopping rules defined in the protocol or a clear clinical benefit for patients is observed. This will be decided by the Sponsor in discussion with study Steering Committee.

In case a cohort/indication is expanded to up to 70 patients, the primary analysis for efficacy will occur once all patients have been followed up for 9 months after last patient had been enrolled in that cohort, or the patient develops progressive disease, withdraws consent, or is lost to follow-up, whichever occurs first.

The final analysis for each cohort will take place when all patients in that cohort have been followed for survival for a minimum of 12 months after the last patient has been enrolled or until all patients have died withdrawn consent or are lost to follow up, whichever occurs first. More details are provided in Efficacy Data Analysis (see below).

8.3.1.1 Hypothesis Testing

The adaptive two-stage design allows the original estimation of the Stage II RR to be reassessed, based on information at Stage I, in the event that it was too optimistic or too sceptical to be the true RR.

For example, for patients in each cohort, we assume that an RR of 15% would be a very low RR and vemurafenib would be “under-performing” for this cohort. An RR of 45% would be a high desirable RR, whereas an RR of 35% would be a low desirable RR, for Stage II.

The hypotheses for all cohorts for Stage I are:

H_0: $\pi_{N1} < \pi_0$ where $\pi_0 = 15\%$

H_1: $\pi_{N1} \geq \pi_0$ where $\pi_0 = 15\%$

If H_0 is rejected (and H_1 is accepted at Stage I), further patients will be enrolled based on the number of responders in Stage I and their data will be collected in the second stage.

The hypotheses for all cohorts at the end of Stage II for a low desirable response, π1L, are:

i) H_1 is accepted at Stage I and

ii) H_0: $\pi_N \leq \pi_{1L}$ where $\pi_{1L} = 35\%$

H_1: $\pi_N > \pi_{1L}$ where $\pi_{1L} = 35\%$

The N notifies the total number of patients for each cohort.

The hypotheses for all cohorts at the end of Stage II for a high desirable response, π1H, are:

i) H_1 is accepted at Stage I and

ii) H_0: $\pi_N \leq \pi_{1H}$ where $\pi_{1H} = 45\%$

H_1: $\pi_N > \pi_{1H}$ where $\pi_{1H} = 45\%$

Cohort 3b

For this cohort, first, the recommended dose for Stage I/II part should be established based on 3+3 classical design. Then the second part will include a stage I and II parts similar to what is planned for the other cohorts and same statistical hypotheses at Stage I and Stage II will be applied.

8.3.1.2 Stopping Rules for Enrolment and Screening

If no patients are enrolled in the remaining cohorts one year after any of the cohorts has completed enrolment, then enrolment in those remaining cohorts will be stopped (patients already in screening will be allowed to enrol if eligible).

Individual cohorts may temporarily stop enrolment to allow for the stage I analysis before progressing to stage II.

Individual cohorts may temporarily stop screening to allow for the stage I analysis before progressing to stage II.

The decision to carry on enrolment of CRC patients into Cohort 3a (vemurafenib monotherapy) and/or enrol patients into Cohort 3b (combination of vemurafenib and cetuximab) will be based on the stage I analysis for Cohort 3a (vemurafenib monotherapy). This will be decided by the Sponsor in discussion with study Steering Committee.

The decision to continue enrolment in Cohort 3b after the Part I dose escalation phase will be decided by the Sponsor in discussion with study Steering Committee.

1. <u>Rules for Stage I</u>

Stage I will be stopped if the number of responders (unconfirmed) is less than the pre-specified number in the Table 15 (e.g. if there is none or only one responder out of first seven patients). However if a clear clinical benefit has been observed for patients in the cohort, e.g. majority of patients recorded SD at Week 8 and no CR or PR is recorded, then enrolment into Stage II might be allowed for this cohort.

If there is the required response during Stage I or a good clinical benefit is observed for particular cohort as mentioned above, then additional patients will be enrolled in the second stage of the corresponding cohort, in order to achieve total number of patients as specified in the Table 15 and Table 16 below (Sample Size estimation section).

Cohort 7 will be closed to enrolment when all other cohorts are closed and results are reported, regardless of the number of patients recruited at that time. This cohort may be quite heterogeneous and will be examined primarily to seek efficacy signals in the relatively rare BRAF V600 mutation-positive tumours.

2. Rules for Stage II

A study treatment will be considered to be efficacious in a cohort in Stage II if

- there is no unacceptable toxicity and
- the number of responders is equal or above the specified number in the sample size calculations, as presented in Table 16 or
- best overall response, BOR (confirmed) is higher than 15%.

3. Cohort Expansion

There will be no formal statistical hypothesis tested as part of the expansion cohort analysis. The analysis of the expanded cohort will allow estimation of RR and other efficacy parameters (please refer to secondary efficacy parameters in Section 8.1.2) with increased precision and more insight concerning the safety profile.

8.3.2 Efficacy Data Analysis

The primary efficacy endpoint is RR at Week 8 in each cohort, as assessed by the Investigator using RECIST, v1.1 or IMWG response criteria.

This is an early phase II study and cohorts are independent, hence there will be no adjustment for multiplicity.

Number and percentage of responders with corresponding Clopper-Pearson 95% confidence intervals will be provided for each cohort. The clinical benefit rate, BOR and RR at the end of Stage II will be analysed in a similar way to RR at Week 8. Estimates for the survivor function for the time-to-event variables, such as time to progression (TTP), PFS, OS, duration of response, and time to response, will be obtained by using the Kaplan-Meier (KM) approach together with associated 95% CI.

Due to the small sample size in Cohort 7 (patients with other solid tumours), only descriptive statistics will be applied. If there are at least 5 patients with the same tumour type, number (percentage) of patients will be summarized in the frequency table and listed for RR at Week 8, clinical benefit rate and BOR. If there are fewer patients, only listings will be provided. For response criteria for patients with prostate cancer, ECD and/or LCH enrolled in this cohort, see Appendix 9 and Appendix 10, respectively.

In case a cohort/indication is expanded up to 70 patients, the primary analysis for efficacy will occur once all patients have been followed up for 9 months after last patient had been enrolled in that cohort, or the patient develops progressive disease, withdraws consent, or is lost to follow-up, whichever occurs first.

For all patients in Cohort 1, the CT scans during the patient's last therapy prior to this study, as well as CT scans made during this study, will be collected and reviewed retrospectively by an IRC. Scans from the prior therapy will be used to establish plTTP, and this may be examined in relation to the TTP achieved from study treatment. During the study, the investigator-assessed response

rate will remain as the primary efficacy endpoint and the IRC assessment will be a supportive secondary endpoint. The concordance tables between Investigator and IRC assessment will be produced. The IRC assessment of response rates will focus on Week 8, Week 16 and BOR. For other cohorts, collection of scans are described in the study assessment sections. Analyses will be performed as described above for Cohort 1.

8.3.3 Safety Data Analysis

The safety variables will be summarized for the safety population where the safety population is SP1 to SP7. All safety variables will be summarized for each cohort.

All AEs will be assessed according to the NCI CTCAE, v4.0, grading system. The analysis of AEs will focus on treatment-emergent AEs, i.e., AEs occurring on the day of or after first administration of study drug (vemurafenib). Non-treatment emergent AEs (i.e., those occurring before commencement of study medication) will only be listed.

The incidence, type, and severity of AEs will be summarized according to the primary system-organ class (SOC) and within each SOC, by MedDRA preferred term. Summary tables may be presented for time to first onset of the AE of special interest.

AEs leading to treatment interruption and discontinuation and SAEs will be analysed in a similar way to all AEs. Cause of death will also be summarized and listed.

Results from skin evaluation, head and neck evaluations, chest CT scan (e.g., number of lesions, SCC - keratoacanthoma type, etc.) will be summarized using frequencies and percentages. The number of patients prematurely discontinued from the treatment with corresponding reason for discontinuation will be summarized and listed. The discontinuation from study will be also summarized and listed.

Descriptive statistics will be presented for cumulative vemurafenib doses and duration of exposure.

Laboratory parameters, haematology, and serum biochemistry will be presented in shift tables of NCI-CTCAE grade at baseline versus worst grade during the Treatment Period. The summary of laboratory parameters presented by means, standard deviation, minimum, and maximum will be also presented.

Vital signs (blood pressure, temperature, heart rate, and respiratory rate) and ECG (heart rate, PR interval, QRS duration, QT interval and QTc interval) will be summarized over time by means of mean, median, and range (mean and maximum). The ECG findings will be also presented by frequency tables over time. The ECOG PS will be summarized by frequency tables over time and percentage of patients in different categories will be presented by bar charts at different time points. Physical examination variables collected only at baseline (e.g., height) will be summarized for baseline only while other physical examination variables will be summarized over time by visits and reported in patients' listings. Concomitant therapy will be summarized by frequency tables and percentages.

For Cohort 3b, there will be a summary of DLT safety parameters (as defined in Section 6.3.2.2) by dose levels.

For Cohort 7 (patients with other solid tumours), if there are at least 5 patients with the same tumour type, number (percentage) of patients for safety parameters will be summarized and listed. If there are less patients then only listings will be provided for this cohort.

8.3.4 Interim Analysis

The study will be analysed for efficacy at Stage I and Stage II and the dose escalation for Part 1 of Cohort 3b (Section 6.3.2.1) and at week 16 for expanded cohorts. All cohorts will be analysed at the end of the study.

8.3.5 Pharmacokinetic Analysis

The population PK model developed in melanoma patients will be used to obtain individual vemurafenib PK parameters from the sparse sampling collected in newly enrolled patients. Summary statistics (such as mean, median and standard deviation) will be used as appropriate for the vemurafenib plasma concentrations and PK parameters.

The relationship between appropriate clinical and pharmacodynamic endpoints and the plasma concentrations of vemurafenib will be explored, as appropriate.

8.3.6 Exploratory Analyses

The correlation between plasma and tissue BRAF V600 mutation status as well as the concordance of the Roche CoDx cobas 4800 BRAF V600 Test or other standard methodologies may be explored. The relationship between appropriate clinical endpoints and the mutation status (including, but not limited to, allelic frequencies of the BRAF V600 mutation and its dynamic changes from pre-dose to on-treatment) in tissue and/or plasma will be explored. Mutation status in tissue and/or plasma will also be correlated to demographics, medical history and clinical parameters.

8.3.7 Other Analyses

Demographics and medical history will be summarized for each cohort.

8.4 SAMPLE SIZE ESTIMATION

The sample size estimation is based on the method of Lin and Shih (70) and corresponding SAS program.

There will be up to 170 patients enrolled in this study for the Stage I/II analysis (see Table 15). Recruitment into any cohort/indication can be expanded up to a total of 70 patients if a response rate has been demonstrated in Stage II of that cohort as per stopping rules defined in the protocol or a clear clinical benefit for patients is observed. This will be decided by the Sponsor in discussion with study Steering Committee. The maximum number of patients in this study is therefore 490 (7 cohorts up to 70 patients each).

There will be 7 cohorts with patients with different indications. There will be two sub- cohorts with patients with colorectal cancer, one treated only with vemurafenib while other treated with vemurafenib and cetuximab.

Cohorts (except Cohort 3b and Cohort 7) will have a minimum of 13 and a maximum of 19 patients (depending on results in Stage I).

If there are enough patients enrolled in individual tumour type, Cohort 7 will have 13 or 19 patients and Lin and Shin's method of Stage I and Stage II design will be applied. If there are not enough patients in individual tumour type, data for cohort 7 will be only listed.

Cohort 3b will have a dose escalation phase based on a classical 3+3 design and will enrol a maximum of 18 patients. Cohort of patients with MTD will be expanded to 7 patients as per rule of Stage I design. Then a further 6 or 12 patients will be enrolled to a maximum of 13 or 19 patients will be enrolled depending on the results for stage I (see Table 16). The maximum number of patients for this cohort might be up to 37 patients.

A proportion of 15% is chosen for a low response, based on Section 8.3.1.1 in the protocol and on our present knowledge.

However, if the number of responders is 2, 3, or 4 out of 7 patients in Stage I, then the study medication is possibly efficacious for that cohort and further data at stage II will be collected based on the "low desirable response at Stage II" Sample Size estimation, i.e., an additional 12 patients will be enrolled in order to have a total of 19 patients for that cohort. Stage I will be stopped if the number of responders is less than the pre-specified number in the Table 15 (e.g. if there is none or only one responder out of first seven patients). However if a clear clinical benefit has been observed for patients in the cohort, e.g. majority of patients recorded SD at Week 8 and no CR or PR is recorded, then enrolment into Stage II will be allowed for this cohort after discussion with the Sponsor and study Steering Committee.

If there are 5 or more responders out of 7, then further data will be collected based on "high desirable response at Stage II" Sample Size estimation, i.e., an additional 6 patients will be enrolled in order to have a total of 13 patients for that cohort.

Assuming RRs as specified in the prior hypothesis testing, a power of 80% for high desirable response and 70% for low desirable response and two-sided alpha of 0.1, the number of patients required in each cohort is presented in Table 16.

Table 15:
Sample Size for Each Cohort – Stage I/II

	Dose Finding [a]	Sample size following Stage I analysis	
		Low desirable response	High desirable response
NSCLC		19	13
Ovarian cancer		19	13
Colorectal cancer (Cohort 3a vemurafenib only)		19	13
Colorectal cancer (Cohort 3b vemurafenib and cetuximab)	3+3 Design up to 18	19	13
Cholangiocarcinoma/cancer of biliary tract		19	13
Breast Cancer		19	13
Multiple Myeloma		19	13
Other tumours [b]		19	13
Total number for Stage I/II	**up to 170 patients [c]**		

a. Cohort 3b Part 1 only

b. The n's presented are for each individual tumour type, with enough patients available to follow the 2 stage study design

c. The total number of patients may exceed the original estimate of 170 patients if any cohort is expanded (see Table 16).

Details regarding Stage I and number of responders are presented in Table 16.

Table 16:
Sample Size for Each Cohort (except Cohort 6) and Stage I/II

	Stage (Two-Stage Design)		Total Number of Patients in Each Cohort	Two-Sided Alpha Level / Power
	Stage I	Stage II [b]		
All Cohorts				
Low response at the end of Stage I				
Number of patients	7	19	19	10% / 70%
Number of responders [a]	≥ 2 and ≤ 4	≥ 5		
High response at the end of Stage I				
Number of patients	7	13	13	10% / 80%
Number of responders [a]	≥ 5	≥ 6		

The sample size was estimated using the method of Lin and Shih's paper (Biometrics. 2004;60:482-490) and corresponding SAS program.

Number of patients needed to respond in order to continue into Stage II or have a positive result at the end of trial.

a. This columns display a maximum number of patients required for each cohort and number of responders that should be present at end of Stage II in order to declare efficacious treatment.

8.4.1 Sample Size Estimation for Expansion of Cohorts following Promising Stage II Results

Recruitment into any cohort/indication can be expanded up to a total of 70 patients if a response rate has been demonstrated in Stage II of that cohort as per stopping rules defined in the protocol or a clear clinical benefit for patients is observed. This will be decided by the Sponsor in discussion with study Steering Committee.

Assuming a preferable BOR of 40% in the cohort with promising Stage II results and aiming at a distance from the estimated proportion to the CI limits of 12%, a total of 70 patients would need to be enrolled. The observed BOR of 40% could then be estimated to be within 28% and 52%, with a probability of 95% (Clopper-Pearson exact confidence intervals).

Estimation of the sample size was calculated by SAS (Version 9.2) and nQuery (Version 6). Details are presented in the Table 17.

Table 17:
Estimation of Sample Size

Sample Size	BOR	95% Clopper Pearson Exact Confidence Intervals
70 patients	36% (25 patients)	25% – 48%
	40% (28 patients)	28% – 52%
	46% (32 patients)	34% – 58%
	50% (35 patients)	38% – 62%

9. DATA COLLECTION, MANAGEMENT AND QUALITY ASSURANCE

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

Accurate and reliable data collection will be assured by verification and cross–check of the eCRFs against the Investigator's records by the study monitor (source document verification), by checks through data management and the maintenance of a drug–dispensing log by the Investigator.

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

A comprehensive validation check program utilizing front-end checks in the eCRF will verify the data and discrepancy reports will be generated accordingly and transferred electronically to the eCRF at the site for resolution by the Investigator.

9.1 ASSIGNMENT OF PREFERRED TERMS AND ORIGINAL TERMINOLOGY

For classification purposes, preferred terms will be assigned by the Sponsor to the original terms entered on the eCRF, using the most up-to-date version of the Medical Dictionary for Regulatory Activities (MedDRA) terminology for adverse events and diseases and the International Non-proprietary Name (INN) Drug Terms and Procedures Dictionary for treatments and surgical and medical procedures.

10. REFERENCES

1. Alberts B, Johnson A, Lewis J, Raff M, Roberts K, Walter P. Mechanisms of Cell Communication. Molecular biology of the cell. 5th ed. New York: Garland Science; 2008.
2. Forbes SA, Bhamra G, Bamford S, Dawson E, Kok C, Clements J, et al. The Catalogue of Somatic Mutations in Cancer (COSMIC). Curr Protoc Hum Genet. 2008;Chapter 10:Unit 10 1.
3. Forbes SA, Bindal N, Bamford S, Cole C, Kok CY, Beare D, et al. COSMIC: mining complete cancer genomes in the Catalogue of Somatic Mutations in Cancer. Nucleic Acids Res. 2011;39:D945-50.
4. Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, et al. Mutations of the BRAF gene in human cancer. Nature. 2002;417:949-54.
5. Helfrich I, Edler L, Sucker A, Thomas M, Christian S, Schadendorf D, et al. Angiopoietin-2 levels are associated with disease progression in metastatic malignant melanoma. Clin Cancer Res. 2009;15:1384-92.
6. Sumimoto H, Hirata K, Yamagata S, Miyoshi H, Miyagishi M, Taira K, et al. Effective inhibition of cell growth and invasion of melanoma by combined suppression of BRAF (V599E) and Skp2 with lentiviral RNAi. Int J Cancer. 2006;118:472-6.
7. Rubinstein JC, Sznol M, Pavlick AC, Ariyan S, Cheng E, Bacchiocchi A, et al. Incidence of the V600K mutation among melanoma patients with BRAF mutations, and potential therapeutic response to the specific BRAF inhibitor PLX4032. J Transl Med. 2010;8:67.
8. Deschoolmeester V, Baay M, Specenier P, Lardon F, Vermorken JB. A review of the most promising biomarkers in colorectal cancer: one step closer to targeted therapy. Oncologist. 2010;15:699-731.
9. Michor F, Iwasa Y, Lengauer C, Nowak MA. Dynamics of colorectal cancer. Semin Cancer Biol. 2005;15:484-93.
10. Jass JR. Colorectal cancer: a multipathway disease. Crit Rev Oncog. 2006;12:273-87.
11. Goel A, Arnold CN, Niedzwiecki D, Chang DK, Ricciardiello L, Carethers JM, et al. Characterization of sporadic colon cancer by patterns of genomic instability. Cancer Res. 2003;63:1608-14.
12. Lee S, Cho NY, Choi M, Yoo EJ, Kim JH, Kang GH. Clinicopathological features of CpG island methylator phenotype-positive colorectal cancer and its adverse prognosis in relation to KRAS/BRAF mutation. Pathol Int. 2008;58:104-13.
13. Maestro ML, Vidaurreta M, Sanz-Casla MT, Rafael S, Veganzones S, Martinez A, et al. Role of the BRAF mutations in the microsatellite instability genetic pathway in sporadic colorectal cancer. Ann Surg Oncol. 2007;14:1229-36.
14. Barault L, Veyrie N, Jooste V, Lecorre D, Chapusot C, Ferraz JM, et al. Mutations in the RAS-MAPK, PI(3)K (phosphatidylinositol-3-OH kinase) signaling network correlate with poor survival in a population-based series of colon cancers. Int J Cancer. 2008;122:2255-9.
15. Ogino S, Nosho K, Kirkner GJ, Kawasaki T, Meyerhardt JA, Loda M, et al. CpG island methylator phenotype, microsatellite instability, BRAF mutation and clinical outcome in colon cancer. Gut. 2009;58:90-6.
16. Price TJ, Hardingham JE, Lee CK, Weickhardt A, Townsend AR, Wrin JW, et al. Impact of KRAS and BRAF Gene Mutation Status on Outcomes From the Phase III AGITG MAX Trial of Capecitabine Alone or in Combination With Bevacizumab and Mitomycin in Advanced Colorectal Cancer. J Clin Oncol. 2011;29:2675-82.

17. Richman SD, Seymour MT, Chambers P, Elliott F, Daly CL, Meade AM, et al. KRAS and BRAF mutations in advanced colorectal cancer are associated with poor prognosis but do not preclude benefit from oxaliplatin or irinotecan: results from the MRC FOCUS trial. J Clin Oncol. 2009;27:5931-7.
18. Roth AD, Tejpar S, Delorenzi M, Yan P, Fiocca R, Klingbiel D, et al. Prognostic role of KRAS and BRAF in stage II and III resected colon cancer: results of the translational study on the PETACC-3, EORTC 40993, SAKK 60-00 trial. J Clin Oncol. 2010;28:466-74.
19. Samowitz WS, Sweeney C, Herrick J, Albertsen H, Levin TR, Murtaugh MA, et al. Poor survival associated with the BRAF V600E mutation in microsatellite-stable colon cancers. Cancer Res. 2005;65:6063-9.
20. Saridaki Z, Papadatos-Pastos D, Tzardi M, Mavroudis D, Bairaktari E, Arvanity H, et al. BRAF mutations, microsatellite instability status and cyclin D1 expression predict metastatic colorectal patients' outcome. Br J Cancer. 2010;102:1762-8.
21. Tol J, Nagtegaal ID, Punt CJ. BRAF mutation in metastatic colorectal cancer. N Engl J Med. 2009;361:98-9.
22. Di Nicolantonio F, Martini M, Molinari F, Sartore-Bianchi A, Arena S, Saletti P, et al. Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. J Clin Oncol. 2008;26:5705-12.
23. Kopetz S, Desai J, Chan E, Hecht JR, O'Dwyer PJ, Lee RJ, et al. PLX4032 in metastatic colorectal cancer patients with mutant BRAF tumors. J Clin Oncol (Meeting Abstracts) 2010;28:3534.
24. Brose MS, Volpe P, Feldman M, Kumar M, Rishi I, Gerrero R, et al. BRAF and RAS mutations in human lung cancer and melanoma. Cancer Res. 2002;62:6997-7000.
25. Marchetti A, Felicioni L, Malatesta S, Grazia Sciarrotta M, Guetti L, Chella A, et al. Clinical features and outcome of patients with non-small-cell lung cancer harboring BRAF mutations. J Clin Oncol. 2011;29:3574-9.
26. Garon EB, Finn RS, Hosmer W, Dering J, Ginther C, Adhami S, et al. Identification of common predictive markers of in vitro response to the Mek inhibitor selumetinib (AZD6244; ARRY-142886) in human breast cancer and non-small cell lung cancer cell lines. Mol Cancer Ther. 2010;9:1985-94.
27. Hollestelle A, Elstrodt F, Nagel JH, Kallemeijn WW, Schutte M. Phosphatidylinositol-3-OH kinase or RAS pathway mutations in human breast cancer cell lines. Mol Cancer Res. 2007;5:195-201.
28. Gonzalez-Bosquet J, Calcei J, Wei JS, Garcia-Closas M, Sherman ME, Hewitt S, et al. Detection of somatic mutations by high-resolution DNA melting (HRM) analysis in multiple cancers. PLoS One. 2011;6:e14522.
29. Ueda M, Toji E, Nunobiki O, Izuma S, Okamoto Y, Torii K, et al. Mutational analysis of the BRAF gene in human tumor cells. Hum Cell. 2008;21:13-7.
30. Janku F, Lee JJ, Tsimberidou AM, Hong DS, Naing A, Falchook GS, et al. PIK3CA Mutations Frequently Coexist with RAS and BRAF Mutations in Patients with Advanced Cancers. PLoS One. 2011;6:e22769.
31. Hollestelle A, Nagel JH, Smid M, Lam S, Elstrodt F, Wasielewski M, et al. Distinct gene mutation profiles among luminal-type and basal-type breast cancer cell lines. Breast Cancer Res Treat. 2010;121:53-64.
32. Cho KR. Ovarian cancer update: lessons from morphology, molecules, and mice. Arch Pathol Lab Med. 2009;133:1775-81.

33. Nakayama N, Nakayama K, Yeasmin S, Ishibashi M, Katagiri A, Iida K, et al. KRAS or BRAF mutation status is a useful predictor of sensitivity to MEK inhibition in ovarian cancer. Br J Cancer. 2008;99:2020-8.

34. Pohl G, Ho CL, Kurman RJ, Bristow R, Wang TL, Shih Ie M. Inactivation of the mitogen-activated protein kinase pathway as a potential target-based therapy in ovarian serous tumors with KRAS or BRAF mutations. Cancer Res. 2005;65:1994-2000.

35. Sieben NL, Macropoulos P, Roemen GM, Kolkman-Uljee SM, Jan Fleuren G, Houmadi R, et al. In ovarian neoplasms, BRAF, but not KRAS, mutations are restricted to low-grade serous tumours. J Pathol. 2004;202:336-40.

36. Singer G, Oldt R, 3rd, Cohen Y, Wang BG, Sidransky D, Kurman RJ, et al. Mutations in BRAF and KRAS characterize the development of low-grade ovarian serous carcinoma. J Natl Cancer Inst. 2003;95:484-6.

37. Dansonka-Mieszkowska A, Ludwig AH, Kraszewska E, Kupryjanczyk J. Geographical variations in TP53 mutational spectrum in ovarian carcinomas. Ann Hum Genet. 2006;70:594-604.

38. Kohler MF, Marks JR, Wiseman RW, Jacobs IJ, Davidoff AM, Clarke-Pearson DL, et al. Spectrum of mutation and frequency of allelic deletion of the p53 gene in ovarian cancer. J Natl Cancer Inst. 1993;85:1513-9.

39. Salani R, Kurman RJ, Giuntoli R, 2nd, Gardner G, Bristow R, Wang TL, et al. Assessment of TP53 mutation using purified tissue samples of ovarian serous carcinomas reveals a higher mutation rate than previously reported and does not correlate with drug resistance. Int J Gynecol Cancer. 2008;18:487-91.

40. Kupryjanczyk J, Thor AD, Beauchamp R, Merritt V, Edgerton SM, Bell DA, et al. p53 gene mutations and protein accumulation in human ovarian cancer. Proc Natl Acad Sci U S A. 1993;90:4961-5.

41. Wen WH, Reles A, Runnebaum IB, Sullivan-Halley J, Bernstein L, Jones LA, et al. p53 mutations and expression in ovarian cancers: correlation with overall survival. Int J Gynecol Pathol. 1999;18:29-41.

42. Quaye L, Gayther SA, Ramus SJ, Di Cioccio RA, McGuire V, Hogdall E, et al. The effects of common genetic variants in oncogenes on ovarian cancer survival. Clin Cancer Res. 2008;14:5833-9.

43. Quaye L, Song H, Ramus SJ, Gentry-Maharaj A, Hogdall E, DiCioccio RA, et al. Tagging single-nucleotide polymorphisms in candidate oncogenes and susceptibility to ovarian cancer. Br J Cancer. 2009;100:993-1001.

44. Kyle RA, Rajkumar SV. Multiple myeloma. N Engl J Med. 2004;351:1860-73.

45. Fonseca R, Bergsagel PL, Drach J, Shaughnessy J, Gutierrez N, Stewart AK, et al. International Myeloma Working Group molecular classification of multiple myeloma: spotlight review. Leukemia. 2009;23:2210-21.

46. Chng WJ, Glebov O, Bergsagel PL, Kuehl WM. Genetic events in the pathogenesis of multiple myeloma. Best Pract Res Clin Haematol. 2007;20:571-96.

47. Bezieau S, Devilder MC, Avet-Loiseau H, Mellerin MP, Puthier D, Pennarun E, et al. High incidence of N and K-Ras activating mutations in multiple myeloma and primary plasma cell leukemia at diagnosis. Hum Mutat. 2001;18:212-24.

48. Liu P, Leong T, Quam L, Billadeau D, Kay NE, Greipp P, et al. Activating mutations of N- and K-ras in multiple myeloma show different clinical associations: analysis of the Eastern Cooperative Oncology Group Phase III Trial. Blood. 1996;88:2699-706.

49. Bonello L, Voena C, Ladetto M, Boccadoro M, Palestro G, Inghirami G, et al. BRAF gene is not mutated in plasma cell leukemia and multiple myeloma. Leukemia. 2003;17:2238-40.

50. Chapman MA, Lawrence MS, Keats JJ, Cibulskis K, Sougnez C, Schinzel AC, et al. Initial genome sequencing and analysis of multiple myeloma. Nature. 2011;471:467-72.

51. Kim K, Kong SY, Fulciniti M, Li X, Song W, Nahar S, et al. Blockade of the MEK/ERK signalling cascade by AS703026, a novel selective MEK1/2 inhibitor, induces pleiotropic anti-myeloma activity in vitro and in vivo. Br J Haematol. 2010;149:537-49.

52. Hezel AF, Deshpande V, Zhu AX. Genetics of biliary tract cancers and emerging targeted therapies. J Clin Oncol. 2010;28:3531-40.

53. Zhu AX, Hezel AF. Development of molecularly targeted therapies in biliary tract cancers: reassessing the challenges and opportunities. Hepatology. 2011;53:695-704.

54. Hori H, Ajiki T, Mita Y, Horiuchi H, Hirata K, Matsumoto T, et al. Frequent activation of mitogen-activated protein kinase relative to Akt in extrahepatic biliary tract cancer. J Gastroenterol. 2007;42:567-72.

55. Saetta AA, Papanastasiou P, Michalopoulos NV, Gigelou F, Korkolopoulou P, Bei T, et al. Mutational analysis of BRAF in gallbladder carcinomas in association with K-ras and p53 mutations and microsatellite instability. Virchows Arch. 2004;445:179-82.

56. Tannapfel A, Sommerer F, Benicke M, Katalinic A, Uhlmann D, Witzigmann H, et al. Mutations of the BRAF gene in cholangiocarcinoma but not in hepatocellular carcinoma. Gut. 2003;52:706-12.

57. Goldenberg D, Rosenbaum E, Argani P, Wistuba, II, Sidransky D, Thuluvath PJ, et al. The V599E BRAF mutation is uncommon in biliary tract cancers. Mod Pathol. 2004;17:1386-91.

58. Stevens G, Fife K. Cerebral metastases. In: Thompson JF, Morton DL, Kroon BBR, editors. Textbook of Melanoma: Pathology, Diagnosis, and Management. Independence, KY: Taylor & Francis; 2004. p. 519-29.

59. Bollag G, Hirth P, Tsai J, Zhang J, Ibrahim PN, Cho H, et al. Clinical efficacy of a RAF inhibitor needs broad target blockade in BRAF-mutant melanoma. Nature. 2010;467:596-9.

60. Yang H, Higgins B, Kolinsky K, Packman K, Go Z, Iyer R, et al. RG7204 (PLX4032), a selective BRAFV600E inhibitor, displays potent antitumor activity in preclinical melanoma models. Cancer Res. 2010;70:5518-27.

61. Flaherty KT, Puzanov I, Kim KB, Ribas A, McArthur GA, Sosman JA, et al. Inhibition of mutated, activated BRAF in metastatic melanoma. N Engl J Med. 2010;363:809-19.

62. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011;364:2507-16.

63. Sosman J, Kim K, Schuchter L, Gonzalez R, Pavlick A, Weber J, et al. An open-label, multicenter phase II study of continuous oral dosing of RG7204 (PLX4032) in previously treated patients with BRAF V600E mutation-positive metastatic melanoma. Pigment Cell Melanoma Res. 2010;23:886.

64. Ribas A, Kim KB, Schuchter LM, Gonzalez R, Pavlick AC, Weber JS, et al. BRIM-2: An open-label, multicenter phase II study of vemurafenib in previously treated patients with BRAF V600E mutation-positive metastatic melanoma. J Clin Oncol (Meeting Abstracts). 2011;29:Abstract 8509.

65. Mandrell JC, Santa Cruz D. Keratoacanthoma: hyperplasia, benign neoplasm, or a type of squamous cell carcinoma? Semin Diagn Pathol. 2009;26:150-63.
66. Kopetz S, Desai J, Chan E, Hecht JR, O'Dwyer PJ, Lee RJ, et al. PLX4032 in metastatic colorectal cancer patients with mutant BRAF tumors. J Clin Oncol (Meeting Abstracts). 2010;28:3534.
67. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-47.
68. Durie BG, Harousseau JL, Miguel JS, Blade J, Barlogie B, Anderson K, et al. International uniform response criteria for multiple myeloma. Leukemia. 2006;20:1467-73.
69. Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. Leukemia. 2009;23:3-9.
70. Lin Y, Shih WJ. Adaptive two-stage designs for single-arm phase IIA cancer clinical trials. Biometrics. 2004;60:482-90.
71. Amaravadi R et al, Society for Melanoma Research 2011 (Abstract #SMR-P3)
72. Prahallad A, Sun C, Huang S, Di Nicolantonio F, Salazar R, Zecchin D et al. Unresponsiveness of colon cancer to BRAF V600E inhibition through feedback activation of EGFR. Nature. 2012;483:100-103.
73. Sosman JA et al. Survival in BRAF V600–Mutant Advanced Melanoma Treated with Vemurafenib. N Engl J Med. 2012;366:707-714.
74. Chapman P. ASCO 2012 Abstract #8502 (1 Feb 2012 data cut)
75. Vemurafenib Investigator Brochure, version 11. Please refer to www.vemurafenibtrials.com.
76. Aithal GP, Watkins PB, Andrade RJ, et al. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmacol Ther. 2011;89:806-15.
77. Callahan MK, Rampal R, Harding JJ, et al. Progression of RAS-mutant leukemia during RAF inhibitor treatment. N Engl J Med. 2012 367:2316-21.
78. Harding JJ, Lacouture ME, Pulitzer M, et al. Hypersensitivity skin reactions in melanoma patients treated with vemurafenib after ipilimumab therapy J Clin Oncol 30, 2012 (suppl; abstr 8515).
79. Cetuximab Summary of Product Characteristics.
80. NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. See http://evs.nci.nih.gov/ftp1/CTCAE/About.html
81. Lankisch PG, Droge M, Gottesleben F. Drug induced acute pancreatitis: incidence and severity. Gut 1995; 37:565-7.

PART II: ETHICS AND GENERAL STUDY ADMINISTRATION

11. ETHICAL ASPECTS

11.1 LOCAL REGULATIONS / DECLARATION OF HELSINKI

The Investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline [January 1997] or with local law if it affords greater protection to the subject. For studies conducted in the EU/EEA countries, the Investigator will ensure compliance with the EU Clinical Trial Directive [2001/20/EC]. For studies conducted in the USA or under US IND, the Investigator will additionally ensure adherence to the basic principles of "Good Clinical Practice" as outlined in the current version of 21 CFR, subchapter D, part 312, "Responsibilities of Sponsors and Investigators", part 50, "Protection of Human Subjects", and part 56, "Institutional Review Boards".

In other countries where "Guideline for Good Clinical Practice" exist Roche and the Investigators will strictly ensure adherence to the stated provisions.

11.2 INFORMED CONSENT

11.2.1 Main Study Informed Consent

It is the responsibility of the Investigator, or a person designated by the Investigator [if acceptable by local regulations], to obtain signed written informed consent from each patient prior to participating in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. For patients not qualified or incapable of giving legal consent, written consent must be obtained from the legally acceptable representative. In the case where both the patient and her legally acceptable representative are unable to read, an impartial witness should be present during the entire informed consent discussion. After the patient and representative have orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood.

The Investigator or designee must also explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, for any reason.

The electronic Case Report Forms (eCRFs) for this study contain a section for documenting patient informed consent, and this must be completed appropriately. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All patients (including those already being treated) should be informed of the new information, given a copy of the revised form and give their consent to continue in the study.

For US-IND studies: In a life-threatening situation where a subject is unconscious or otherwise unable to communicate, the emergency is such that there is not enough time to obtain consent from the subject's legally acceptable representative, and there is no other or better treatment available, it is permissible to treat the subject under protocol with consent of both the investigator and another physician not involved in the study, with appropriate documentation submitted to the

IRB within 5 days. If this collaboration is not immediately possible, there must be a written evaluation by a physician independent of the study and the appropriate documentation be submitted to the IRB within 5 days of treating the subject. In addition, the subject or his/her legally acceptable representative should be informed about the trial as soon as possible and consent to continue, giving written consent as described above.

For non-US-IND studies: In a life-threatening situation where a subject is unconscious or otherwise unable to communicate, the emergency is such that there is not enough time to obtain consent from the subject's legally acceptable representative, and there is no other or better treatment available, it is permissible to treat the subject under protocol with consent of the investigator, with appropriate documentation that the IEC had approved the procedures used to enrol subjects in such situations. In addition, the subject or his/her legally acceptable representative should be informed about the trial as soon as possible and consent to continue, giving written consent as described above.

11.3 INDEPENDENT ETHICS COMMITTEES (IEC)/INSTITUTIONAL REVIEW BOARD (IRB)

The protocol, informed consent form and any accompanying material provided to the patient in the U.S. will be submitted by the Investigator to an IRB for review. For EEA member states, the Sponsor will submit to the Competent Authority and IEC, the protocol and any accompanying material provided to the patient. In both the US and EEA member states, the accompanying material may include patient information sheets, descriptions of the study used to obtain informed consent and terms of any compensation given to the patient as well as advertisements for the trial.

An approval letter or certificate (specifying the protocol number and title) from the IEC/IRB must be obtained before study initiation by the Investigator specifying the date on which the committee met and granted the approval. This applies whenever subsequent amendments/modifications are made to the protocol.

Any modifications made to the protocol, informed consent or material provided to the patient after receipt of the IEC/IRB approval must also be submitted by the Investigator in the U.S. and by the Sponsor in the EEA member states in accordance with local procedures and regulatory requirements.

When no local review board exists, the Investigator is expected to submit the protocol to a regional committee. If no regional committee exists, Roche will assist the Investigator in submitting the protocol to the European Ethics Review Committee.

Roche shall also submit an Annual Safety Report once a year to the IEC and Competent Authorities (CAs) according to local regulatory requirements and timelines of each country participating in the study. In the U.S. Roche submits an IND Annual Report to the FDA according to local regulatory requirements and timelines.

11.4 FINANCIAL DISCLOSURE

The Investigator(s) will provide the Sponsor with sufficient accurate financial information (PD35) to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. The Investigator is responsible to promptly

update any information provided to the Sponsor if relevant changes occur in the course of the investigation and for 1 year following the completion of the study (last patient, last visit).

12. CONDITIONS FOR MODIFYING THE PROTOCOL

Requests from Investigators to modify the protocol to ongoing studies will be considered only by consultation between an appropriate representative of the Sponsor and the Investigator [Investigator representative[s] in the case of a multicentre trial]. Protocol modifications must be prepared by a representative of the Sponsor and initially reviewed and approved by the International Medical Leader and Biostatistician.

All protocol modifications must be submitted to the appropriate Independent Ethics Committee or Institutional Review Board for information and approval in accordance with local requirements, and to Regulatory Agencies if required. Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial patients, or when the change[s] involves only logistical or administrative aspects of the trial.

13. CONDITIONS FOR TERMINATING THE STUDY

Both the Sponsor and the Investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange the procedures on an individual study basis after review and consultation. In terminating the study, Roche and the Investigator will assure that adequate consideration is given to the protection of the patient's interests. The appropriate IRB/IEC and Regulatory Agencies should be informed accordingly.

14. STUDY DOCUMENTATION, CRFS AND RECORD KEEPING

14.1 INVESTIGATOR'S FILES / RETENTION OF DOCUMENTS

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two different separate categories: 1) Investigator's Study File, and 2) patient clinical source documents.

The Investigator's Study File will contain the protocol/amendments, Case Report and Query Forms, schedule of assessments, Independent Ethics Committee/Institutional Review Board and governmental approval with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms and other appropriate documents/correspondence, etc.

Patient clinical source documents [usually defined by the project in advance to record key efficacy/safety parameters independent of the eCRFs] would include patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, EEG, X-ray, pathology and special assessment reports, signed informed consent forms, consultant letters, and patient screening and enrolment logs. The Investigator must keep the two categories of documents on file as described above (including the archival CD) on file for at least 15 years after completion or discontinuation of the study. After that period of time the documents may be destroyed, subject to local regulations.

Should the Investigator wish to assign the study records to another party or move them to another location, Roche must be notified in advance.

If the Investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the Investigator and Roche to store these in a sealed container[s] outside of the site so that they can be returned sealed to the Investigator in case of a regulatory audit. Where source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the site.

ICH GCP guidelines require that Investigators maintain information in the study subject's records which corroborate data collected on the eCRF(s). Completed eCRF will be forwarded to Roche.

14.2 SOURCE DOCUMENTS AND BACKGROUND DATA

The Investigator shall supply the Sponsor on request with any required background data from the study documentation or clinic records. This is particularly important when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

14.3 AUDITS AND INSPECTIONS

The Investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Roche Quality Assurance or its designees, or to health authority inspectors after appropriate notification. The verification of the eCRF data must be by direct inspection of source documents.

14.4 CASE REPORT FORMS OR ELECTRONIC CASE REPORT FORMS

Data for this study will be captured via an EDC system by using an online eCRFs. An audit trail will maintain a record of initial entries and changes made; reasons for change; time and date of entry; and user name of person authorizing entry or change. For each patient enrolled, an eCRF must be completed and electronically signed by the principal Investigator or authorized delegate from the study staff. This also applies to records for those patients who fail to complete the study [even during a pre-enrolment screening period if an eCRF was initiated]. If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

The Investigator should ensure the accuracy, completeness and timeliness of the data reported to the Sponsor in the eCRFs and in all required reports.

15. MONITORING THE STUDY

It is understood that the responsible Monitor will contact and visit the Investigator and will be allowed, on request, to inspect the various records of the trial [eCRFs and other pertinent data] provided that patient confidentiality is maintained in accord with local requirements.

It will be the monitor's responsibility to inspect the eCRFs throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them. The monitor should have access to laboratory test reports and other patient records needed to verify the entries on the eCRF. The Investigator [or deputy] agrees to cooperate

with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

16. CONFIDENTIALITY OF TRIAL DOCUMENTS AND PATIENT RECORDS

The Investigator must assure that patients' anonymity will be maintained and that their identities are protected from unauthorized parties. On eCRFs or other documents submitted to the Sponsor, patients should not be identified by their names, but by an identification code. The Investigator should keep a patient enrolment log showing codes, names and addresses.

17. CLINICAL STUDY REPORT (CSR)

A clinical study report will be written and distributed to Health Authorities as required by applicable regulatory requirements.

18. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

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

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

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

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

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

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

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

19. APPENDICES

19.1 APPENDIX 1 - FORMULAE FOR CRCL AND BODY SURFACE AREA

a. Cockroft and Gault Method for Calculated Creatinine Clearance

$$\text{Calculated creatinine clearance (ml/min)} = \frac{(140 - \text{age [yrs]}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/100 mL)}}$$

Female patients**:** multiply by 0.85

Cockcroft DW, Gault MH. Prediction of Creatinine Clearance from Serum Creatinine. Nephron 1976; 16: 31-41.

b. Body surface area formula

Body Surface Area in $m^2 = 0.007184 \times (\text{Height in cm})^{0.725} \times (\text{Weight in kg})^{0.425}$

19.2 APPENDIX 2 - AGENTS METABOLIZED BY CYP1A2, CYP2C9, AND CYP3A4

Substrate		
CYP1A2[a]	**CYP2C9[a]**	**CYP3A4[b]**
amitriptyline	NSAIDs:	Macrolide antibiotics:
caffeine	diclofenac	clarithromycin
clomipramine	ibuprofen	erythromycin
clozapine	lornoxicam	telithromycin
cyclobenzaprine	meloxicam	
estradiol	S-naproxen	Anti-arrhythmics:
fluvoxamine	Norpiroxicam	quinidine 3OH
haloperidol	suprofen	
imipramine N-DeMe		Benzodiazepines:
mexilletine	Oral Hypoglycemic:	alprazolam
naproxen	tolbutamide	diazepam 3OH
olanzapine	glipizide	midazolam
ondansetron	glyburide	triazolam
phenacetin_	glibenclamide/glyburide	
acetaminophen	glipizide	Immune Modulators:
propranolol	glimepiride	cyclosporine
riluzole	nateglinide	tacrolimus (FK506)
ropivacaine	rosiglitazone	
tacrine		HIV Antivirals:
theophylline	Angiotensin II	indinavir
tizanidine	Blockers:	nelfinavir
verapamil	losartan	ritonavir
(R) warfarin	irbesartan	saquinavir
zileuton		
zolmitriptan	Miscellaneous:	Prokinetic:
	amitriptyline	cisapride
	celecoxib	
	fluoxetine	Antihistamines:
	fluvastatin	astemizole
	phenytoin-4-OH2	chlorpheniramine
	tamoxifen	terfenadine
	torsemide	
	S-warfarin	Calcium Channel Blockers:
		amlodipine
		diltiazem
		felodipine
		lercanidipine
		nifedipine2

Substrate		
CYP1A2[a]	CYP2C9[a]	CYP3A4[b]
		nisoldipine nitrendipine verapamil <u>HMG CoA Reductase Inhibitors:</u> atorvastatin cerivastatin lovastatin simvastatin <u>Steroid 6beta-OH:</u> estradiol hydrocortisone progesterone testosterone <u>Miscellaneous:</u> alfentanyl aprepitant aripiprazole buspirone cafergot caffeine cilostazol cocaine codeine-N demethylation dapsone dexamethasone dextromethorphan docetaxel domperidone eplerenone fentanyl finasteride gleevec haloperidol irinotecan lidocaine methadone nateglinide ondansetron pimozide

Substrate		
CYP1A2[a]	CYP2C9[a]	CYP3A4[b]
		propranolol quetiapine quinine risperidone salmeterol sildenafil sirolimus tamoxifen taxol terfenadine trazodone vincristine zaleplon ziprasidone zolpidem

a. Exposure of these drugs may be increased following vemurafenib treatment.

b. Exposure of these drugs may be decreased following vemurafenib treatment.

19.3 APPENDIX 3 - MEDICATIONS AFFECTING QT INTERVALS

Albuterol	Doxepin	Lithium	Quinidine
Alfuzosin	Droperidol	Mesoridazine	Ranolazine
Amantadine	Ephedrine	Metaproterenol	Risperidone
Amiodarone	Epinephrine	Methadone	Ritodrine
Amitriptyline	Erythromycin	Methylphenidate	Roxithromycin
Amphetamine	Felbamate	Mexiletine	Salmeterol
Arsenic trioxide	Fenfluramine	Midodrine	Sertindole
Astemizole	Flecainide	Moexipril	Sertraline
Atazanavir	Fluconazole	Moxifloxacin	Sibutramine
Atomoxetine	Fluoxetine	Nicardipine	Sibutramine
Azithromycin	Foscarnet	Nilotinib	Solifenacin
Bepridil	Fosphenytoin	Norepinephrine	Sotalol
Chloral hydrate	Galantamine	Nortriptyline	Sparfloxacin
Chloroquine	Gatifloxacin	Octreotide	Sunitinib
Chlorpromazine	Gemifloxacin	Ofloxacin	Tacrolimus
Ciprofloxacin	Granisetron	Ondansetron	Tamoxifen
Cisapride	Halofantrine	Oxytocin	Telithromycin
Citalopram	Haloperidol	Paliperidone	Terbutaline
Clarithromycin	Ibutilide	Paroxetine	Terfenadine
Clomipramine	Imipramine	Pentamidine	Thioridazine
Clozapine	Indapamide	Perflutren lipid microspheres	Tizanidine
Cocaine	Isoproterenol	Phentermine	Tolterodine
Desipramine	Isradipine	Phenylephrine	Trimethoprim-Sulfa
Dexmethylphenidate	Itraconazole	Phenylpropanolamine	Trimipramine
Disopyramide	Ketoconazole	Pimozide	Vardenafil
Dobutamine	Lapatinib	Probucol	Venlafaxine
Dofetilide	Levafloxacin	Procainamide	Voriconazole
Dolasetron	Levalbuterol	Protriptyline	Ziprasidone
Domperidone	Levomethadyl	Pseudoephedrine	
Dopamine	Lisdexamfetamine	Quetiapine	

a. Information available at http://www.azcert.org.

19.4 APPENDIX 4 - NEW RESPONSE EVALUATION CRITERIA IN SOLID TUMORS – VERSION 1.1 – MODIFIED EXCERPT FROM ORIGINAL PUBLICATION WITH SUPPLEMENTARY EXPLANATIONS [1]

1 MEASURABILITY OF TUMOR AT BASELINE

1.1 DEFINITIONS

For prostate cancer, ECD and/or LCH specific guidance, see Appendix 9 and Appendix 10, respectively.

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

1.1.1 MEASURABLE TUMOR LESIONS

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

- 10 mm by CT or MRI scan (CT/MRI scan slice thickness/interval no greater than 5 mm).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be not greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also Section 2.2 below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

1.1.2 NON-MEASURABLE TUMOR LESIONS

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

1.1.3 SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic-blastic lesions, *with identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as

measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are non-measurable.

Cystic lesions:

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

1.2 TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

1.2.1 MEASUREMENT OF LESIONS

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

1.2.2 METHOD OF ASSESSMENT

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during study. Imaging based evaluation should always be the preferred option.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the subject at baseline and during study, should be guided by

the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed, should also be based on the tumor type, anatomic location of the disease and should be optimized to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor markers, Cytology, Histology: The utilization of these techniques for objective tumor evaluation cannot generally be advised but will be dependent on the study design.

2 TUMOR RESPONSE EVALUATION

2.1 ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above in Section 1.1.1).

2.2 BASELINE DOCUMENTATION OF 'TARGET' AND 'NON-TARGET' LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

This means in instances where patients have only one or two organ sites involved a maximum of two (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in that organ will be recorded as non-measurable lesions (even if size is greater than 10mm by CT scan).

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

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As noted in Section 1.1.1, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded

as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

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

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (see also Section 2.3.4).

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2.3 RESPONSE CRITERIA

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

2.3.1 EVALUATION OF TARGET LESIONS

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study including baseline (nadir). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

2.3.2 SPECIAL NOTES ON THE ASSESSMENT OF TARGET LESIONS

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

Target lesions that become *'too small to measure'*: while on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may

not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form:

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

If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and BML (below measurable limit) should be ticked (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm and in that case BML should not be ticked (BML is equivalent to a less than sign <).

Lesions that split or coalesce on treatment: when non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.3.3 EVALUATION OF NON-TARGET LESIONS

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions (and, if applicable, normalization of tumor marker level). All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression (see Section 2.3.4) of existing non-target lesions. The appearance of one or more new lesions is also considered progression.

2.3.4 SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET DISEASE

When the patient also has measurable disease: **in this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.** A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for **unequivocal progression** status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease: this circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as **'sufficient to require a change in therapy'**. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be **substantial**.

2.3.5 NEW LESIONS

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

2.4 EVALUATION OF RESPONSE

2.4.1 TIME POINT RESPONSE (OVERALL RESPONSE)

It is assumed that at each protocol specified time point, a response assessment occurs. Table A provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table B is to be used.

Table A Time Point Response – Target (w/wo non- target) Lesions

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

Table B Time Point Response – Non-Target Lesions only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.

a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

2.4.2 MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

For example, if a patient had a baseline sum of 50 mm with three measured lesions and during study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done, or could not be assessed because of poor image quality or obstructed view, the Response for Target Lesions should be "Unable to Assess" since the patient is not evaluable. Similarly, if one or more

non-target lesions are indicated as 'not assessed', the response for non-target lesions should be "Unable to Assess" (except where there is clear progression). Overall response would be "Unable to Assess" if either the target response or the non-target response is "Unable to Assess" (except where this is clear evidence of progression) as this equates with the case being not evaluable at that time point.

Table C Best Overall Response when Confirmation is required

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

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

2.4.3 SPECIAL NOTES ON RESPONSE ASSESSMENT

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

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

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

In studies where patients with advanced disease are eligible (i.e. primary disease still or partially present), the primary tumor should be also captured under target or non-target lesions as appropriate. This is to avoid wrong assessments of complete overall response by statistical programs while the primary is still present but not evaluable.

19.5 APPENDIX 5 - INTERNATIONAL MYELOMA WORKING GROUP (IMWG) UNIFORM RESPONSE AND RELAPSE CRITERIA FOR MULTIPLE MYELOMA

	IMWG criteria[2]
Response	
sCR[2]	CR as defined below plus: ○ Normal FLC ratio and ○ Absence of clonal cells in bone marrow[3] by immunohistochemistry or immunofluorescence[4]
CR[2]	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and ≤ 5% plasma cells in bone marrow[3]
VGPR[2,5]	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥ 90% or reduction in serum M-protein plus urine M-protein level < 100 mg per 24 hour
PR[2,5]	≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hours If the serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30% In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
MR	NA
No change / SD	Not meeting criteria for CR, VGPR, PR or progressive disease
Plateau	NA
Relapse	
Progressive disease[6]	Increase of ≥ 25% from lowest response value in any one or more of the following: ○ Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dL)[7] ○ Urine M-component and/or (the absolute increase must be ≥ 200 mg per 24 hours) ○ Only in patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL ○ Bone marrow plasma cell percentage. The absolute percentage must be ≥ 10%[8] ○ Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas

Response	IMWG criteria[2]
	○ Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder
Relapse[6]	Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features).[7] It is not used in calculation of time to progression or progression-free survival but is listed here as something that can be reported optionally or for use in clinical practice. 1. Development of new soft tissue plasmacytomas or bone lesions 2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion 3. Hypercalcemia (> 11.5 mg/dL) [2.65 mmol/L] 4. Decrease in hemoglobin of ≥ 2 g/dL [1.25 mmol/L] 5. Rise in serum creatinine by 2 mg/dL or more [177 µmol/L or more]
Relapse from CR[6] (to be used only if the end point studied is DFS)[9]	Any one or more of the following: ○ Reappearance of serum or urine M-protein by immunofixation or electrophoresis ○ Development of ≥ 5% plasma cells in the bone marrow[8] ○ Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia)

CR, complete response; DFS, disease-free survival; FLC, free light chain; PR, partial response; SD, stable disease; sCR, stringent complete response; VGPR, very good partial response.

1. Adapted from Durie BGM, et al. Leukemia 2006;20:1467-1473; and Kyle RA, Rajkumar SV. Leukemia 2008;23:3-9.

2. All response categories require two consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.

3. Confirmation with repeat bone marrow biopsy not needed.

4. Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is kappa/lambda of > 4:1 or < 1:2.

5. A clarification to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients is defined as a normal FLC ratio of 0.26–1.65 in addition to CR criteria listed above. VGPR in such patients is defined as a > 90% decrease in the difference between involved and uninvolved free light chain (FLC) levels.

6. All relapse categories require two consecutive assessments made at any time before classification as relapse or disease progression and/or the institution of any new therapy. In the IMWG criteria, CR patients must also meet the criteria for progressive disease shown here to be classified as progressive disease for the purposes of calculating time to progression and progression-free survival. The definitions of relapse, clinical relapse and relapse from CR are not to be used in calculation of time to progression or progression-free survival.

7. For progressive disease, serum M-component increases of ≥ 1 gm/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL.

8. Relapse from CR has the 5% cut-off versus 10% for other categories of relapse.

9. For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease.

19.6 APPENDIX 6 - ECOG PERFORMANCE STATUS SCALE

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

19.7 APPENDIX 7 - NATIONAL CANCER INSTITUTE-COMMON TOXICITY CRITERIA FOR ADVERSE EVENTS, V4.0

The Common Terminology Criteria for Adverse Events v4.0, updated June 14, 2010, is available at: http://evs.nci.nih.gov/ftp1/CTCAE/About.html

19.8 APPENDIX 8 - ICH GUIDELINES FOR CLINICAL SAFETY DATA MANAGEMENT, DEFINITIONS, AND STANDARDS FOR EXPEDITED REPORTING, TOPIC E2

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

- is fatal (i.e., the adverse event actually causes or leads to death); (results in **death**; NOTE: death is an outcome, not an event)
- is Life-Threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

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

Medical and scientific judgment should be exercised in deciding whether expedited reporting to the Sponsor is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definitions above. These situations should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

An unexpected AE is one, the nature or severity of which is not consistent with the applicable product information.

Causality is initially assessed by the Investigator. For Serious Adverse Events, possible causes of the event **are** indicated by selecting one or more options. (Check all that apply)

- Pre-existing/Underlying disease - specify
- Study treatment – specify the drug(s) related to the event
- Other treatment (concomitant or previous) – specify
- Protocol-related procedure
- Other (e.g. accident, new or intercurrent illness) - specify

The term severe is a measure of intensity, thus a severe AE is not necessarily serious. For example, nausea of several hours' duration may be rated as severe, but may not be clinically serious.

A serious adverse event occurring during the study or which comes to the attention of the Investigator within 15 days after stopping the treatment or during the protocol-defined follow-up period, if this is longer, whether considered treatment-related or not, must be reported. In addition,

a serious adverse event that occurs after this time, if considered related to test “drug”, should be reported.

Such preliminary reports will be followed by detailed descriptions later which will include copies of hospital case reports, autopsy reports and other documents when requested and applicable.

For serious adverse events, the following must be assessed and recorded on the AEs page of the eCRF: intensity, relationship to test substance, action taken, and outcome to date.

The Investigator must notify the Ethics Review Committee/Institutional Review Board of a serious adverse event in writing as soon as is practical and in accordance with international and local laws and regulations.

ROCHE LOCAL COUNTRY CONTACT for SAEs: Local Monitor

The local Monitor will be the initial point of contact for all study related issues. The local monitor is responsible to provide administrative details and contact information of the Roche study team as required.

ROCHE HEADQUARTERS CONTACT for SAEs and other medical emergencies: Clinical Operations

The local Monitor will be the initial point of contact for all study related issues. The local monitor is responsible to provide administrative details and contact information of the Roche study team as required.

c. 24-HOUR MEDICAL COVERAGE

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Monitor, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor contact information, will be distributed to all Investigators.

19.9 APPENDIX 9 - ADDITIONAL GUIDANCE FOR PATIENTS WITH PROSTATE CANCER INCLUDED IN COHORT 7 (OTHER TUMOURS)

Cohort 7 (Other solid tumours) may include prostate cancer patients. For these patients, the following prostate specific eligibility criteria will be used. These will only apply to patients with prostate cancer and are in addition to the main study criteria for solid tumours.

Additional inclusion criteria for patients with prostate cancer:

1. Patients with measurable and non-measurable disease according to RECIST v1.1, for soft tissue lesions and/or according to the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) for bone lesions are eligible
2. Evidence of progressive metastatic disease since the most recent change of therapy as assessed by the investigator with the following:
    - Increasing serum prostate specific antigen (PSA) levels, the most recent value ≥ 2 ng/mL. (Increasing levels must be confirmed by 3 consecutive PSA measurements, preferably with 14 days, but with at least 7 days between each measurement.)
    - Progression of soft tissue metastasis (computed tomography [CT] scan or magnetic resonance imaging [MRI] according to RECIST v1.1)
    - Progression of bone disease (at least 1 new bone lesion as measured by bone scan)

Additional exclusion criteria for patients with prostate cancer:

1. Prostate cancer pain that warrants the initiation of radio- or chemotherapy.
2. Concurrent administration of any anti-cancer therapies (e.g., radiotherapy, chemotherapy, other targeted therapy, vaccines, antiandrogens, experimental drug, etc.) other than those administered in this study. In patients with prostate cancer, ongoing treatment with luteinizing hormone-releasing hormone (LHRH) agonists or antagonists, denosumab (Prolia) or bisphosphonate (e.g., zoledronic acid) is allowed. At the discretion of the investigator, castrate resistant prostate cancer (CRPC) patients receiving gonadotropin-releasing hormone agonist therapy or bisphosphonate (e.g., zoledronic acid) may have that treatment continued while they are enrolled in this study.

Duration of treatment:

Vemurafenib will be given until the development of progressive disease (as per Investigator assessment), unacceptable toxicity, withdrawal of consent, protocol violation endangering the patient's safety, death, reasons deemed critical by the treating physician, or study termination by the Sponsor, however a minimum of 16 weeks treatment will be given to allow sufficient time to assess any response in prostate cancer as per the PCWG2 guidelines.

Additional assessments for patients with prostate cancer:

- Tumour assessment will be performed at 8-weekly intervals according to the Response Evaluation Criteria In Solid Tumours (RECIST v1.1), for soft tissue lesions and/or the PCWG2 for bone lesions[3]
- PSA levels will be measured every 8 weeks and monitored according to the PCWG2 guidance for PSA[3].

PCWG2 guidance for bone lesions[3]

Assessment of bone lesions will be based on radionuclide scans. The outcome of bone scans should be recorded as either new lesions or no new lesions. If there are new lesions present on cycle 3, Day 1 (the first scan) then a confirmatory scan should be performed 8 weeks later. If new lesions are confirmed at Cycle 5 Day 1 reassessment then this is defined as disease progression according to PCWG2. For subsequent scans from Cycle 5 Day 1 onwards, any new bone lesions present are defined as disease progression according to PCWG2.

PCWG2 guidance for PSA[3]

A PSA progression is defined as the time from start of therapy to first PSA increase that is ≥ 25% and ≥ 2 ng/mL above the nadir, and which is confirmed by a second PSA value 4 weeks later (i.e., a confirmed rising trend)

APPENDICES References

1. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
2. Bogaerts J, Ford R, Sargent D, et al, Individual patient data analysis to assess modifications to the RECIST criteria Eur J Cancer 2009;45:
3. Scher et al, Design and End Points of Clinical Trials for Patients With Progressive Prostate Cancer and Castrate Levels of Testosterone: Recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol. 2008 Mar 1;26(7):1148-59

19.10 APPENDIX 10 - ADDITIONAL GUIDANCE FOR PATIENTS WITH ECD AND/OR LCH INCLUDED IN COHORT 7 (OTHER TUMOURS)

Cohort 7 (Other solid tumours) may include patients with ECD and/or LCH. For these patients, the following ECD/LCH specific eligibility criteria will be used. These will only apply to patients with ECD and/or LCH and are in addition to the main study criteria for solid tumours.

Additional inclusion criteria for patients with ECD and/or LCH:

1. Patients with non-measurable disease according to RECIST v1.1 are eligible if in the opinion of the investigator the tumour response can be reliably morphologically evaluated by one or more of the below tests (depending on the location and extent of disease[1,2]):
    - Brain MRI
    - Cardiac MRI (or cardiac echography for patients who cannot undergo MRI and have cardiac involvement)
    - Bone scan
    - ^{18}F-FDG PET
    - CT chest/abdomen/pelvis
2. Patients with concurrent ECD and LCH[3] are eligible
3. Patients with ECD and/or LCH and active or untreated CNS involvement[4] are eligible

Duration of treatment:

Vemurafenib will be given until the development of progressive disease (assessed according to RECIST v1.1 for patients with baseline measurable disease, and for all other patients as per Investigator assessment), unacceptable toxicity, withdrawal of consent, protocol violation endangering the patient's safety, death, reasons deemed critical by the treating physician, or study termination by the Sponsor. Because the natural history of the disease in patients with ECD/LCH is not known, changes in bone scans prior to cycle 5 (approximately 16 weeks) of treatment should not be used as sole evidence of progression.

Patients with ECD/LCH have the option of discontinuing vemurafenib treatment after one year, if the investigator considers it to be in the best interest of the patient. Patients can then resume vemurafenib treatment if they become symptomatic or if their scans show worsening of their disease.

Additional assessments for patients with ECD and/or LCH:

- Baseline tumour assessments must include CT/MRI of the chest, abdomen and pelvis [C/A/P]) and any additional assessment as clinically relevant as described above to define baseline extent of disease (brain MRI, cardiac MRI/echo, bone scan, ^{18}F-FDG PET).
- For patients with baseline measurable disease according to RECIST v1.1, the following tumour assessments will consist of the same method(s) used at baseline to determine measurable disease (CT/MRI of [C/A/P], brain MRI, cardiac MRI), and will be performed at 8-weekly intervals according to RECIST v1.1 by the investigator.
- For all other patients the following tumour assessments will consist of the same method/s used at baseline that have defined the area involved by the disease (brain MRI, cardiac MRI/echo,

bone scan, ^{18}F-FDG PET, CT chest/abdomen/pelvis) as described above, and will be performed at 8-weekly intervals and response will be assessed by the investigator.

- For the assessments of bone lesions, the PCWG2 guidance for bone lesions[5], and for the assessment of ^{18}F-FDG PET, the PET Response Criteria (PRC) will be used.
- C-reactive protein (CRP), considered a tumour marker in this disease, should be closely monitored.[2] CRP should be measured on Day 1, Day 29, Day 57 and every 8 weeks thereafter until study drug discontinuation.

PCWG2 guidance for bone lesions[5]

Assessment of bone lesions will be based on radionuclide scans. The outcome of bone scans should be recorded as either new lesions or no new lesions. If there are new lesions present on cycle 3, Day 1 (the first scan) then a confirmatory scan should be performed 8 weeks later. If new lesions are confirmed at Cycle 5 Day 1 reassessment then this is defined as disease progression according to PCWG2. For subsequent scans from Cycle 5 Day 1 onwards, any new bone lesions present are defined as disease progression according to PCWG2.

Positron Emission Response Criteria in Solid Tumors (PERCIST) 1.0 Criteria[6] for the assessment of Tumour Response to Treatment

Background

- ^{18}Fluorodeoxyglucose (^{18}F-FDG) PET is especially valuable in assessing activity of anticancer therapies that stabilize disease rather than shrink tumours (cytostatic vs. cytocidal), and has been demonstrated to be important in assessing response to treatment in some specific tumors (e.g., gastrointestinal solid tumours) (Van den Abbeele et al. 2008)
- Reduced metabolic activity has been shown to indicate response to treatment and/or improved survival in patients with cancers of the breast, oesophagus, lung, osteosarcoma and others (Dose Schwarz et al. 2005; Smith et al. 2000; Brucher et al. 2001; Swisher et al. 2004; Wieder et al. 2004; MacManus et al. 2003; Hellwig et al. 2004; Hawkins et al. 2009; Costelloe et al. 2009; Costelloe et al. 2010; Weber et al. 2006)
- Some tumours may be more suitable for assessment of response to treatment by metabolic activity than by anatomic measurements, especially those with bone metastases or with RECIST non-measurable disease (Stroobants et al. 2003; Gayed et al. 2004)
- FDG PET can provide more rapid response data than anatomical-based measurements (Wahl et al. 2009)
- Principles of assessing tumour response by PERCIST are similar to RECIST in many aspects, except response is evaluated by metabolic rather than anatomical criteria:
  - single target lesion assessed as primary response classifier between consecutive scans
  - up to 5 target lesions for each scan (maximum of 2 per organ) provide secondary response classifier data
  - metabolic response criteria defined for complete response, partial response, stable disease and progressive disease

PET Response Criteria

As the PERCIST criteria have yet to be validated as a response classification for solid tumours, a simplified PET Response Criteria has been proposed for the current study.

A primary target lesion and up to 4 other target lesions will be identified at baseline. These target lesions should be followed consistently at each tumour assessment. Lesions should be identified as per the RECIST criteria, as described below:

- maximum of 2 target lesions per organ, and up to 5 target lesions in total, representative of all involved organs
- lesions selected on basis of their avidity and reproducibility across assessments

As a guide, to be considered “avid” and evaluable for these criteria, the SUVmax-BW (SUVmax normalized to actual body weight) must be > SUVmax background liver normalized to actual body weight, i.e., SUVmax-BW(liver).

The following data should be captured for each lesion.

- PET scan date
- lesion location (general anatomical location from “drop-down” menu)
- longest diameter if applicable (mm)
- Standardized Uptake Value maximum normalized to body weight (SUVmax-BW) defined as the maximum value of SUV observed (xx.x units) within each target lesion’s region of interest (ROI) normalized to actual body weight

Note: ROI is defined as maximum voxel within a 1.2 cm diameter (1 cm^3) centred around the hottest/most avid part of the tumour.

Additionally:

- Actual body weight (BW)
- Standardized Uptake Value maximum normalized to body weight for the Liver (SUVmax-BW(liver)) defined as the maximum value of SUV observed in the background liver normalized to actual body weight.

Response should be determined as described in the table below:

PET Response Criteria Based on SUVmax-BW

Response Category	Criteria based on SUV of the most avid target lesion	Criteria based on SUV from up to 5 target lesions
Complete Metabolic Response	Normalization of the most avid target lesion’s SUVmax-BW to SUVmax-BW(liver)*	Normalization of all lesions’ (target and non-target) SUVmax-BW to SUVmax-BW(liver)
Partial Metabolic Response	≥ 50% decrease from baseline in SUVmax-BW in most avid target lesion relative to SUVmax-BW(liver)*	≥ 50% decrease from baseline in sum of SUVmax-BW of all target lesions relative to SUVmax-BW(liver)
Progressive Metabolic Disease	≥ 50% increase from baseline in SUVmax-BW in most avid target lesion relative to SUVmax-BW(liver)*	≥ 50% increase from baseline in sum of SUVmax-BW of all target lesions relative to SUVmax-BW(liver)
	New (evaluable) lesions	New (evaluable) lesions
Stable Metabolic Disease	Does not meet other criteria	Does not meet other criteria

*Primary outcome determination is measured on the single most avid lesion at each time point, not necessarily the same lesion. Secondary outcome determination is based on the activity of the (up to) 5 selected target lesions at baseline.

References:

Brücher BL, Weber W, Bauer M, Fink U, Avril N, Stein HJ, Werner M, Zimmerman F, Siewert JR, Schwaiger M. Neoadjuvant therapy of esophageal squamous cell carcinoma: response evaluation by positron emission tomography. Ann Surg. 2001 Mar;233(3):300-9.

Costelloe CM, Macapinlac HA, Madewell JE, Fitzgerald NE, Mawlawi OR, Rohren EM, Raymond AK, Lewis VO, Anderson PM, Bassett RL Jr, Harrell RK, Marom EM. 18F-FDG PET/CT as an indicator of progression-free and overall survival in osteosarcoma. J Nucl Med. 2009 Mar;50(3):340-7. doi: 10.2967/jnumed.108.058461.

Costelloe CM, Raymond AK, Fitzgerald NE, Mawlawi OR, Nunez RF, Madewell JE, Harrell RK, Bassett RL, Marom EM. Tumor necrosis in osteosarcoma: inclusion of the point of greatest metabolic activity from F-18 FDG PET/CT in the histopathologic analysis. Skeletal Radiol. 2010 Feb;39(2):131-40. doi: 10.1007/s00256-009-0785-8. Epub 2009 Sep 17.

Dose Schwarz J, Bader M, Jenicke L, Hemminger G, Jänicke F, Avril N. Early prediction of response to chemotherapy in metastatic breast cancer using sequential 18F-FDG PET. J Nucl Med. 2005 Jul;46(7):1144-50.

Gayed I, Vu T, Iyer R, Johnson M, Macapinlac H, Swanston N, Podoloff D. The role of 18F-FDG PET in staging and early prediction of response to therapy of recurrent gastrointestinal stromal tumors. J Nucl Med. 2004 Jan;45(1):17-21.

Hawkins DS, Conrad EU 3rd, Butrynski JE, Schuetze SM, Eary JF. [F-18]-fluorodeoxy-D-glucose-positron emission tomography response is associated with outcome for extremity osteosarcoma in children and young adults. Cancer. 2009 Aug 1;115(15):3519-25. doi: 10.1002/cncr.24421.

Hellwig D, Graeter TP, Ukena D, Georg T, Kirsch CM, Schäfers HJ. Value of F-18-fluorodeoxyglucose positron emission tomography after induction therapy of locally advanced bronchogenic carcinoma. J Thorac Cardiovasc Surg. 2004 Dec;128(6):892-9.

MacManus MP, Hicks RJ, Matthews JP, McKenzie A, Rischin D, Salminen EK, Ball DL. Positron emission tomography is superior to computed tomography scanning for response-assessment after radical radiotherapy or chemoradiotherapy in patients with non-small-cell lung cancer. J Clin Oncol. 2003 Apr 1;21(7):1285-92.

Smith IC, Welch AE, Hutcheon AW, Miller ID, Payne S, Chilcott F, Waikar S, Whitaker T, Ah-See AK, Eremin O, Heys SD, Gilbert FJ, Sharp PF. Positron emission tomography using [(18)F]-fluorodeoxy-D-glucose to predict the pathologic response of breast cancer to primary chemotherapy. J Clin Oncol. 2000 Apr;18(8):1676-88.

Stroobants S, Goeminne J, Seegers M, Dimitrijevic S, Dupont P, Nuyts J, Martens M, van den Borne B, Cole P, Sciot R, Dumez H, Silberman S, Mortelmans L, van Oosterom A. 18FDG-Positron emission tomography for the early prediction of response in advanced soft tissue sarcoma treated with imatinib mesylate (Glivec). Eur J Cancer. 2003 Sep;39(14):2012-20.

Swisher SG, Erasmus J, Maish M, Correa AM, Macapinlac H, Ajani JA, Cox JD, Komaki RR, Hong D, Lee HK, Putnam JB Jr, Rice DC, Smythe WR, Thai L, Vaporciyan AA, Walsh GL, Wu TT, Roth JA. 2-Fluoro-2-deoxy-D-glucose positron emission tomography imaging is predictive of pathologic response and survival after preoperative chemoradiation in patients with esophageal carcinoma. Cancer. 2004 Oct 15;101(8):1776-85.

Van den Abbeele AD. The lessons of GIST--PET and PET/CT: a new paradigm for imaging. Oncologist. 2008;13 Suppl 2:8-13. doi: 10.1634/theoncologist.13-S2-8.

Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: Evolving Considerations for PET response criteria in solid tumors. J Nucl Med. 2009;50 Suppl 1:122S-50S.

Weber WA, Wieder H. Monitoring chemotherapy and radiotherapy of solid tumors. Eur J Nucl Med Mol Imaging. 2006 Jul;33 Suppl 1:27-37.

Wieder HA, Brücher BL, Zimmermann F, Becker K, Lordick F, Beer A, Schwaiger M, Fink U, Siewert JR, Stein HJ, Weber WA. Time course of tumor metabolic activity during chemoradiotherapy of esophageal squamous cell carcinoma and response to treatment. J Clin Oncol. 2004 Mar 1;22(5):900-8.

AN OPEN-LABEL, PHASE II STUDY OF VEMURAFENIB IN PATIENTS WITH BRAF V600 MUTATION-POSITIVE CANCERS

Protocol Number: MO28072

Amendment History Document for protocol MO28072, Amendment 1

Updated from protocol MO28072, version 1.0, dated 30 November 2011

Date amendment 1 issued: 09 August 2012

Protocol Amendment Details

Note: Changes in this section are described in the order they first appear in the body of the protocol.

The protocol synopsis and Informed Consent Form have also been updated to reflect these changes.

1. **Revision:** the protocol version has been modified from 1 to 2, and the protocol date has been updated.

   Rationale: the original protocol has been amended.

2. **Revision:** the Glossary has been modified.

   Rationale: updated to reflect abbreviations added as part of the protocol amendment

3. **Revision:** Cohort 3 has been split into two – the pre-existing Cohort 3a - vemurafenib only and a new Cohort 3b - combination therapy with vemurafenib and cetuximab. The background section of the protocol has also been updated to include rationale for vemurafenib and cetuximab treatment in this patient population.

   Rationale: A recent Nature publication (Prahallad et al, Nature 2012;483:100-103) investigated the mechanisms of the limited therapeutic effect observed with vemurafenib in BRAF V600 positive CRC patients. BRAF inhibition causes a feedback activation of the epidermal growth factor receptor (EGFR) which is responsible for the continued proliferation in the presence of BRAF inhibition. Preclinical studies also demonstrated that when vemurafenib is combined with an EGFR inhibitor (cetuximab or gefitinib or erlotinib) in mutant CRC cell lines, there is a strong synergic effect of the combination in both the in vitro and in vivo settings. These data provide a strong rationale for a clinical trial investigating the combination of vemurafenib and cetuximab in BRAF-mutated colorectal cancer patients, who have a poor clinical outcome and for whom there are no effective treatment options after failure of standard chemotherapy.
   In light of this strong scientific evidence and after discussion with the study Steering Committee, the decision was made to investigate the combination of vemurafenib and cetuximab in combination in CRC. As a consequence, Cohort 3 CRC has been amended to include two new sub cohorts

investigating vemurafenib alone (Cohort 3a) and investigating the combination of vemurafenib and cetuximab (Cohort 3b).

4. **Revision:** some sections of the Background have been updated.

   Rationale: background sections have been updated based on newly available information from vemurafenib trials BRIM2 and BRIM3 and safety data in melanoma.

5. **Revision:** the latest Investigator's Brochure (IB) is now version 8 with addendum 1.

   Rationale: an updated IB is available.

6. **Revision:** although the study is primarily exploring vemurafenib monotherapy, the newly added Cohort 3b consisting of BRAF V600-positive metastatic CRC patients will receive vemurafenib in combination with cetuximab. Guidance regarding storage, accountability, destruction, administration, pre-medications and dosing have been added for cetuximab.

   Rationale: With the addition of cetuximab in Cohort 3b as a new IMP, there are additional details specific to the storage, accountability, destruction, administration and pre-medications for cetuximab added. These are based on the cetuximab Summary of Product Characteristics SPC.

7. **Revision:** new secondary outcomes have been added. These include a) to determine the maximum tolerated dose (MTD) and recommended dose for stage I/II of the combination of vemurafenib and cetuximab in BRAF V600-positive metastatic CRC patients (Cohort 3b only) and b) to investigate the safety, tolerability, efficacy of the combination of vemurafenib and cetuximab in BRAF V600-positive metastatic CRC patients (Cohort 3b only). A new Schedule of Assessments has been created for this cohort.

   Rationale: have been added as a result of the newly added Cohort 3b. As these outcomes include determination of the MTD and recommended dose, sections addressing the dosing, dose levels and dose escalation of the combination of cetuximab and vemurafenib in Cohort 3b have been added. The dose levels to be investigated in Part 1 of Cohort 3b of the combination of vemurafenib and cetuximab have been determined through guidance from the study Steering committee and have been adapted from the dosing and dose

levels recommended in the cetuximab SPC for CRC. The starting dose level 1 represents 75% of the standard dose of vemurafenib and cetuximab respectively.

8. **Revision:** additional guidance has been added for patients with prostate cancer, including eligibility criteria, duration of treatment, additional efficacy assessments and reporting of results.

   Rationale: As recommended by the Prostate Cancer Clinical Trials Working Group (PCWG2) guidance, patients with prostate cancer should have specific consideration to eligibility criteria, outcome measures and definitions of response. As a consequence Appendix 9 has been added to include specific guidance for prostate cancer patients included in Cohort 7 (Other solid tumours). This additional appendix is adapted from the guidance that is recommended for phase II clinical trials investigating prostate cancer (Scher et al, JCO 2008;26(7):1148-59). For prostate cancer patients there are eligibility criteria, additional efficacy assessments and additional guidance on evaluation of response (based on PCWG2) in addition to those specified in the main study protocol (RECIST v1.1).

9. **Revision:** the term “vemurafenib” has been replaced with “study medication” where appropriate.

   Rationale: study treatment is no longer only vemurafenib monotherapy, as Cohort 3b will receive vemurafenib in combination with cetuximab.

10. **Revision:** the prostate cancer cohort has been removed as an individual cohort and prostate cancer patients will be included in the cohort including other solid tumours (new Cohort 7). Therefore the number of cohorts has been reduced from 8 to 7. Original Cohort 7 has been changed to Cohort 6 and no longer includes prostate cancer. Original Cohort 8 has been changed to Cohort 7. The background section specific to prostate cancer has been removed.

    Rationale: The frequency of BRAF mutations in prostate cancer is very low, and new information has become available from individual centers participating in the study (personal communication), indicating that the frequency of BRAF mutation in prostate cancer may be even lower than reported in the literature. Therefore recruitment into the prostate cancer cohort would be a significant challenge and the dedicated prostate cancer cohort

(Cohort 6) has been removed. Any eligible patients with prostate cancer will be enrolled into the other solid tumours cohort. As a consequence, Cohort 6 and Cohort 7 have been realigned to include multiple myeloma patients (new Cohort 6) and patients with other solid tumors (new Cohort 7) respectively. Therefore original Cohort 8 will no longer exist.

11. **Revision:** sample size increased from 152 patients to up to 170 patients. For Cohort 3b, the expected maximum number of patients has been increased from 19 to 37. The number of patients in a cohort can be less than 13 if closed early. Table 12 has been updated to reflect the revised sample size for each cohort, if applicable.

    Rationale: as this study will investigate the combination of vemurafenib and cetuximab for the first time, a dose finding phase will be included in Cohort 3b to determine the MTD and the recommended dose for stage I/II. This dose escalation phase (Part 1 of Cohort 3b will be a classic 3+3 design investigating up to 3 dose levels of the combination of vemurafenib and cetuximab. Therefore up to 18 additional patients maybe included into Cohort 3b. These patients also impact the overall study sample size.

12. **Revision:** all patients are required to undergo an examination of the anus for monitoring of SCCs. In addition, female patients must also have a pelvic examination for monitoring of SCCs, including an evaluation of the uterine cervix, performed by a gynaecologist or other qualified practitioner.

    Rationale: the monitoring for non-cutaneous SCCs has been amended to align with the monitoring guidance in section 4.4 of the Zelboraf Summary of Product Characteristics.

13. **Revision:** For patients included in Cohort 3b, there will be weekly visits throughout the treatment phase. These visits include the administration of cetuximab and assessments including physical examination, vital signs, ECOG PS, hematology and biochemistry. A separate Schedule of Assessments has been added for patients in Cohort 3b to capture these additional visits. A physical examination will be done on all remaining (non-Cohort 3b) patients every 28 days, instead of every 8 weeks.

    Rationale: Cetuximab is administered weekly and therefore there are weekly visits for Cohort 3b. Additional assessments have been included to monitor key parameters at each visit. These have been recommended by the study

Steering Committee and are consistent with the visit schedule for other cetuximab CRC protocols.

14. **Revision:** assessments of dose-limiting toxicities have been added on days 8, 15, 22 and 29 during the dose escalation phase of Cohort 3b (Part 1).

    Rationale: dose-limiting toxicity assessments are required in Part1 of Cohort 3b to determine the MTD and the recommended combination dose of cetuximab and vemurafenib for stage I/II.

15. **Revision:** a head and neck examination will also be performed 6 months following study drug discontinuation or until initiation of another anti-neoplastic therapy.

    Rationale: the head and neck assessments for monitoring of cutaneous SCCs has been amended to align with the monitoring guidance in section 4.4 of the Zelboraf Summary of Product Characteristics.

16. **Revision:** a dermatology evaluation by a dermatologist must be performed 6 months following study drug discontinuation or until initiation of another anti-neoplastic therapy.

    Rationale: the dermatology assessments for monitoring of cutaneous SCCs has been amended to align with the monitoring guidance in section 4.4 of the Zelboraf Summary of Product Characteristics.

17. **Clarification:** the study safety follow-up visit done 28 days after the discontinuation of vemurafenib has an added time window of ± 5 days.

    Rationale: a time window has been added to allow flexibility which is more realistic to clinical routine.

18. **Revision:** the amount of vemurafenib given to a study patient at various study visits has been revised.

    Rationale: the vemurafenib drug dispensing dates have been aligned to Day 1 and day 28 thereafter throughout the protocol, correcting an error.

19. **Revision:** guidance regarding cetuximab-specific safety has been added.

Rationale: cetuximab-specific safety guidance has been added as Cohort 3b will now also receive cetuximab in combination with vemurafenib. This is based on the cetuximab SPC.

20. **Revision:** the collection of adverse events and serious adverse events experienced by the patient after signing consent but before receiving study treatment has been clarified.

    Rationale: only serious adverse events will be collected if related to protocol-mandated interventions.

21. **Revision:** after the last dose of study medication, all new adverse events considered to be related to study drug are to be reported indefinitely.

    Rationale: clarification of the duration of the reporting of all new AEs that are related to study drug.

22. **Revision:** progression-free survival, overall survival and time to progression are now defined based on first day of study treatment, instead of enrolment into the study. Time to response is now defined based on the first day of study treatment, instead of the date of randomization.

    Rationale: to provide clarity and consistency of the efficacy outcome definitions, the start dates are all aligned to the first day of study treatment.

23. **Revision:** for Cohort 3b there will be a summary of dose-limiting toxicities by dose level.

    Rationale: to summarize toxicities associated with each dose level during the dose escalation period.

24. **Revision:** the rule for closing cohorts based on minimal responses has been revised. If a clear clinical benefit has been observed for patients in the cohort, e.g. majority of patients recorded SD at Week 8 and no CR or PR is recorded, then enrolment into Stage II will be allowed for this cohort after discussion with the Sponsor and study Steering Committee.

    Rationale: to provide more specific guidance on when a cohort should progress to Stage II if the majority of patients record SD at week 8.

25. **Clarification:** the hypotheses for all cohorts at the end of Stage II for a low desirable response now includes the alternative hypothesis (H_1) being accepted at Stage I.

    Rationale: clarification of the original intent

26. **Revision:** the statistical section has been revised to accommodate the addition of the establishment of the recommended dose for Cohort 3b.

    Rationale: the new Cohort 3b has two parts, Part I (the dose escalation phase) and Part II (the Stage I/II phase). This section has been amended to describe the analysis of the newly added secondary endpoint to find the MTD in Part I (the dose escalation phase) and how the recommended dose arm will be the investigated in Part II based on the Stage I/II design for Cohort 3b.

27. **Revision:** individual cohorts may be temporarily stop enrolment to allow for stage I analysis before progressing to stage II.

    Rationale: to allow sufficient time for the stage I analysis if the first 7 patients are enrolled in a specific cohort, the option to temporarily hold screening/enrolment into that cohort has been added. This ensures that additional patients will only be enrolled if the pre-specified efficacy is achieved at stage I.

28. **Revision:** Additional guidance has been added on how the decision to enrol patients in Cohort 3a and/or 3b will be made.

    Rationale: Cohort 3a and Cohort 3b will include the same patient population. Therefore a decision will be made whether both cohorts are open simultaneously or if Cohort 3a is closed and Cohort 3b is only open for CRC patients. This decision will be based on the efficacy and safety data available at stage I of the vemurafenib monotherapy CRC cohort. The decisions will be made by the sponsor in consultation with the study Steering Committee.

29. **Revision:** The definitions of an efficacious study treatment have been revised.

    Rationale: Both safety and efficacy parameters will be taken into consideration for a cohort to be considered efficacious at Stage II. This is to

ensure a more robust decision when deciding to enrol further patients within a specific cohort.

30. **Revision:** only descriptive statistics will be applied to Cohort 7 (other solid tumours). Different safety and ITT populations may be defined for the different tumour types depending on the number of patients enrolled.

    Rationale: due to the small sample size, and assortment of different tumour types within this cohort, only descriptive analysis will be used.

31. **Clarification:** although not formal in nature, interim analyses will include the efficacy analysis of response rate at Stage 1 and the dose escalation for Part I of Cohort 3b.

    Rationale: clarification of the original intent as well as taking into account the new addition of a 3x3 design in Cohort 3b.

32. **Revision:** references have been slightly modified.

    Rationale: updated to conform to revisions in body of protocol.

33. **Revision:** body surface area calculations have been added to Appendix 1.

    Rationale: cetuximab is administered based on body surface area (mg/m^2).

34. **Clarification:** tables in Appendix 4 have been re-numbered

    Rationale: to remove duplication with other numerically labelled tables within the body of the protocol.

PROTOCOL

TITLE:	**AN OPEN-LABEL, PHASE II STUDY OF VEMURAFENIB IN PATIENTS WITH BRAF V600 MUTATION-POSITIVE CANCERS**
PROTOCOL NUMBER:	MO28072
VERSION NUMBER:	3
EUDRACT NUMBER:	2011-004426-10
IND NUMBER:	73,620
TEST PRODUCT:	Vemurafenib (RO5185426)
MEDICAL MONITOR:	Dr. Luisa Veronese
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 30 November 2011 Version 2: 09 August 2012
DATE AMENDED:	See the latest signature date below

PROTOCOL AMENDMENT APPROVAL

Name:	**Signature:**	**Date:**
Luisa Veronese Senior International Medical Leader		12 June 2013
Susan Lasserre Senior Statistician GMA		12 June 2013

PROTOCOL AMENDMENT, VERSION 3: I. RATIONALE

Recruitment and patient treatment is currently ongoing in study MO28072. Several sections of the protocol have been amended to improve clarity or make corrections.

The detailed rationales for amending this protocol are described below:

Study Design

1. Survival follow-up period and end of study

The protocol has been revised so that the Survival Follow-up will last a minimum of 12 months after the last patient has been enrolled or until all patients have died, withdrawn consent or are lost to follow-up, whichever occurs first. After study end, no further data will be collected on the clinical database for this study.

The Survival Follow-up period has been amended to ensure that a minimum of 12 months' patient treatment and follow-up data from enrolment is available to measure study outcomes.

Impacted Sections of the Protocol:

Synopsis – Trial Design
Synopsis – Length of Study
Synopsis – End of Study
Synopsis – Study Assessments (Survival Follow-up Period)
Synopsis – Statistical Model (Secondary efficacy variables)
Schedule of Assessments – Table 3a, footnotes
Schedule of Assessments – Table 3b, footnotes
Section 3.1 – Overview of Study Design
Section 3.1.3 – End of Study
Schedule of Assessments – Table 7a, footnotes
Schedule of Assessments – Table 7b, footnotes
Section 5 – Schedule of Assessments
Section 5.3.5 – Survival Follow-Up
Section 8.3.1 – Statistical Model
Informed Consent Form

2. Cohort 7

It has been clarified that the sample size of 19 patients for Cohort 7 (other solid tumours) is not the total sample size for the cohort, but rather it represents the

number of enrolled patients of each individual tumour type within the cohort, should a sufficient number of patients with any given individual tumour be enrolled so that the Stage I and II analysis could be performed. This number will provide sufficient patients to allow the assessment of desirable response for that individual tumour type at the end of Stage Two.

Impacted Sections of the Protocol:

Synopsis – Table 1 – Sample Size for each Cohort

Section 8.4 – Sample Size Estimation

Table 12 – Sample Size for each Cohort

Patient Population

3. CNS metastases

As per the current protocol, patients with active or untreated CNS metastases are not eligible for the study unless they are asymptomatic, off corticosteroid therapy and without evidence of disease progression for ≥ 2 months. However to make this study consistent with other vemurafenib protocols, patients with incidental brain metastases that are asymptomatic and for which no treatment is planned can now be entered into the study.

Impacted Sections of the Protocol:

Synopsis – Target Population (Exclusion Criteria)

Section 4.3 – Exclusion Criteria

4. Narcotic analgesics in patients with prostate cancer

Patients with prostate cancer pain that required ongoing treatment with narcotic analgesics were previously excluded. However as the majority of prostate patients who would enter this study are expected to have already tried, and failed, most of the known effective treatments for their disease, almost all of these patients will be receiving narcotics for pain control of their bone metastases. Therefore these patients are now considered eligible for the study if the Investigator deems it to be in the patient's best interest.

Impacted Sections of the Protocol:

Appendix 9 – Additional guidance for patients with prostate cancer included in Cohort 7 (other tumours)

5. Erdheim-Chester disease and/or Langerhans cell histiocytosis

As Erdheim-Chester disease (ECD) and/or Langerhans cell histiocytosis (LCH) have some unique characteristics as compared to other types of solid tumours, Appendix 10 has been created to provide additional guidance for these patients, including eligibility criteria, duration of treatment, additional efficacy assessments and reporting of results.

Impacted Sections of the Protocol:

Synopsis - Objectives

Synopsis – Target Population

Synopsis – Efficacy

Synopsis – Procedures (Summary)

Synopsis – Study Assessments (Screening Period)

Synopsis – Study Assessments (Treatment Period)

Synopsis – Efficacy Data Analyses

Schedule of Assessments – Table 3a, footnotes

Glossary of Abbreviations

Section 2.1 – Primary Objective

Section 4.2 – Inclusion Criteria

Section 4.3 – Exclusion Criteria

Schedule of Assessments – Table 7a, footnotes

Section 5.3.1 – Screening Period

Section 5.3.2 – Treatment Period

Section 5.3.6.1 – Solid tumors

Section 8.1.1 – Primary Variable

Section 8.3.2 – Efficacy Data Analysis

Appendix 4 – New Response Evaluation Criteria in Solid Tumors

Appendix 10 – Additional guidance for patients with ECD and/or LCH included in Cohort 7 (other tumours)

Informed Consent Form

Study Treatment and Concomitant Medications

6. Visit window for cetuximab administration

Cohort 3b previously had an allowed visit window of ± 3 days from cycle 2 onwards. To help facilitate alignment with the weekly administration schedule of cetuximab in Cohort 3b, there will be a ± 1 day visit window starting on Day 8 of Cycle 1 and onwards.

Impacted Sections of the Protocol:

Synopsis – Study Assessments (Treatment Period)

Schedule of Assessments – Table 3b, footnotes

Schedule of Assessments – Table 7b, footnotes

Section 5.3.2 – Treatment Period

7. Cohort 3b

Based on safety data collected to-date from the colorectal cancer patients receiving combination therapy with vemurafenib and cetuximab (three patients each in the first two dose levels, with no dose-limiting toxicities observed to-date), and following the recommendation from the Study Steering Committee, for the remaining dose levels of the dose-finding phase of Cohort 3b, three patients can now be enrolled simultaneously into the same dose level, i.e. there is no longer a requirement for the first patient to be observed for at least 28 days prior to the enrollment of the next two patients. Close monitoring as per the current protocol will still be required.

Impacted Sections of the Protocol:

Section 6.3.2.1 – Dose Escalation Guidelines (Cohort 3b only)

Study Assessments

8. Time window for eligibility assessments

For clarification and consistency across all study patients and the Interactive Web Response System (IWRS), the date of patient signature on the informed consent form is considered the start date of the screening period. Patient eligibility will be determined during the 28-day period following this date of signature.

Impacted Sections of the Protocol:

Schedule of Assessments – Table 3a, footnotes

Schedule of Assessments – Table 3b, footnotes

Schedule of Assessments – Table 7a, footnotes

Schedule of Assessments – Table 7b, footnotes

9. Schedule of Assessments

In patients with multiple myeloma, the skeleton survey will only be required at Screening/baseline. Thereafter it will be done as per routine clinical practice. The Schedule of Assessments has been made consistent with the rest of the protocol regarding this detail.

Impacted Sections of the Protocol:

Schedule of Assessments – Table 3a, footnotes

Schedule of Assessments – Table 7a, footnotes

10. Biochemistry

As treatment with vemurafenib might be associated with an increased risk of pancreatitis, amylase and lipase have been added to the biochemistry measurements in order to ensure adequate monitoring of the patients.

Impacted Sections of the Protocol:

Synopsis – Study Assessments (Screening Period)

Schedule of Assessments – Table 3a, footnotes

Schedule of Assessments – Table 3b, footnotes

Schedule of Assessments – Table 7a, footnotes

Schedule of Assessments – Table 7b, footnotes

Section 5.3.1 – Screening Period

Section 5.4.1 – Safety Laboratory Assessments

Safety

11. Dose interruptions and modification criteria for vemurafenib

Table 8 of the protocol stipulated a 50% reduction of vemurafenib, depending on the starting dose, at the first appearance of grade 4 toxicities. Vemurafenib is only provided as 240 mg tablets which cannot be divided. The guidelines for dose interruptions/modifications have therefore been clarified for patients receiving vemurafenib at a starting dose of 720 mg b.i.d. For these patients treatment can start at a reduced dose of 480 mg b.i.d. once the adverse event has resolved to grade 0 or 1.

Impacted Sections of the Protocol:

Table 8 - Dose Interruption/Modification Criteria for Vemurafenib

12. Grade 3 laboratory abnormalities

The protocol currently requires treatment to be held and dose reductions to occur for any grade 3 toxicity. However, following the recommendation from the Study Steering Committee, an exception will be made for grade 3 hematological abnormalities (except for neutropenia and thrombocytopenia). According to the Steering Committee, these conditions can be very often observed in previously treated cancer patients, and, in the best interest of the patient, the decision to interrupt treatment and/or reduce the dose should be at the Investigator's discretion.

Impacted Sections of the Protocol:

Table 8 - Dose Interruption/Modification Criteria for Vemurafenib (footnotes)

Table 10 - Dose Interruption/Modification Criteria for Cetuximab (footnotes)

13. Possible vemurafenib side effects

The table in the ICF listing possible vemurafenib side effects has been updated to be aligned with other BRAF protocols with regards to side effects of vemurafenib.

Impacted Sections of the Protocol:

Informed Consent Form

14. Second primary malignancies

The potential for second primary malignancies is an important potential risk for vemurafenib, and these events should be reported as an SAE according to protocol section 7.3.3.2. This was now also added to the synopsis for completeness.

In section 7.3.3.2 it was clarified that, regardless if a patient is admitted to hospital, any suspected cutaneous squamous cell carcinoma (SCC) as well as any suspected SCC needs to be reported as an SAE.

As based on mechanism of action, vemurafenib may cause progression of cancers associated with RAS mutations, vemurafenib should be used with caution in patients with prior or concurrent cancers associated with RAS mutation. The protocol was updated to include this information.

Impacted Sections of the Protocol:

Synopsis – Safety

Section 1.3.5 – Clinical Safety in Melanoma

Section 7.1 – Warnings and Precautions

Section 7.3.3.2 – Cutaneous Squamous Cell Carcinoma / Keratoacanthoma & Second Primary Malignancies

Informed Consent Form

Administrative

15. Recruitment period

The original protocol stipulates a planned recruitment period of approximately 18 months. Based on recruitment rates to-date, this has been modified to approximately 24 months.

Impacted Sections of the Protocol:

Synopsis – Length of Study

16. Roche staff

The job title for Luisa Veronese has been updated. A new statistician is now associated with the project.

Impacted Sections of the Protocol:

Protocol title page

17. Correction of typographical errors

Tables 10 and 11, as related to the sample size estimation, should have been referred to as Tables 1 and 2 within the synopsis. The calculation of body surface area has been corrected. A reference to intent-to-treat population 8 (ITT8) has been corrected to ITT7. In the Schedule of assessments, corrections have been made for the timepoints regarding Dermatology evaluation, head and neck assessment for SCC and the Vemurafenib dosing exception diary in order to correctly reflect the protocol wording. A sentence in the ICF, which was previously crossed-out with the intentions of being deleted, has now been deleted.

Impacted Sections of the Protocol:

Synopsis – Statistical Model (stopping rules)

Schedule of assessments – Table 3b and 7b

Section 8.2 – Study Populations

Appendix 1 – Formulae for CrCl and Body Surface Area

Informed Consent Form

18. Protocol version number and date

The protocol version number and date have been updated to reflect this latest amendment.

Impacted Sections of the Protocol:

Protocol title page

Protocol footer

Informed Consent Form

Please refer to the **Section II** of this document for the changes implemented in each section of the protocol.

PROTOCOL

TITLE:	**AN OPEN-LABEL, PHASE II STUDY OF VEMURAFENIB IN PATIENTS WITH BRAF V600 MUTATION-POSITIVE CANCERS**
PROTOCOL NUMBER:	MO28072
VERSION NUMBER:	5
EUDRACT NUMBER:	2011-004426-10
IND NUMBER:	73,620
TEST PRODUCT:	Vemurafenib (RO5185426)
MEDICAL MONITOR:	Dr. Vladan Antic
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	10th March 2014
DATES AMENDED:	Version 1: 30 November 2011 Version 2: 9 August 2012 Version 3: 7 January 2013 *for U.S. sites only* Version 3: 12 June 2013 *for ex-U.S. sites only* Version 4: 10 September 2013 *for U.S. sites only* Version 5: See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

[electronic signatures]

PROTOCOL AMENDMENT, VERSION 5: RATIONALE

Protocol MO28072 has been amended to allow additional patients to be recruited into a study cohort if a promising response rate has been demonstrated in Stage II of that cohort. In addition, the exploratory objectives for the study have been revised.

Enrolment of additional patients

This study is composed of seven different cohorts, with Cohorts 1 to 6 each representing a specific indication, and Cohort 7 consisting of patients with other assorted indications. In general, recruitment into each cohort/indication is based on two Stages. The initial set of patients entered into Stage I must meet a pre-specified response rate (or a clear clinical benefit as approved by the study's Steering Committee) in order for cohort recruitment to proceed to Stage II. Although the number of patients subsequently enrolled into Stage II is dependent on whether a "high" or "low" response rate was seen in Stage I patients of that cohort/indication, the maximum total patients to be enrolled into each cohort/indication (Stages I and II combined) is 19 patients.

This amendment will allow up to 70 patients in total to be enrolled into a cohort/indication if a promising response rate, as determined in discussion with the study's Steering Committee, is seen in Stage II of any cohort/indication. The data from these additional patients will help further characterize the safety and efficacy of vemurafenib in the specific indication. As study sites are already in place and recruiting into this study, this approach is more efficient that initiating a separate indication-specific phase II study to confirm safety and efficacy.

Exploratory Objectives

Roche recognizes that molecular diagnostic technology as well as the associated testing paradigm is changing rapidly. At this time, a single–mutation companion diagnostic test may be no longer suitable in the rare-disease setting, as it could be considered an ethical challenge to request submission of tumour biopsy samples in order to conduct a single test in which the majority of the results will be negative (e.g., as would be the case in approximately 99% of NSCLC samples), particularly given the limited availability of tumour tissue and the need to test for additional biomarkers. Embracing this from the time of study inception, Roche has allowed screening via acceptable local standard methodologies, including multiplex platforms, PCR and DNA sequencing, for BRAF mutation for eligibility into the VE BASKET study. Many of these employ multiplex testing for a number of known genetic mutations. Given the diversity of the methodologies allowed, use of a single acceptable standard testing methodology to perform concordance testing for these samples would be desirable in order to substantiate the validity and utility of these real world testing methodologies employed for screening purposes.

Reporting of Adverse Events

The post-study collection of adverse events has been updated to the latest Roche requirements.

Other Changes

Additional changes to the protocol are as follows:

- To accommodate for possible cohort expansion, the study recruitment period will be extended from 24 months to approximately 40 months
- The total number of patients to be recruited into the study may exceed the original estimate of 170 patients if any cohort is expanded. It currently is not possible to predict the final number of study patients, as the efficacy of each cohort has not yet been determined.
- A correction has been made on the timing of ECGs post-Cycle 8 in the study's Schedule of Assessments (for vemurafenib-only cohorts)
- Although the primary statistical analysis of response rate will be based on the Investigator's assessment, a secondary analysis based on the assessment of an Independent Review Committee may also be performed
- As of July 2013, the Warning and Precautions section of the Vemurafenib Core Safety Information has been updated. The protocol will be updated to reflect these changes, including possible drug reactions with eosinophilia and systemic symptoms (DRESS)
- The background vemurafenib safety section of the protocol has been updated with additional toxicity information (liver injury and neutropenia) associated with the use of vemurafenib
- The patient replacement policy has been revised such that patients who never received study treatment as per protocol, or patients who did not have measurable disease at baseline, will be replaced
- As version 4 of the protocol has been already been written (for U.S. sites only), this revised protocol represents version 5.

  Version 3 (7 January 2013; *U.S. sites only*)

  On 7 January 2013, Study MO28072 was amended to add the protocol acceptance form, as required for U.S. studies. This amendment was only submitted in the United States.

  Version 4 (10 September 2013; *U.S. sites only*)

  On 10 September 2013, Study MO28072 was amended again to incorporate changes made to the global protocol (Version 3, 12 June 2013) and to add the protocol acceptance form. This amendment was only submitted in United States.

  The changes from both U.S.-only amendments have now been incorporated in Version 5 (described here) to align the protocol globally.

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

PROTOCOL AMENDMENT, VERSION 5:
SUMMARY OF CHANGES

GLOBAL CHANGES

Throughout the document, the protocol version has been revised from version 3 to version 5, and the protocol date updated to 10th March 2014.

TABLES

Table 3 has been added into the synopsis; subsequent tables have been renumbered accordingly.

PROTOCOL TITLE PAGE

Dr. Vladan Antic has replaced Dr. Luisa Veronese as the Senior International Medical Leader.

PROTOCOL SYNOPSIS

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

GLOSSARY OF ABBREVIATIONS

CMML	*chronic myelomonocytic leukemia*
DRESS	*Drug Reaction with Eosinophillia and Systemic Symptoms syndrome*
G-CSF	*Granulocyte colony-stimulating factor*

SECTION 1.3.5 Clinical Safety in Melanoma

Further details of cSCC findings across all vemurafenib melanoma clinical trials can be found in the latest vemurafenib IB (current version ~~8~~ *10*).

….

An analysis of liver-related adverse events reported with vemurafenib use showed that 63 cases (out of estimated exposure of approximately 20,000 patients) of medically confirmed serious adverse events were consistent with drug-induced liver injury based on clinical chemistry criteria from the DILI Expert Working Group (76). Of these 63 cases, two were assessed as severe, both reported as hepatic failure. There were no reported deaths among the 63 cases of liver injury; the outcome of one case of severe liver injury was reported as completely resolved with vemurafenib discontinuation, while information on the outcome of the second case of severe liver injury is not available at this time. The median time to onset of the adverse events was 44 days after initial dose. The median ALT to ALP ratio was calculated as 1.5, suggesting a trend towards a cholestatic pattern of liver injury. The analysis did not reveal any risk factors or populations at risk.

A review of the Roche safety database found neutropenia to be an uncommon (6 cases per 1000 person-years, 0.6%) adverse drug reaction associated with the use of vemurafenib, typically occurring during the first 6-12 weeks of treatment. It appeared to be reversible usually within 2 weeks, with either temporary interruption,

dose reduction or discontinuation of vemurafenib, and in some cases was managed with granulocyte colony-stimulating factor (G-CSF).

One case of progression of NRAS-mutated chronic myelomonocytic leukemia (CMML) occurred in a male patient with metastatic melanoma treated with vemurafenib for less than two weeks (77). After the first dose of vemurafenib, laboratory results showed a marked leucoytosis and monocytosis and vemurafenib treatment was subsequently stopped. There was a temporal relationship between vemurafenib treatment and increase in white blood cell (WBC) and absolute monocyte counts, through multiple cycles of de-challenge and re-challenge. In vitro studies demonstrated proliferation of the leukemic cell population, an effect that was reversed upon drug withdrawal. Further, the cells exhibited dose-dependent and reversible activation of ERK in the NRAS-mutated leukemic clone. On the basis of its mechanism of action, vemurafenib may cause progression of cancers associated with RAS mutations. Vemurafenib should be used with caution in patients with a prior or concurrent cancer associated with RAS mutation. Full details are provided in the vemurafenib IB (version 10).

As of March 31st 2013, 12 cases of Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) syndrome have been observed with vemurafenib treatment. No cases have been reported to result in death. The time to onset was 7 to 25 days. In the majority of patients (7 patients), vemurafenib was discontinued. Five patients were treated with systemic steroids with corresponding improvement or resolution of symptoms. In addition, two patients with Grade 3 rash, who were treated with vemurafenib after ipilimumab, had biopsies that showed pathology consistent with drug hypersensitivity reaction (78). Full details are provided in the vemurafenib IB (version 10).

SECTION 2.3 Exploratory Objective

~~To evaluate the Roche Companion Diagnostic (CoDx) cobas® 4800 BRAF V600 Test for the detection of BRAF V600 in tumor samples.~~ *To perform concordance testing for the detection of BRAF V600 mutation in tumor samples via either the Roche Companion Diagnostic (CoDx) cobas® 4800 BRAF V600 Test or other acceptable standard methodology.*

SECTION 3.1 Overview of Study Design

Recruitment into any cohort/indication can be expanded up to a total of 70 patients if a response rate has been demonstrated in Stage II of that cohort as per stopping rules defined in the protocol or a clear clinical benefit for patients is observed. This will be decided by the Sponsor in discussion with study Steering Committee.

SECTION 3.1.1 Rationale for Study Design

Recruitment into any cohort/indication can be expanded up to a total of 70 patients if a response rate has been demonstrated in Stage II of that cohort as per stopping rules defined in the protocol or a clear clinical benefit for patients is observed. This will be decided by the Sponsor in discussion with study Steering Committee. The data from these additional patients will help further characterize the safety and efficacy of vemurafenib in the specific indication.

SECTION 3.2 Number of Patients / Assignment to Treatment Groups

It is estimated that up to 170 patients with solid tumors or multiple myeloma will be enrolled in this study *for the Stage I/II analysis*. Approximately 13–37 patients per indication (cohort) will be included. The number of patients in a cohort can be less than 13 if a cohort is closed earlier as a result of stopping rules for the cohort.

Recruitment into any cohort/indication can be expanded up to a total of 70 patients if a response rate has been demonstrated in Stage II of that cohort as per stopping rules defined in the protocol or a clear clinical benefit for patients is observed. This will be decided by the Sponsor in discussion with study Steering Committee. The maximum number of patients in this study is therefore 490 (7 cohorts at 70 patients each).

SECTION 4.6.1 Replacement Policy – for Patients

~~Patients enrolled into the study will not be replaced~~ *The following patients will be replaced:*

- *patients who never received study treatment as per protocol*
- *patients who did not have measurable disease at baseline*

SECTION 5 Schedule of Assessments and Procedures

Table 8a (Cohorts 1, 2, 3a, 4-7)

	Cycle 9 onwards
12-lead ECG	~~X~~ *C11* (*then* Q12 weeks)

Footnote 25: During screening AEs are not recorded in the eCRF unless they are SAEs which are related to protocol-mandated procedures. ALL AEs (including SAEs) must be recorded from the time of first vemurafenib administration. After the last dose of vemurafenib any new, AEs should be reported up to 28 days after last dose. ~~Any AEs (including SAEs) reported after last dose which the Investigator considers related to study drug must be reported indefinitely.~~ *The Sponsor should be notified if the Investigator becomes aware of any SAE or non-serious AEs of special interest occurring after the end of the adverse event reporting period, regardless of causality.*

Table 8b (Cohorts 3b)

Footnote 23: During screening AEs are not recorded in the eCRF unless they are SAEs which are related to protocol-mandated procedures. ALL AEs (including SAEs) must be recorded from the time of first vemurafenib administration. After the last dose of vemurafenib any new, AEs should be reported up to 28 days after last dose. ~~Any AEs (including SAEs) reported after last dose which the Investigator considers related to study drug must be reported indefinitely~~. *The Sponsor should be notified if the Investigator becomes aware of any SAE or non-serious AEs of special interest occurring after the end of the adverse event reporting period, regardless of causality.*

SECTION 5.3.6.1 Response Criteria – Solid tumors

Scans used for RECIST and/or other tumor assessments might be collected and provided for independent review.

SECTION 6.2 Dose and Schedule of Vemurafenib

If recruitment is expanded in any cohort (due to promising efficacy seen in Stage II), patients who are part of this expansion will receive the same treatment as patients who were treated in Stage II of that cohort.

SECTION 7.3.1 Reporting of Adverse Events

All adverse events experienced after the patient has started study treatment must be recorded on the AE form of the eCRF, as well as all new adverse events experienced during the study and up to 28 days after the last dose of study treatment. ~~AEs (including SAEs) considered related to study drug are to be reported indefinitely.~~

The Investigator is not required to actively monitor patients for adverse events after the end of the adverse event reporting period (defined as 28 days after the last dose of study drug). However the Sponsor should be notified if the Investigator becomes aware of any SAE or non-serious AEs of special interest occurring after the end of the adverse event reporting period, regardless of causality.

SECTION 7.3.2 Reporting of Serious Adverse Events (immediately reportable)

~~Related Serious Adverse Events MUST be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed. Related SAEs must be collected and reported indefinitely.~~ *The investigator is not required to actively monitor patients for adverse events after the end of the adverse event reporting period (defined as 28 days[insert time of 21 days or longer; corresponds to time needed to eliminate drug (~5 half-lives)] after the last dose of study drug). However, the Sponsor should be notified if the investigator becomes aware of any serious adverse event, or non-serious adverse event of special interest occurring after the end of the adverse event reporting period, regardless of causality.*

….

All adverse events must be collected and reported during the study and for up to 28 days after the last dose of study medication. ~~AEs (incl. SAEs) considered related to study drug are to be reported indefinitely.~~

SECTION 8.2 Study Populations

The per-protocol (PP) population will not be defined due to the small number of patients per cohort, but protocol deviations will be listed *(including patients with non-measurable disease at baseline).*

SECTION 8.3.1 Statistical Model

Recruitment into any cohort/indication can be expanded up to a total of 70 patients if a response rate has been demonstrated in Stage II of that cohort as per stopping rules defined in the protocol or a clear clinical benefit for patients is observed. This will be decided by the Sponsor in discussion with study Steering Committee.

In case a cohort/indication is expanded to 70 patients, the primary analysis for efficacy will occur once all patients have at least 16 weeks of treatment, or the patient develops progressive disease, withdraws consent, or is lost to follow-up, whichever occurs first.

The final analysis ~~for OS~~ for each cohort will take place when all patients in that cohort have been followed for survival for a minimum of 12 months after the last patient has been enrolled or until all patients have died withdrawn consent or are lost to follow up, whichever occurs first. More details are provided in Efficacy Data Analysis (see below).

~~The final analysis for RR for each cohort will be at the end of Stage II.~~

SECTION 8.3.1.2 Stopping Rules for Enrollment and Screening

Cohort Expansion

There will be no formal statistical hypothesis tested as part of the expansion cohort analysis. The analysis of the expanded cohort will allow estimation of RR with increased precision and more insight concerning the safety profile.

SECTION 8.3.2 Efficacy Data Analysis

In case a cohort/indication is expanded to 70 patients, the primary analysis for efficacy will occur once all patients have at least 16 weeks of treatment, or the patient develops progressive disease, withdraws consent, or is lost to follow-up, whichever occurs first.

SECTION 8.3.4 Interim Analysis

The study will be analyzed for efficacy at Stage I and Stage II and the dose escalation for Part 1 of Cohort 3b (Section 6.3.2.1) *and at week 16 for expanded cohorts. All cohorts will be analyzed at the end of the study*. No additional interim analysis for efficacy will be performed in this study.

SECTION 8.4 Sample Size Estimation

There will be up to 170 patients enrolled in this study *for the Stage I/II analysis* (see Table 13). *Recruitment into any cohort/indication can be expanded up to a total of 70 patients if a response rate has been demonstrated in Stage II of that cohort as per stopping rules defined in the protocol or a clear clinical benefit for patients is observed. This will be decided by the Sponsor in discussion with study Steering Committee. The maximum number of patients in this study is therefore 490 (7 cohorts at 70 patients each).*

…

Table 13 – Sample Size for Each Cohort – Stage I/II

	~~At the end of Stage Two~~ *Sample size following Stage I analysis*
Total number for ~~the whole study~~ *Stage I/II*	up to 170 patients [c]

c. *The total number of patients may exceed the original estimate of 170 patients if any cohort is expanded (see Table 14).*

Table 14 – Sample Size for Each Cohort (except Cohort 6) and ~~Each~~ Stage *I/II*

(no change to table)

SECTION 8.4.1 Sample Size Estimation for Expansion of Cohorts following Promising Stage II Results

Recruitment into any cohort/indication can be expanded up to a total of 70 patients if a response rate has been demonstrated in Stage II of that cohort as per stopping rules defined in the protocol or a clear clinical benefit for patients is observed. This will be decided by the Sponsor in discussion with study Steering Committee.

Assuming a preferable BOR of 40% in the cohort with promising Stage II results and aiming at a distance from the estimated proportion to the CI limits of 12%, a total of 70 patients would need to be enrolled. The observed BOR of 40% could then be estimated to be within 28% and 52%, with a probability of 95% (Clopper-Pearson exact confidence intervals).

Estimation of the sample size was calculated by SAS (Version 9.2) and nQuery (Version 6). Details are presented in the ***Table 15****.*

Table 15 – Estimation of Sample Size

Sample Size	***BOR***	***95% Clopper Pearson Exact Confidence Intervals***
70 patients	*36% (25 patients)*	*25% – 48%*
	40% (28 patients)	*28% – 52%*
	46% (32 patients)	*34% – 58%*
	50% (35 patients)	*38% – 62%*

REFERENCES

One reference has been updated and three references have been added; subsequent references have been renumbered accordingly, both in the Reference section as well as throughout the protocol.

75. Vemurafenib Investigator Brochure, version ~~8~~ *10*. Please refer to www.vemurafenibtrials.com

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

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

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

SAMPLE INFORMED CONSENT FORM

The sample Informed Consent Form has been revised with additional safety information and modified to reflect the changes to the protocol.

A new ICF Addendum has also been created to reflect these latest changes for patients who have already signed an Informed Consent Form.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**AN OPEN-LABEL, PHASE II STUDY OF VEMURAFENIB IN PATIENTS WITH BRAF V600 MUTATION-POSITIVE CANCERS**
PROTOCOL NUMBER:	MO28072
VERSION NUMBER:	5
EUDRACT NUMBER:	2011-004426-10
IND NUMBER:	73,620
TEST PRODUCT:	Vemurafenib (RO5185426)
MEDICAL MONITOR:	Dr. Vladan Antic
SPONSOR:	F. Hoffmann-La Roche Ltd.

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

{Name}
{Address}

PROTOCOL

TITLE:	**AN OPEN-LABEL, PHASE II STUDY OF VEMURAFENIB IN PATIENTS WITH BRAF V600 MUTATION-POSITIVE CANCERS**
PROTOCOL NUMBER:	MO28072
VERSION NUMBER:	6
EUDRACT NUMBER:	2011-004426-10
IND NUMBER:	73,620
TEST PRODUCT:	Vemurafenib (RO5185426)
MEDICAL MONITOR:	Dr. Vladan Antic
SPONSOR:	F. Hoffmann-La Roche Ltd.
DATE FINAL:	13 January 2015
DATES AMENDED:	Version 1: 30 November 2011 Version 2: 9 August 2012 Version 3: 7 January 2013 *for U.S. sites only* Version 3: 12 June 2013 *for ex-U.S. sites only* Version 4: 10 September 2013 *for U.S. sites only* Version 5: 18 March 2014 Version 6: See electronic date stamp below

PROTOCOL AMENDMENT, VERSION 6:
RATIONALE

Protocol MO28072 has been amended as described below:

Patient Population

1. It has been clarified that patients must be able to submit a tumour sample (preferably tissue; alternatively DNA) for retrospective confirmation of the BRAF mutation by a central laboratory in order to be eligible for the study. This tumour sample should preferably be from the original specimen used to detect the BRAF mutation. If archival samples are not available, the patient should be biopsied in order to obtain adequate tissue. Exceptions may be considered upon discussion with the Sponsor (e.g. ≥ 250 ng of DNA may be sent instead of tissue samples).
2. The lower age limit has been decreased from 18 to 16 years of age.

Study Treatment

3. Details regarding post-trial access to vemurafenib and cetuximab have been added to align with the most recent Roche protocol template.
4. Patients with Erdheim-Chester disease (ECD) and/or Langerhans cell histiocytosis (LCH) have the option of discontinuing vemurafenib treatment after one year, if the Investigator considers it to be in the best interest of the patient. Patients can then resume vemurafenib treatment if scans show worsening of their disease or they become symptomatic.

Study Assessments

5. For all cohorts other than Cohort 3b, the time window for study visits has been modified to ± 2 days for Cycle 1 / Day 15, and to ± 5 days from Cycle 2 onwards. For Cohort 3b only (which has weekly visits throughout the Treatment period), the visit window will remain ± 1 day from Cycle 1 / Day 8 onwards.
6. For all patients in Cohort 1, the CT scans during the patient's last therapy prior to this study, as well as CT scans made during this study, will be collected reviewed retrospectively by an Independent Review Committee (IRC).

   Scans from the prior therapy will be used to establish the previous line's time-to-progression (plTTP). An exploratory objective has been added to the protocol, examining the plTTP to the TTP achieved from study treatment.

   During the study, the Investigator-assessed response rate will remain as the primary efficacy endpoint and the IRC assessment will be a supportive secondary endpoint. The concordance tables between Investigator and IRC assessment will be produced. The collection of scans and IRC review may also be considered for efficacy assessments for other cohorts where clinically meaningful efficacy is demonstrated with Investigator assessment.
7. As part of safety follow-up, patients must have a chest CT, dermatology evaluation and head and neck exam at the Safety Follow-up Visit. It has been clarified that a subsequent assessment should be done either 6 months following study drug discontinuation or prior to the initiation of another anti-neoplastic therapy, whichever occurs first.
8. The protocol states that tumour assessments are required during Screening for patients with solid tumours (CT/MRI of the chest, abdomen and pelvis). However for patients who have a primary brain malignancy, the CT/MRI of the chest, abdomen and pelvis may now be omitted.

9. In order to assess population pharmacokinetics (PK) and to investigate exposure-response relationships, the PK characteristics of vemurafenib has been added as an exploratory objective. For all newly enrolled patients in all cohorts, plasma samples are now required at the following time points:

    a. Cycle 1, Day 1 and Day 15

    b. Cycles 2 – 4, Day 1

    Samples will be taken pre-dose and at 2 – 4 hours post-dose of the morning dose on the corresponding days. Approximately 2 mL of blood will be collected at each time point. Pending approval of the current protocol amendment, it is anticipated that the first PK samples will be obtained from study patients early 1Q 2015. As Cohort 3b is closed to recruitment, PK assessments have not been added to that cohort's Schedule of Assessments. Collected samples will be destroyed no later than five years after the end of the study.

10. Optional blood samples for exploratory biomarkers have been added, and can be collected from any newly enrolled patient in any cohort. Blood samples will be taken at pre-dose Cycle 1 (Day 1) and Cycle 2 (Day 1), as well as at the Safety Follow-up Visit or at time of disease progression (whichever occurs first), with approximately 10 mL blood being required at each time point. As Cohort 3b is closed to recruitment, biomarker assessments have not been added to that cohort's Schedule of Assessments. Any collected samples will be destroyed no later than five years after the end of the study.

    For these patients, BRAF V600 mutations in tissue may be correlated to BRAF V600 mutations in plasma and assessed in relation to clinical parameters and clinical outcome. Further exploratory analysis may include, but are not limited to, markers relevant in the pathogenesis, course and outcome of vemurafenib treatment, such as genetic alterations and candidate biomarkers.

11. In patients with an elevated total bilirubin, the protocol requires fractionation into direct and indirect bilirubin. If only one of these components is available (i.e. either direct or indirect bilirubin), it has been clarified that the other component can be calculated and recorded in the eCRF.

12. For study patients with ECD/LCH, bone lesions are currently assessed using the Positron Emission Response Criteria in Solid Tumors (PERCIST). At the time of development in 2009, the authors of PERCIST acknowledged that PERCIST criteria should serve as a starting point, and that subsequent revisions to the criteria would undoubtedly be required (Wahl et al. 2009).

    For the purposes of evaluation of response to treatment in ECD/LCH, PERCIST has several limitations:

    - PERCIST measures fluorodexoyglucose (FDG)-avidity with a metric called SULpeak, the peak standardized update value normalized to lean body mass (SUV) based on lean body mass measured from a 1 cm sphere around the most avid portion of the lesion. SULpeak works well for lesions with high FDG-avidity, however SULpeak often suffers from poor reproducibility for lesions with lower FDG-avidity. Separate measurements of the same lesion by different people result in different values, depending of the region of interest selected. Therefore, as lesions in ECD/LCH often demonstrate lower levels of FDG-avidity, there are limitations to using SULpeak.

    - PERCIST uses only the single most avid lesion for comparisons. ECD/LCH patients often have multiple lesions, and these lesions typically have lower levels of FDG-avidity. In addition, these lesions are frequently near physiologic structures with FDG-

avidity which can interfere and complicate measurements (e.g. the ocular muscles adjacent to retrobulbar lesions). Therefore the measurement of a single lesion may be inadequate for determining treatment response in these patients.

- PERCIST is not widely used and very few institutions measure SULpeak in clinical or research scans, making the extension of PERCIST results into typical clinical imaging difficult.

To overcome these limitations, we have proposed PET Response Criteria (PRC) as a method of measuring metabolic treatment response on FDG PET. PRC criteria are actually more analogous to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria than PERCIST. As with RECIST, up to 5 target lesions are chosen in PRC. Response is based on the response in these target lesions, measured by SUVmax (the maximum SUV based on body weight from a region of interest drawn around the entire lesion). SUVmax is highly reproducible, even for lesions with lower FDG-avidity. Response in PRC is analogous to RECIST.

Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: Evolving Considerations for PET response criteria in solid tumors. J Nucl Med. 2009;50 Suppl 1:122S-50S.

Safety

13. The background section has been updated to include information on pancreatitis experienced by 17 patients treated with vemurafenib. The workup of any suspected case of pancreatitis should include serum amylase and lipase testing in addition to other appropriate testing (e.g. CT of the abdomen).
14. It has been clarified that events of actinic keratoses do not need to be reported as serious adverse events (SAEs) under the current cSCC reporting guidelines.
15. Protocol wording has been aligned with the most recent Roche protocol template.

    These changes include:

    - description of safety parameters and definitions
    - description and reporting of adverse events which are persistent or recurrent, are associated with laboratory test abnormalities, abnormal vital sign values, abnormal liver function tests, an overdose or an error in drug administration, or adverse events which are associated with individuals not enrolled in the study
    - reporting of adverse events via electronic data capture (EDC) and reporting requirements if the EDC system is unavailable
    - immediate reporting requirements from Investigator to Sponsor
    - SAE reporting procedures for SAEs caused by protocol-mandated interventions which occur after the signing of informed consent but prior to the initiation of any study medication, and SAEs reporting requirements once the adverse event reporting period or the study has ended
    - details of the Emergency Medical Call Center Help Desk.

Statistics

16. If a cohort/indication is expanded to 70 patients, the primary analysis for efficacy was to occur once all patients had received at least 16 weeks of treatment. This analysis will now occur once all patients have been followed for 9 months after the last patient has been enrolled in that cohort. The 9 months follow-up is required to provide an early reasonable

estimate of the median progression-free survival and to capture late responders. The safety follow-up will be conducted as per protocol (12 months).

17. A PK analysis has been added. The population PK model developed in melanoma patients will be used to obtain individual vemurafenib PK parameters from the sparse sampling collected in newly enrolled patients. Summary statistics will be used as appropriate for the vemurafenib plasma concentrations and PK parameters. The relationship between appropriate clinical and pharmacodynamic endpoints and the plasma concentrations of vemurafenib will be explored.

    An additional exploratory objectives has been added for newly enrolled patients as related to the correlation of BRAF V600 mutation between tissue and plasma samples.

18. The IRC's assessment of efficacy has been added as a secondary objective for Cohort 1 (NSCLC) and other cohorts that demonstrate clinically meaningful efficacy per Investigator assessment. The IRC assessment of response rate will focus on Week 8, Week 16 and best overall response.

Administrative

19. The wording of the Roche Companion Diagnostic cobas® 4800 BRAF V600 Test has been made consistent throughout the protocol.
20. References to the vemurafenib Investigator's Brochure have been updated to refer to version 11.
21. The number of countries has been updated from "approximately 4" to "6" countries to reflect current status.
22. The wording regarding the publication of data and protection of trade secrets has been aligned with the most recent Roche protocol template.
23. The protocol has been re-formatted to improve legibility. These changes have not been marked.
24. The protocol has been revised so that British English is used throughout. These changes have not been marked.
25. The protocol version and protocol date have been revised based on this latest amendment.

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

Statistical Analysis Plan

F. HOFFMANN-LA ROCHE LTD

Protocol: MO28072

Treatment: VEMURAFENIB

AN OPEN-LABEL, PHASE II STUDY OF VEMURAFENIB IN PATIENTS WITH BRAF V600 MUTATION-POSITIVE CANCERS

Author(s): Karin Hoffmann

Document Status: Final 1 Version 1

Version Dates: Draft 6 Version 1: 14Jul2013
Final Draft 1 Version 1: 17Sep2013
Final Draft 2 Version 1: 18Sep2013
Final Draft 3 Version 1: 23Sep2013
Final 1 Version 1: 28Nov2013

Pages: 55

Contents

Abbreviations

^{18}F-FDG PET	Fluorodeoxyglucose positron emission tomography
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT(SGPT)	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST (SGOT)	Aspartate Aminotransferase
b.i.d	twice daily
BOR	Best Overall Response
BORR	Best Overall Response Rate
BRAF	v-raf murine sarcoma viral oncogene homolog B1
BUN	Blood Urea Nitrogen
CBR	Clinical Bebefir Rate
CI	Confidence Interval
CMR	Complete Metabolic Response
CR	Complete Response
cSCC	Cutaneous Squamous Cell Carcinoma
CT	Computer Tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DFA	Dose Finding Analysis
DOR	Duration of Response
DLT	Dose limiting toxicities
ECD	Erdheim Chester Disease
ECG	Electrocardiogram
ECOG	Eastern Co-operative Oncology Group
eCRF	Electronic Case Report Form
FA	Final Analysis
HEENT	Head, Eyes, Ears, Nose and Throat
IA	Interim Analysis
ID	Identification
IMWG	International Myeloma Working Group
ITT	Intent-to-Treat
KM	Kaplan-Meier
LCH	Langerhans Cell Hystiocytosis
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple Myeloma
MR	Minimal Response
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NE	Non-Evaluable
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease

PERCIST	Positron Emission Response Criteria in Solid Tumors
PFS	Progression-Free Survival
PMD	Partial Metabolic Disease
PMR	Partial Metabolic Response
PR	Partial Response
QTc	Corrected QT Interval
PT	Preferred Term
RR	Response Rate
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Steering Committee
SCC	Squamous Cell Carcinoma
sCR	Stringent Complete Response
SD	Stable Disease or Standard Deviation
SIA	Stage I Analysis
SIIA	Stage II Analysis
SII6A	6 month on treatment Stage II Analysis
SMD	Stable Metabolic Disease
SOC	System Organ Class
TTP	Time to Tumour Progression
TTR	Time to Response
VGPR	Very Good Partial Response
WBC	White Blood Cell

1 Introduction

This document presents the statistical analysis plan (SAP) for Hoffmann-La Roche Ltd, Protocol No. MO28072: An open-label, multicenter, phase II study of vemurafenib in patients with BRAF V600 mutation-positive cancers.

This analysis plan is based on the final protocol version 3 dated 12 June 2013.

This SAP provides the description of the different analyses for the study. The study includes 7 different cohorts, one of them consisting of two sub-cohorts, each which will be reported separately. For each cohort, in addition to the final analysis, an abbreviated interim analysis (IA) will be carried out when a pre-specified number of patients (cf. sample size section 3.10) will have a minimum of 8 weeks of treatment, develop progressive disease, prematurely withdraw from study, or die, whichever occurs first. The final analysis of each cohort will be done when all patients of the corresponding cohort have finished the study.

Note: The details for cohort 7 patients with Erdheim Chester disease or Langerhans Cell Histiocytosis will be defined after the eCRF amendment related to protocol version 3 is implemented. These details will be updated in this SAP and the SAP will be re-approved. This will include updates to SAP text and shells

2 Study Objectives

This is an open-label, multicenter, multinational, phase II study exploring the efficacy and safety of vemurafenib monotherapy in a diverse population of patients with cancers (excluding melanoma and papillary thyroid cancer) known to harbor BRAF V600 mutations.

In the population of colorectal cancer patients, the safety and efficacy of vemurafenib in combination with cetuximab will also be explored in addition to vemurafenib.

The trial will include 7 cohorts of patients with the following cancers:

Cohort 1. Non-small cell lung cancer (NSCLC)

Cohort 2. Ovarian cancer

Cohort 3. Colorectal cancer:

Cohort 3b. Vemurafenib only

Cohort 3b. Combination therapy with vemurafenib and cetuximab

Cohort 4. Cholangiocarcinoma/cancer of the biliary tract

Cohort 5. Breast cancer

Cohort 6. Multiple myeloma (MM)

Cohort 7. Solid tumors other than the above

For cohort 3b, the study consists of two parts:

- Part 1 is a dose finding phase for vemurafenib in combination with cetuximab (based on a classical 3+3 design)
- Part 2 is investigating the efficacy and safety of the recommended dose for stage I/II of the combination of vemurafenib and cetuximab

As part 2 of cohort 3b with the optimal dose selected is the same stage I/II design as for other cohorts, it is described along them; whilst for part 1, separate subsections are included in where considered necessary for each dose level examined.

The **primary objective** of this trial is to evaluate the efficacy of vemurafenib, in patients with cancers harboring BRAF V600 mutations as response rate (RR) at Week 8 determined by the Investigator using Response Evaluation Criteria In Solid Tumors, Version 1.1 (RECIST, v1.1)* or International Myeloma Working Group (IMWG) uniform response criteria and to identify tumor types for further development.

* Note, see Appendix 9 of protocol for prostate cancer, Appendix 10 of protocol for Erdheim Chester Disease (ECD) and/or Langerhans Cell Hystiocytosis (LCH) response criteria

Secondary objectives are as follows:

- To evaluate the safety and tolerability of vemurafenib in this patient population.
- To evaluate in solid tumors and multiple myeloma (MM):
    - Overall response rate (ORR)

  - Clinical benefit rate (CR (or sCR), PR (or VGPR)) and stable disease [SD]
  - Duration of response (DOR)
  - Time to response
  - Time to tumor progression (TTP)
  - Progression free survival (PFS)
  - Overall survival (OS).

- To determine the maximum tolerated dose (MTD) and recommended dose for stage I/II of the combination of vemurafenib and cetuximab in BRAF V600-positive metastatic CRC patients (Cohort 3b only).
- To investigate the safety, tolerability, efficacy of the combination of vemurafenib and cetuximab in BRAF V600-positive metastatic CRC patients (Cohort 3b only).

An **exploratory objective** is to evaluate the Roche Companion Diagnostic (CoDx) cobas® 4800 BRAF V600 Test for the detection of BRAF V600 in tumor samples.

2.1 Primary endpoint

The primary endpoint is Response Rate (RR) at Week 8, as assessed by the Investigator using RECIST, v1.1 for patients with solid tumors and using IMWG uniform response criteria for patients with MM.

Possible overall response results for Solid Tumours according to RECIST, v1.1, are:

- Complete Response (CR)
- Partial Response (PR)
- Stable Disease (SD)
- Non-CR/Non-PD
- Progressive Disease (PD)
- Non-Evaluable (NE)

Possible overall response results for Multiple myeloma according IMWG uniform response criteria are:

- Stringent Complete Response (sCR)
- Complete Response (CR)
- Very Good Partial Response (VGPR)
- Partial Response (PR)
- Minimal Response (MR)
- No Change/Stable Disease (SD)
- Plateau
- Progressive Disease (PD)
- Relapse

- Relapse from CR

For patients with solid tumors, responders at Week 8 will be defined based on tumor assessment status of PR or CR at Week 8. For patients with MM, responders at Week 8 will be defined based on tumor assessment status of CR, sCR, VGPR or PR at week 8. Only patients with measurable disease at baseline will be included in the analysis of the RR. Patients without a post-baseline tumor assessment will be considered to be non-responders.

For patients with LCH/ECD the tumor response assessment will be based on:

- RECIST v1.1
- PERCIST v1.0
- Multiple assessments (as per protocol depending on involved area of disease)

Best Overall response for PERCIST can be:

- Complete Metabolic Response (CMR)
- Partial Metabolic Response (PMR)
- Stable Metabolic Disease (SMD)
- Progressive Metabolic Disease (PMD)

Patients with a CMR or PMR are considered responders.

Tumour response assessment based on Multiple assessments uses at least one of the following methods to assess Best Overall response:

a. Brain MRI
b. Cardiac MRI (or cardiac echography for patients who cannot undergo MRI and have cardiac involvement)
c. Bone scan
d. ^{18}F-FDG PET
e. CT chest/abdomen/pelvis

Laboratory parameters may also be used.

The patients will be classified as either Reponder or Non responder.

For patients with Multiple myeloma, according IMWG, all response categories require two consecutive assessments.

For solid tumour patients to be assigned a status of partial response (PR) or complete response (CR) (i.e., a responder), changes in tumour measurements must be confirmed by repeat assessments performed at least 4 weeks after the criteria for response are first met, i.e., patients need to have two consecutive assessments of PR or CR to be responders.

The main analysis for the response rate will be based on Adaptive design based on Simon's two stage design for a single proportion; Lin and Shih (2004). Adaptive Two-stage design for Single-Arm Phase II A Cancer Clinical Trials. Biometrics 60, 482-490 (1).

Stage I will be defined as when 7 patients with measurable disease in corresponding cohort (cf. Sample Size section 8.4 of the protocol) will have a minimum of 8 weeks of treatment, and their schedule Tumor assessment reported or develop progressive disease, prematurely

withdraw from study, or die, whichever occurs first. Note that for stage I analysis only and for stage I stopping rules, response criteria are based on unconfirmed assessments.

If a pre-specified minimal response rate will not be achieved in certain cohorts in the first stage of the study, the corresponding cohort should not enrol any further patients. However if a clear clinical benefit has been observed for patients in the respective cohort, e.g. majority of patients recorded SD at Week 8 and no CR or PR is recorded, then enrolment into Stage II might be allowed for this cohort. In that case, stage II of that cohort would be handled like "Low response at the end of Stage I" and another 12 patients enrolled, to have 19 patients in total for that cohort.

The final decision about further recruitment into stage II will be taken by the Sponsor in discussion with study Steering Committee (SC).

If further recruitment is approved, enrolment continues into Stage II until a pre-determined number of additional patients is reached. This number depends on the response rate seen after stage I, as detailed in sample size section 3.10 (the exact numbers are found in Table 4).

An exception will be made for Cohort 7 which includes patients with different solid tumor types. For patients with the same tumor type within this cohort a pooled analysis may be performed when at least 5 patients have been enrolled.

The analysis at end of Stage II (for lower or higher desirable confirmed response) for each Cohort will be performed when all patients enrolled in the study will have a minimum of 8 weeks of treatment (including a confirmed response assessment if applicable), develop progressive disease, withdraw, or are lost to follow-up, whichever occurs first.

The final analysis will be done for each cohort after all patients of the respective cohort have finished the study, i.e. have died, been followed up for survival for a minimum of 12 months after the last patient has been enrolled or until all patients have died, withdrawn consent or been lost to follow-up, whichever occurs first.

2.2 Secondary endpoints

Secondary endpoints for each cohort and for patients with solid tumors and MM are as follows:

- Progression free survival (PFS)
- Time to progression (TTP)
- Best overall response (BOR)
- Time to response (TTR)
- Duration of response (DOR)
- Clinical benefit rate (CBR)
- Overall survival (OS)

2.3 Safety endpoints

The safety endpoints for the study are:

- Adverse events (AEs)
- Laboratory parameters

- Exposure to study medication
- Dermatologic evaluations
- Head/neck evaluations
- Chest CT scan
- Pelvic Examination (for women)
- Anal examination
- Vital signs
- Electrocardiogram (ECG)
- ECOG performance status
- Physical examination.

For cohort 3b, dose finding part, only:

- Dose-limiting toxicities

3 Study Design

3.1 Discussion of Study Design

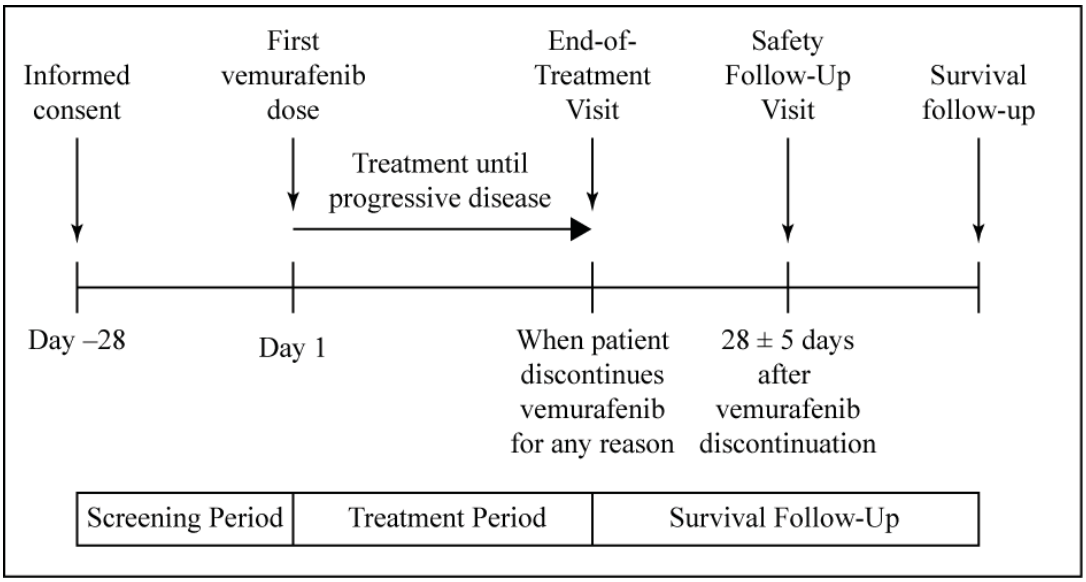
This is an open-label, multicenter, multinational, phase II study exploring the efficacy and safety of vemurafenib in a diverse population of patients with cancers (excluding melanoma and papillary thyroid cancer) known to harbor BRAF V600 mutations and for whom vemurafenib is deemed the best treatment option in the opinion of the Investigator.

In the population of colorectal cancer patients, the safety and efficacy of vemurafenib in combination with cetuximab will also be explored in addition to vemurafenib monotherapy.

Patients with BRAF V600 mutation-positive cancers will be identified through mutation analysis assays as routinely performed at each participating site according to their local procedure. The BRAF V600 mutation identified at the site, as well as the specific BRAF mutation assay that was performed, will be recorded in the electronic case report form (eCRF). The presence of BRAF V600 mutations will be retrospectively confirmed by the cobas® 4800 BRAF V600 Mutation Test.

The trial will consist of a Screening Period (Day –28 to −1), a Treatment Period, an End-of-Treatment Visit occurring when study treatment is discontinued for any reason, a Safety Follow-Up Visit occurring 28 days after the last dose of study treatment and a Survival Follow-Up Period lasting for a minimum of 12 months after enrolment of the last patient to monitor survival status. Day 1 of the study (baseline) is defined as the first day a patient receives study medication. One cycle of therapy is defined as 28 days of treatment.

Figure 1: Study Design



The study includes 7 cohorts of patients with the following cancers:

Cohort 1. Non-small cell lung cancer (NSCLC)

Cohort 2. Ovarian cancer

Cohort 3. Colorectal cancer

Cohort 3a. Vemurafenib only

Cohort 3b. Combination therapy with vemurafenib and cetuximab

Cohort 4. Cholangiocarcinoma/cancer of the biliary tract

Cohort 5. Breast cancer

Cohort 6. Multiple myeloma (MM)

Cohort 7. Solid tumors other than the above

For each of the cohorts, the study is divided into 2 stages. Stage I of the study is completed when 7 patients with measurable disease have been enrolled and completed a minimum of 8 weeks of treatment, developed progressive disease, prematurely withdraw from study, or died, whichever occurs first. Dependent on the RR of patients completing Stage I, more patients may be enrolled to Stage II. An exception to this will be made to cohort 7 as it may not be able to enrol sufficient patients within the different other Solid tumor types which can be combined.

The Cohort 3b is designed to investigate the safety, tolerability, efficacy and to determine the MTD and the recommended dose for stage I/II of the combination of vemurafenib and cetuximab. Therefore, cohort 3b has two parts:

- Part 1 is a dose finding phase of vemurafenib in combination with cetuximab (based on a classical 3+3 design).
- Part 2 is investigating the efficacy and safety of the recommended dose for stage I/II of the combination of vemurafenib and cetuximab; the same Stage I/II design as for the other cohorts will be used.

The decision to carry on enrolment of CRC patients into Cohort 3a (vemurafenib monotherapy) and/or enrol patients into Cohort 3b (combination of vemurafenib and cetuximab) will be based on the stage I analysis for Cohort 3a (vemurafenib monotherapy). This will be decided by the Sponsor in discussion with study Steering Committee.

The decision to continue enrolment in Cohort 3b after the Part I dose escalation phase will be decided by the Sponsor in discussion with study Steering Committee.

Recruitment/enrolment in any of the above cohorts may present some challenges due to the low frequency of BRAF V600 mutations in the specific disease settings. Therefore the following rule on cohort closure will be applied: if no patients are enrolled in the remaining cohorts one year after any of the cohorts has completed enrolment, then enrolment in those remaining cohorts will be stopped. Cohort 7 (Other solid tumours) will be closed to enrolment when all other cohorts are closed, regardless of the number of patients recruited at that time. This cohort is quite heterogeneous and will be examined primarily to seek efficacy signals in the relatively rare BRAF V600 mutation-positive tumours.

3.2 Study Treatment

Patients enrolled in the study receive the following study treatment:

- Cohorts 1 to 7 (except patients in the Cohort 3b):
  - continuous oral dosing of vemurafenib at 960 mg twice daily (b.i.d)
- Cohort 3b:
  - In part 1 vemurafenib and cetuximab at the doses allocated for dose escalation (see section 3.2.1) or
  - In part 2 vemurafenib and cetuximab at the doses recommended for stage I/II during the dose escalation part.

Treatment will continue until the development of progressive disease (as per Investigator assessment), unacceptable toxicity, withdrawal of consent, protocol violation endangering the patient‘s safety, death, reasons deemed critical by the treating physician, or study termination by the Sponsor.

Patients who develop disease progression but, in the opinion of the Investigator, would still benefit from continuing study treatment may continue treatment with study treatment after discussion with the Sponsor.

3.2.1 Study Treatment during Dose-finding Part (Cohort 3b only)

For Part 1 of Cohort 3b, the planned dose escalation levels of vemurafenib and cetuximab combination will be as follows:

Dose Level	vemurafenib	cetuximab
1	720 mg b.i.d. starting on Day 2 of cycle 1	Cetuximab: 300 mg/m^2 loading dose on Day 1 of Treatment Phase, then 200 mg/m^2 weekly
2	720 mg b.i.d. starting on Day 2 of cycle 1	Cetuximab: 400 mg/m^2 loading dose on Day 1 of Treatment Phase, then 250 mg/m^2 weekly
3	960 mg b.i.d. starting on Day 2 of cycle 1	Cetuximab: 400 mg/m^2 loading dose on Day 1 of Treatment Phase, then 250 mg/m^2 weekly

If the dose levels above are not tolerated then the following dose levels will be considered as appropriate after discussion between the sponsor and study Steering Committee.

Dose Level	vemurafenib	cetuximab
-1	720 mg b.i.d. starting on Day 2 of cycle 1	Cetuximab: 200 mg/m^2 loading dose on Day 1 of Treatment Phase, then 125 mg/m^2 weekly
-2	720 mg b.i.d. starting on Day 2 of cycle 1	Cetuximab: 300 mg/m^2 loading dose on Day 1 of Treatment Phase, then 250 mg/m^2 weekly
-3	960 mg b.i.d. starting on Day 2 of	Cetuximab: 300 mg/m^2 loading dose on Day 1 of Treatment

	cycle 1	Phase, then 250 mg/m^2 weekly

Once assigned to specific dosages of vemurafenib and cetuximab in combination, each patient will continue to be treated, without interruption throughout the study unless dose modification or interruption is indicated. (Refer to Section 6.3.3 of the protocol for dose modification guidelines for the combination of vemurafenib and cetuximab.)

3.3 Guidelines for Dose-finding Part (Cohort 3b only)

3.3.1 Dose Escalation Guidelines

A minimum of 3 patients initially will be enrolled at the first dose level (Dose level 1 Section 3.2.14.6.2).

The first patient at any dose level will be observed for at least 28 days before the next two patients receive vemurafenib and cetuximab at that dose level.

The dose escalation rules proceed as follows, escalating in cohorts of 3-6 patients per dose level.

For patients treated at the current dose level, the following rules will be applied:

- If at least 2 patients are observed to have a dose-limiting toxicity (DLT) [see section 3.3.3] during the 28 days following the first administration of vemurafenib and cetuximab (DLT assessment period), the MTD will have been exceeded and no further patients will be enrolled at this dose level or at any higher dose level. The prior dose level is defined as the MTD (unless only 3 patients have been treated at that level, in which case it is the tentative MTD).
- If 0 of the 3 patients are observed to have DLT during the DLT assessment period, the dose level is escalated one step for the next cohort of 3 patients, and the process continues as above.
- If exactly 1 of the 3 patients treated shows DLT during the DLT assessment period, 3 additional patients are treated at the current dose level.

If none of these additional 3 patients show DLT during the DLT assessment period, the dose level is escalated for the next cohort of 3 patients, and the process continues as above; otherwise, the prior dose level is defined as the MTD (unless only 3 patients have been treated at that level, in which case it is the tentative MTD).

A tentative MTD becomes the final MTD when a total of 6 patients are treated with less than 2 of them showing DLT.

3.3.2 Recommended dose of vemurafenib and cetuximab

A dose will be considered non-tolerable and dose escalation will cease if 2 or more of up to 6 evaluable patients experience a DLT at a dose level. Once the non-tolerable dose is defined the MTD will be confirmed at the previous dose-level below or a dose between the MTD and the last tolerable dose. Six evaluable patients are required to determine the MTD.

Expected dose levels for the dose escalation are described in Section 3.2.1. The dose escalation guidelines are summarised in Section 3.3.1. Decisions to escalate or de-escalate the doses will be made based on a review of all available safety data both from the study i.e. nature of the DLTs that occurred at one dose level together with all other available data including generally available data on vemurafenib and cetuximab.

The MTD is defined to be the highest dose of vemurafenib in combination with cetuximab which can be given to 6 patients such that less than 2 subjects experience DLT within 28 days (or no more than one-third if there are more than 6 treated patients).

The recommended dose for stage I/II will be based on considerations of the estimated MTD, and on an overall assessment of safety taking into consideration tolerability data from subsequent cycles at all different dose levels tested. The recommended dose for stage I/II will be determined once the MTD is determined by the Sponsor after discussion with the study Steering Committee. The decision to continue enrolment in Cohort 3b after the Part I dose escalation phase will be decided by the Sponsor in discussion with study Steering Committee.

3.3.3 Dose-limiting toxicities

A DLT is defined as a clinically significant adverse event or abnormal laboratory value assessed as unrelated to disease progression, undercurrent illness, or concomitant medications and occurring during the first 4 weeks of treatment with the combination of vemurafenib and cetuximab.

For the purposes of this protocol, the following adverse events determined to be possibly, probably or definitely related to the combination of cetuximab and vemurafenib that occur during the 28 days following the first administration of the combination of vemurafenib and cetuximab at any dose level and that meet any of the following criteria are considered to be DLTs that count for the determination of the MTD.

Toxicity grades are defined in the NCI CTCAE v 4.0 (2).

- Grade ≥ 3 non-hematological toxicity (other than untreated nausea, vomiting and diarrhea and excluding alopecia)
- Grade ≥ 3 nausea, vomiting or diarrhea refractory to appropriate treatment for at least 2 days
- Grade 4 anemia lasting > 7 consecutive days
- Neutropenia Grade 4 lasting > 7 consecutive days
- Neutropenia Grade 3 or 4 complicated by fever and/or infection (ANC <1.0 x 109/L; fever ≥ 38.5^{0}C
- Grade 4 thrombocytopenia lasting >7 consecutive days
- Treatment delay >33% of the scheduled doses over 28 days due to treatment related toxicity

Skin and subcutaneous tissue toxicity is not considered a DLT unless a dose reduction of study treatment is required to permit continuous dosing.

3.4 Study Schedule

The clinical assessments and procedures outlined in **Tables Schedule of Assessments for Cohorts 1, 2, 3a, 4 – 7** and **Schedule of Assessments for Cohort 3b** will be completed for all patients enrolled in the screening and treatment periods. The clinical assessments and procedures described in the End of Treatment Visit will be completed for patients who withdraw from the study during the treatment period.

The visit window for all cycles from cycle 2 onwards is -4/+1 day for all cohorts; with the exception of cohort 3b with a visit window of ± 3 days.

Table 3a.
Schedule of Assessments for Cohorts 1, 2, 3a, 4 – 7 (cohorts with Vemurafenib study treatment only)

	Screening Period [1]	**Treatment Period** [2] **(Allowed visit window: –4 days / +1 day from cycle 2 onwards)**									**End of Treatment Visit** [3]	**Safety-Follow-Up Visit** [4]	**Survival Follow-Up** [5]
Cycle		1		2	3	4	5	6	7	8	9 onwards		Post treatment d/c	Every 3 months
Day	–28 to –1	1	15	29	57	85	113	141	169	197	Every 28 Days		28 (±5) days	
Informed consent [6]	X													
Documentation of BRAF V600 mutation and test performed	X													
Medical history and demographics	X													
Physical examination [7]	X	X	X	X	X	X	X	X	X	X	X	X		
Vital signs [8]	X	X	X	X	X	X	X	X	X	X	X (Q8 weeks)	X		
12-lead ECG [9]	X			X	X	X	X			X	X (Q12 weeks)	X	X	
ECOG performance status	X	X	X	X	X	X	X	X	X	X	X (Q8 weeks)	X		
Hematology [10]	X	X[11]	X	X	X	X	X	X	X	X	X	X		
Biochemistry [12]	X	X[11]	X	X	X	X	X	X	X	X	X	X		
Serum pregnancy test [13]	X													
Solid tumor assessments (CT/MRI) [14]	X				X		X		X		X (every 8 weeks)	X		
Assessments for Multiple Myeloma [15]	X				X[16]	X[16]	X[16]	X[16]	X[16]	X[16]	X[16]	X[16]		
Dermatology evaluation [17]	X			X			X			X	C11 (then Q12	X	X[20]	At 6 months

	Screening Period [1]	**Treatment Period** [2] **(Allowed visit window: –4 days / +1 day from cycle 2 onwards)**										**End of Treatment Visit** [3]	**Safety-Follow-Up Visit** [4]	**Survival Follow-Up** [5]
Cycle		1		2	3	4	5	6	7	8	9 onwards		Post treatment d/c	Every 3 months
Day	–28 to –1	1	15	29	57	85	113	141	169	197	Every 28 Days		28 (±5) days	
											weeks)			
Head and neck assessment for SCC [18]	X					X			X		C10 (then Q12 weeks)	X	X[20]	At 6 months
Chest CT for evaluation of SCC [19]	X								X		C13 (then Q6 months)		X[20]	At 6 months
Drug dispensation		X		X	X	X	X	X	X	X	X			
Drug accountability				X	X	X	X	X	X	X	X	X		
Drug Dosing Exception Diary [21]				X	X	X	X	X	X	X	X	X		
Prostate Cancer patients only – PSA Assessment [22]	X				X		X		X		X (Q8 weeks)	X		
Prostate Cancer patients only – Bone Scans [23]	X				X		X		X		X (Q8 weeks)	X		
ECD/LCH patients only – C-reactive protein[27]		X		X	X		X		X		X (Q8 weeks)	X		
ECD/LCH patients only – additional tumor assessments [28]	X				X		X		X		X (Q8 weeks)	X		
Concomitant medications [24]	X	X										X	X	
AEs / SAEs [25]	X	X										X	X	
Vemurafenib administration		X												
Follow-up for disease progression														X

	Screening Period [1]	**Treatment Period** [2] **(Allowed visit window: –4 days / +1 day from cycle 2 onwards)**										**End of Treatment Visit** [3]	**Safety-Follow-Up Visit** [4]	**Survival Follow-Up** [5]
Cycle		1		2	3	4	5	6	7	8	9 onwards		Post treatment d/c	Every 3 months
Day	–28 to –1	1	15	29	57	85	113	141	169	197	Every 28 Days		28 (±5) days	
Survival status [5]													X	X
Next anticancer therapy														X
Anal and pelvic exam [26]	**X**												X	

Notes Day 1 = first dose of study drug (vemurafenib)

1. Apart from obtaining written informed consent, no screening procedure may be performed before the patient has been confirmed to be positive for the BRAF V600 mutation. All efforts should be made to collect a tumor sample (formalin-fixed paraffin-embedded tumor tissue [FFPET] or 3-5 serially cut unstained 5-µm sections from one FFPET block) for retrospective confirmation of the BRAF mutation using the cobas 4800 V600 mutation kit. This tumor sample should preferably be from the original specimen used to detect the BRAF mutation. The original tumour block will be returned to the site.
2. Visits during the Treatment Period are to be completed on Day 1, Day 15, Day 29 and every 28 days thereafter until study drug discontinuation. A window of 4 days prior to the scheduled visit date and one day after the scheduled visit date (–4 days / + 1 day) is allowed for each visit from Cycle 2 onwards.
3. The End of Treatment Visit will be performed when the patient discontinues vemurafenib regardless of when it occurs.
4. The Safety Follow-Up Visit will be performed after 28 (±5) days from discontinuation of vemurafenib.
5. The Survival Follow-Up period will last for a minimum of 12 months after the last patient has been enrolled or until all patients have died, withdrawn consent or are lost to follow-up (whichever occurs first).
6. Informed consent must be obtained prior to performing any study procedure including Screening assessments. The date of signature on the informed consent form signifies the beginning of the 28-day Screening Period.
7. Includes the evaluation of the head, eyes, ears, nose, and throat (HEENT); cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal and neurological systems examination; and height (cm) and weight (kg). Height will only be measured during screening.
8. Includes blood pressure, heart rate, temperature and respiratory rate.
9. Includes heart rate, PR interval, QRS duration, QT and QTc intervals and ECG findings.
10. Includes hemoglobin, hematocrit, platelet count, white blood cell count (WBC) and absolute neutrophil count (ANC)
11. Hematology and biochemistry assessments do not need to be repeated on Day 1 if performed within 7 days of first vemurafenib administration. NB: if it is necessary to repeat these blood tests, the results must be known before the patient receives first dose of vemurafenib to ensure that the inclusion and exclusion criteria related to these tests are met.
12. Includes amylase, lipase, glucose, blood urea nitrogen [BUN], creatinine or creatinine clearance, sodium, potassium, calcium, magnesium, bicarbonate ([if routinely performed on venous blood samples],), total bilirubin with fractionation into direct and indirect (if total bilirubin elevated during the study), alkaline phosphatase, AST ([SGOT]], ALT ([SGPT]],
13. Serum pregnancy test to be performed within 7 days prior to first vemurafenib administration for women with childbearing potential.

14. Includes for solid tumour patients only: CT/MRI of the chest, abdomen and pelvis [C/A/P]). The same imaging technique (CT or MRI) should be used for these patients throughout the study. CT/MRI of the brain may also be performed as per standard of care.
15. , Serum protein electrophoresis (SPEP), Urine protein electrophoresis (UPEP), Serum free light chains, 24 hour urine proteins, Bone marrow for histology, cytogenetics and FISH, and flow cytometery with or without biopsy, Beta 2 microglobulin, albumin and lactate dehydrogenase (LDH). A skeletal survey is done during Screening only; thereafter it should be done as per routine clinical practice.
16. Bone marrow assessment only to be done to confirm complete remission after two consecutive immunofluorescence analyses are negative.
17. Performed by a dermatologist. For patients who develop any suspicious new skin lesion during treatment with vemurafenib. Further confirmation by a designated central pathology laboratory. Only required at the End of Treatment visit if not performed in the previous 12 weeks. Should be done at Safety Follow-up visit at 28 days (±5 days) and at 6 months following study drug discontinuation or until initiation of another anti-neoplastic therapy.
18. Performed by the treating physician as part of the evaluation for SCC. Should also be done at Safety Follow-up visit at 28 days (±5 days) and at 6 months following study drug discontinuation or until initiation of another anti-neoplastic therapy.
19. CT of the chest for the evaluation of noncutaneous SCC (for all patients, solid tumors and MM). For patients with solid tumours, the routinely scheduled radiographic assessment for tumor burden may be used (if available) as the chest CT for the evaluation of noncutaneous SCC while the patient is taking vemurafenib.
20. Must be performed at this visit and 6 months following study drug discontinuation or until initiation of another anti-neoplastic therapy.
21. Patients will keep a diary to record ONLY those occasions when a vemurafenib dose was missed (morning or evening, each day of treatment). The patient will bring this diary with him/her to each study visit to allow missed doses to be recorded by the Investigator.
22. See Appendix 9
23. See Appendix 9 for further details. Bone scans to be performed every 8 weeks or as per institution standard of care, but at a minimum every 16 weeks and at the end of study.
24. All concomitant medications during the study started within 14 days prior to the screening visit and up to the end of study visit must be recorded.
25. During screening AEs are not recorded in the eCRF unless they are SAEs which are related to protocol-mandated procedures. ALL AEs (including SAEs) must be recorded from the time of first vemurafenib administration. After the last dose of vemurafenib any new, AEs should be reported up to 28 days after last dose. Any AEs (including SAEs) reported after last dose which the Investigator considers related to study drug must be reported indefinitely.
26. Pelvic examinations for women (with special attention to cervix) and anal examinations for all patients will be performed at screening and at the Safety follow-up visit for evaluation of SCC. The pelvic examination should include a complete external and internal examination (internal examination of uterine cervix may include a Pap smear, which would be a decision of the investigator). The anal examination should include external examination, digital anorectal examination and anoscopy or proctoscopy. However, if in opinion of the investigator the presence of "abnormal lesions including SCC" can be excluded by the external inspection and the manual examination, this is acceptable. However, if the presence of a lesion is suspected, an anoscopy or proctoscopy are recommended.
27. See Appendix 10 for further details.
28. Baseline tumor assessments must include CT/MRI of the chest, abdomen and pelvis (C/A/P) and any additional assessment as clinically relevant as described in Appendix 10 to define baseline extent of disease (brain MRI, cardiac MRI/echo, bone scan, ^{18}F-FDG PET). For patients with baseline measurable disease according to RECIST v1.1, the following tumor assessments will consist of the same method(s) used at baseline to determine measurable disease (CT/MRI of [C/A/P], brain MRI, cardiac MRI). For all other patients the following tumor assessments will consist of the same method/s used at baseline that have defined the area involved by the disease (brain MRI, cardiac MRI/echo, bone scan, ^{18}F-FDG PET, CT chest/abdomen/pelvis) as described in Appendix 10

Table 3b.
Schedule of Assessments for Cohort 3b (colorectal cohort with Vemurafenib and Cetuximab study treatment)

	Screening Period [1]	**Treatment Period** [2] **(Allowed visit window: ± 1 day starting on Day 8 of Cycle 1 and onwards)**													**End of Treatment Visit** [3]	**Safety-Follow-Up Visit** [4]	**Survival Follow-Up** [5]
Cycle (C)		1					2				3 onwards						
Study Day	–28 to –1	1	2	8	15	22	29	36	43	50						Post treatment d/c	Every 3 months
Cycle Day		1	2	8	15	22	1	8	15	22	1	8	15	22		28 (±5) days	
Informed consent [6]	X																
Documentation of BRAF V600 mutation and test performed	X																
Medical history and demographics	X																
Physical examination [7]	X	X		X	X	X	X	X	X	X	X		X		X		
Vital signs [8]	X	X		X	X	X	X	X	X	X	X		X		X		
12-lead ECG [9]	X						X				X + C4 and C5 (then Q12 weeks)				X	X	
ECOG performance status	X	X		X	X	X	X	X	X	X	X		X		X		
Hematology [10]	X	X[11]		X	X	X	X	X	X	X	X		X		X		
Biochemistry [12]	X	X[11]		X	X	X	X	X	X	X	X		X		X		
Serum pregnancy test [13]	X																
Tumor assessments (CT/MRI) [14]	X										X (Q8 weeks)				X		
Dermatology evaluation [15]	X						X				C5 (then Q12 weeks)				X	X[18]	At 6 months
Head and neck assessment for SCC [16]	X										C4 (then Q12 weeks)				X	X[18]	At 6 months

	Screening Period [1]	**Treatment Period** [2] **(Allowed visit window: ± 1 day starting on Day 8 of Cycle 1 and onwards)**													**End of Treatment Visit** [3]	**Safety-Follow-Up Visit** [4]	**Survival Follow-Up** [5]
Cycle (C)		1					2				3 onwards						
Study Day	–28 to –1	1	2	8	15	22	29	36	43	50						Post treatment d/c	Every 3 months
Cycle Day		1	2	8	15	22	1	8	15	22	1	8	15	22		28 (±5) days	
Chest CT for evaluation of SCC [17]	X										C7 (then Q6 months)					X[18]	At 6 months
Vemurafenib dispensation (**Part 1**)			X[19]				X		X		X (Q4 weeks)						
Vemurafenib dispensation (**Part 2**)		X					X		X		X (Q4 weeks)						
Vemurafenib accountability							X		X		X (Q4 weeks)				X		
Vemurafenib Dosing Exception Diary [20]				X	X	X	X	X	X	X	X (Q4 weeks)				X		
DLTs [21]				X	X	X	X										
Concomitant medications [22]	X	X													X	X	
AEs / SAEs [23]	X	X													X	X	
Cetuximab administration		X		X	X	X	X	X	X	X	X	X	X	X			
Follow-up for disease progression																	X
Survival status [5]																X	X
Next anticancer therapy																	X
Anal and pelvic exam[24]	X															X	

Notes Day 1 = first dose of study drug

1. Apart from obtaining written informed consent, no screening procedure may be performed before the patient has been confirmed to be positive for the BRAF V600 mutation. All efforts should be made to collect a tumor sample (formalin-fixed paraffin-embedded tumor tissue [FFPET] or 3-5 serially cut unstained 5-µm sections from one FFPET block) for retrospective confirmation of the BRAF mutation using the cobas 4800 V600 mutation kit. This tumor sample should preferably be from the original specimen used to detect the BRAF mutation. The original tumour block will be returned to the site.
2. Visits during the Treatment Period are to be completed on Day 1, Day 8, Day 15, Day 22, Day 29 and every 14 days thereafter until study drug discontinuation. A visit window of ± 1 day will apply starting on Day 8 of Cycle 1 and onwards.
3. The End of Treatment Visit will be performed when the patient discontinues study medication regardless of when it occurs.
4. The Safety Follow-Up Visit will be performed after 28 (±5) days from discontinuation of study medication
5. The Survival Follow-Up period will last for a minimum of 12 months after the last patient has been enrolled or until all patients have died, withdrawn consent or are lost to follow-up (whichever occurs first).
6. Informed consent must be obtained prior to performing any study procedure including Screening assessments. The date of signature on the informed consent form signifies the beginning of the 28-day Screening Period.
7. Includes the evaluation of the head, eyes, ears, nose, and throat (HEENT); cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal and neurological systems examination; and height (cm) and weight (kg). Height will only be measured during screening.
8. Includes blood pressure, heart rate, temperature and respiratory rate.
9. Includes heart rate, PR interval, QRS duration, QT and QTc intervals and ECG findings.
10. Includes hemoglobin, hematocrit, platelet count, white blood cell count (WBC) and absolute neutrophil count (ANC)
11. Hematology and biochemistry assessments must be done on Day 1, prior to cetuximab administration.
12. Includes amylase, lipase, glucose, blood urea nitrogen [BUN], creatinine or creatinine clearance, sodium, potassium, calcium, magnesium, bicarbonate ([if routinely performed on venous blood samples],), total bilirubin with fractionation into direct and indirect (if total bilirubin elevated during the study), alkaline phosphatase, AST ([SGOT]], ALT ([SGPT]]
13. Serum pregnancy test to be performed within 7 days prior to first vemurafenib administration for women with childbearing potential.
14. CT/MRI of the chest, abdomen and pelvis [C/A/P]). The same imaging technique (CT or MRI) should be used for these patients throughout the study. CT/MRI of the brain may also be performed as per standard of care.
15. Performed by a dermatologist. For patients who develop any suspicious new skin lesion during treatment with study medication. Further confirmation by a designated central pathology laboratory. Only required at the End of Treatment visit if not performed in the previous 12 weeks. Should be done at Safety Follow-up visit at 28 days (±5 days) and at 6 months following study drug discontinuation or until initiation of another anti-neoplastic therapy.
16. Performed by the treating physician as part of the evaluation for SCC. Should be done at Safety Follow-up visit at 28 days (±5 days) and at 6 months following study drug discontinuation or until initiation of another anti-neoplastic therapy.
17. CT of the chest for the evaluation of noncutaneous SCC. The routinely scheduled radiographic assessment for tumor burden may be used (if available) as the chest CT for the evaluation of noncutaneous SCC while the patient is taking study medication.
18. Must be performed at this visit and 6 months following study drug discontinuation or until initiation of another anti-neoplastic therapy.
19. For patients in Part I of Cohort 3b, vemurafenib will start on Day 2 of Cycle 1 (administered while in hospital).
20. Patients will keep a diary to record ONLY those occasions when a vemurafenib dose was missed (morning or evening, each day of treatment). The patient will bring this diary with him/her to each study visit to allow missed doses to be recorded by the Investigator.
21. Only for patients enrolled in the Part 1 of Cohort 3b (the dose-escalation part of the study)
22. All concomitant medications during the study started within 14 days prior to the screening visit and up to the end of study visit must be recorded.

23. During screening AEs are not recorded in the eCRF unless they are SAEs which are related to protocol-mandated procedures. ALL AEs (including SAEs) must be recorded from the time of first study drug administration. After the last dose of study medication any new AEs should be reported up to 28 days after last dose. Any AEs (including SAEs) reported after last dose which the Investigator considers related to study drug must be reported indefinitely.
24. Pelvic examinations for women (with special attention to cervix) and anal examinations for all patients will be performed at screening and at the Safety follow-up visit for evaluation of SCC. The pelvic examination should include a complete external and internal examination (internal examination of uterine cervix may include a Pap smear, which would be a decision of the investigator). The anal examination should include external examination, digital anorectal examination and anoscopy or proctoscopy. However, if in opinion of the investigator the presence of "abnormal lesions including SCC" can be excluded by the external inspection and the manual examination, this is acceptable. However, if the presence of a lesion is suspected, an anoscopy or proctoscopy are recommended.

3.5 Concomitant Medication

At study initiation, patients should continue with their concomitant medications, as prescribed by their physician, with the exception of study precluded medications (see below).

Due to the underlying illness and the frequency of co-existent medical conditions in this patient population, all concomitant medication or treatment required by the patient will be at the discretion of the treating physician. In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the patient are allowed, provided their use is documented in the patient records and on the eCRF.

For Cohort 3b only, prior to the first infusion of cetuximab, patients must receive premedication with an antihistamine and a corticosteroid. This premedication is recommended prior to all subsequent infusions.

See Appendix 9 of protocol for more details for prostate cancer patients.

The following medications and treatments are not allowed while the patient is on the study:

- Other anti-cancer therapies (except cetuximab for patients in Cohort 3b)
- Concomitant alternative therapies and herbal preparations
- Radiotherapy for the treatment of disease during the study; the exception will be limited field radiotherapy for palliative bone pain due to pre-existing bone metastasis if not considered a target lesion for RECIST assessments

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

All other medications (over the counter or prescription only medication) are permitted during this study at the discretion of the Investigator.

3.6 Study Analysis Populations

The main analysis population for the efficacy analysis will be the intent-to-treat (ITT) population, which will include all patients enrolled in the study irrespective of whether they have received study medication or not. ITT1, ITT2, ITT3a to ITT6 will correspond to the ITT population for each cohort (Cohort 1 to Cohort 6, respectively).

The per-protocol (PP) population will not be defined due to the small number of patients per cohort, but protocol deviations will be listed (see section 4.12).

The safety populations SP1, SP2, SP3a to SP6 will correspond to the safety populations for Cohort 1 to Cohort 6, respectively, and will include, for each cohort, all patients who have received at least one dose of study medication.

Cohort 7 (patients with other solid tumour) will include patients with different tumour types and therefore different safety/ITT populations may be defined given at least 5 patients in one indication. In case there are less than 5 patients in each indication, it will be listed together indicating tumour type into a column.

For Stage I interim analysis, all treated patients will be included in the safety analyses. For all summaries to be performed for the efficacy analysis at week 8 of Stage I, the first 7 patients enrolled into Stage I with measurable disease at baseline will be included. For all listings of efficacy analysis at stage 1, all patients available at that time will be included.

3.7 Withdrawn Patients

Patients who withdraw from the study will not be replaced.

3.8 Randomisation

This is an open label study that includes different cohorts and randomization is not applicable.

3.9 Blinding

This is an open label study. There is no blinding of study treatment.

3.10 Sample Size

The sample size estimation is based on the method of Lin and Shih (1).

There will be up to 170 patients enrolled in this study (see Table 3).

There will be 7 cohorts with patients with different indications, and two sub-cohorts with patients with colorectal cancer, one treated only with vemurafenib while other treated with vemurafenib and cetuximab.

Cohorts (except Cohort 3b) will have a minimum of 13 and a maximum of 19 patients at Stage II (depending on results in Stage I).

Cohort 3b will have a dose escalation phase based on a classical 3+3 design and will enrol a maximum of 18 patients. Cohort of patients with recommended dose will be expanded to 7 patients as per rule of Stage I design. Then a further 6 or 12 patients will be enrolled to a maximum of 13 or 19 patients will be enrolled depending on the results for stage I (see Table 3). The maximum number of patients for this cohort might be up to 37 patients.

A proportion of 15% is chosen for a low response, based on present knowledge.

If the number of responders is 2, 3, or 4 out of 7 patients of the corresponding cohort in Stage I, then the study medication is possibly efficacious for that cohort and further data at stage II will be collected based on the "low desirable response at Stage II" Sample Size estimation, i.e., an additional 12 patients will be enrolled in order to have a total of 19 patients for that cohort. Recruitment into cohort will be stopped if the number of responders is less than the pre-specified number in Table 4 (e.g. if there is none or only one responder out of first seven patients). However if a clear clinical benefit has been observed for patients in the cohort (e.g. majority of patients recorded SD at Week 8 and no CR or PR is recorded), then enrolment into Stage II will be allowed for this cohort after discussion with the Sponsor and study Steering Committee.

If there are 5 or more responders out of 7, then further data will be collected based on "high desirable response at Stage II" Sample Size estimation, i.e., an additional 6 patients will be enrolled in order to have a total of 13 patients for that cohort.

Assuming RRs as specified in the hypothesis testing as of section 3.2.1, a power of 80% for high desirable response and 70% for low desirable response and two-sided alpha of 0.1, the number of patients required in each cohort is presented in Table 3:

Table 3: Sample Size for Each Cohort

	Dose Finding*	At the end of Stage Two	
		Low desirable response	**High desirable response**
NSCLC		19	13
Ovarian cancer		19	13
Colorectal cancer (Cohort 3a vemurafenib only)		19	13
Colorectal cancer (Cohort 3b vemurafenib and cetuximab)	3+3 Design up to 18	19	13
Cholangiocarcinoma/cancer of biliary tract		19	13
Breast cancer		19	13
MM		19	13
Other tumors(cohort 7)**		19	13
Total number for the whole study	**up to 170 patients**		

* Cohort 3b Part 1 only

** The n's presented are for each individual tumor types with enough patients available to follow the 2 stage study design.

Details regarding Stage I and number of responders are displayed in Table 4:

Table 4: Sample Size for Each Cohort and Each Stage

	Stage (Two-Stage Design)		Total Number of Patients in Each Cohort	Two-Sided Alpha Level / Power
	Stage I	**Stage II [a]**		
All Cohorts				
Low response at the end of Stage I				
Number of patients	7	19	19	10% / 70%
Number of responders [b]	≥ 2 and ≤ 4	≥ 5		
High response at the end of Stage I				
Number of patients	7	13	13	10% / 80%
Number of responders [b]	≥ 5	≥ 6		

The sample size was estimated using the method of Lin and Shih (1) and corresponding SAS program.

[a] This column displays the maximum number of patients required for each cohort and the number of responders that should be present at the end of Stage II in order to declare efficacious treatment.

[b] Number of patients needed to respond in order to continue into Stage II or have a positive result at the end of the trial.

4 Statistical Methodology

4.1 Planned Analyses

The following reporting events are planned in this study for each cohort:

- Stage I analysis (8 week response available for 7 pats) (SIA)
- Stage II analysis (confirmed 8 week response available for up to 19 pts) in case Stage II is reached (SIIA)
- 6 month on treatment Stage II analysis (when last patient has been on treatment for 6 month, withdrew consent, lost to follow-up whichever occurs first) (SII6A)
- Final Analysis (FA)
- Dose Finding Analysis (only cohort 3b) (DFA)

4.2 Statistical Analyses

Statistical analyses will be performed for each cohort separately.

For the Stage II respectively final analyses, baseline characteristics and the efficacy endpoints will be summarised using the ITT populations, whilst safety variables will be summarised for the safety populations. For the cohorts, where corresponding ITT and safety populations are different, the baseline characteristics will be also summarised for the safety population.

Generally, summary statistics will be presented for continuous variables, by way of n, mean, standard deviation (SD), median, minimum and maximum and by way of group frequencies and percentages for categories of categorical variables.

Percentages will be calculated using the total patients within the respective cohort. Number and percentage of responders will be presented together with their corresponding Clopper-Pearson 95% confidence intervals.

For time to event type variables and as indicated in corresponding sections below, 95% confidence interval and Kaplan-Meier (KM) estimates will be calculated.

Due to the expected heterogenious indications in Cohort 7 (patients with other solid tumours) may not be summarised. If there are at least 5 patients in a certain tumour type, number (percentage) of patients will be summarised in frequency tables for RR at Week 8, clinical benefit rate, BOR, AEs and Treatment exposure for these tumour types. Listings will include same information as for other cohorts.

For cohort 7, the decision about further enrolment into stage II will be made for each type of tumour separately. For example, if seven patients of the same tumour type are enrolled in Stage I, then Stage I stopping rules may be applied for these patients.

4.3 Interim Analysis

Each cohort will be analysed for efficacy at the end of Stage I (SIA) and, in case enrolment continues, at Stage II when week 8 response rate can be assessed (SIIA) and after all patients have been on treatment for at least 6 months (SII6A). For Cohort 3b, the additional dose-finding Part 1 will be analysed separately (DFA) as explained in section 3.3.

No additional interim analysis for efficacy is planned in this study other than that.

4.4 Disposition of Patients

The number of screen failures, reason for screening failure, the number of patients enrolled, number and percentage in each analysis population, the reasons for discontinuation of treatment, time on treatment and the reasons for discontinuation of study will be presented (Table 14.1.1, Listing 16.2.4.1).

Time on treatment (date of last dose - date of first dose + 1) will be summarised separately for each study treatment using KM approach. Patients who withdrew will be counted as patients with events while patients who did not withdraw will be censored on the date of last study drug intake prior to cut-off date. If date of last study drug intake is partially missing then the 1st of month will be used unless using the 1st of the month produces a date before date of last former study drug intake or interruption (without stop date). In such cases, the date of last study drug intake/start of interruption will be used. If date of last dose is completely missing then the date of last study drug intake + 15 will be used.

- Date of 1st study drug intake = Day 1 of cycle.

4.5 Demographic, Baseline Information and Medical History

Following information will be summarised for each cohort, in the cases where applicable specific to each cohort:

- Demography including: gender, age, age group (<65 and >=65), race, ethnicity, smoking history, height and weight (Table 14.1.2.1, Listing 16.2.4.3)
- Patients by centre (Table 14.1.2.2, Listing 16.2.4.3)
- Cancer disease history including: number and percentage of patients by origin of primary tumour, histological tumour type and grade, stage at diagnosis and current stage (Table 14.1.4.1, Listing 16.2.4.4.1)
- Surgical resection of primary tumour including (not for cohort 6): number and percentage of patients with surgical resection of primary tumour and by type/location of resection (Table 14.1.4.2, Listing 16.2.4.4.2)
- Screening dermatology evaluation including: number and percentage of patients with any history and number and percentage of patients with a history of any of following risk factors: Sorafenib, photochemotherapy for psoriasis, chronic sun exposure, tanning beds, immunosuppresion, prior actinic keratosis, prior keratocanthoma, prior squamous cell carcinoma, prior malignant melanoma and other risk factors for cutaneous squamous cell carcinoma (Table 14.1.6, Listing 16.2.4.4.3)
- Prior systemic therapies including: number of systemic agents, number and percentage of patients previously treated with at least one systemic agent and number and percentage of patients treated with each systemic agent displayed by therapeutic class and preferred term (Table 14.1.5.1, Listing 16.2.4.5.1)
- Prior radiotherapies including: number and percentage of patients previously treated with radiotherapy and by purpose (Table 14.1.5.2, Listing 16.2.4.5.2)
- Relevant Medical and Surgical History (excluding cancer): number of clinically significant diseases, number and percentage of patients with at least one clinically significant disease and number and percentage of patients with each disease displayed by body system and preferred term for diagnosis (Table 14.1.3.1, Listing 16.2.4.6)

- Active Medical and Surgical History (excluding cancer): number of clinically significant diseases, number and percentage of patients with at least one clinically significant disease and number and percentage of patients with each disease displayed by body system and preferred term for diagnosis (Table 14.1.3.2, Listing 16.2.4.6)
- BRAF V600 Mutation Information at baseline (Table 14.1.7, Listing 16.2.4.7)

Notes:

Age will be calculated as the integer ((Date of Consent – Date of Birth) / 365.25). If the day of birth is missing, it will be replaced with the 1st of the month; if the month of birth is missing, it will be replaced with January. Age will be presented/summarised as a whole number.

Female reproduction status will be listed as part of the demography listing (Listing 16.2.4.3)

The diagnosis of the medical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

4.6 Efficacy Analysis

The efficacy parameters will be summarised for the ITT population of each cohort and presented in tables, figures and listings at different times of analysis (StageI, Stage II, 6 month on treatment Stage II analysis, Final Analysis) given there are at least 7 patients available as detailed in the following sections.

In addition for cohort 3B, response rate and best overall response rate (BORR) will be summarised by dose group.

4.6.1 Primary endpoint

Response rate (unconfirmed) at week 8 is the primary endpoint for the statistical analysis of Stage I.

For the Stage II analyses and the final analysis, confirmed response rate at week 8 is the primary endpoint.

A patient is assigned a confirmed 8 week response in case of a response assessment of either CR or PR at week 8 and at a second assessment at least 4 weeks (28 days) afterwards which confirms it. In all other cases, patients are considered non-responders at week 8. Particularly patients who receive study treatment but do not undergo a post-baseline tumor assessment will be counted as non-responders.

Unconfirmed (Stage I) respectively confirmed response (Stage II, final analysis) will be displayed in corresponding versions of Table 14.2.1.1.

Listings for overall response (Listing 16.2.6.1.1) as well as for individual assessments of target (Listing 16.2.6.2) and non-target lesions (Listing 16.2.6.3), in case of solid tumour cancers, will be provided.

Listings for overall response (Listing 16.2.6.1.2) as well as for individual assessment of Multiple myeloma (Listing 16.2.6.4 to 16.2.6.9) will be provided.

In cohort 7, patients with LCH/ECD the tumor response assessment can be based on RECIST v1.1, PERCIST v1.0 or Multiple assessments. The overall response summary table (Table 14.2.1.1) will therefore be split by method and overall results for this indication will also be put together based on Investigator assessment (responder, non responder). The pooled overall

response evaluations will be displayed in Listing 16.2.6.1.3 and the lesion evaluation via PERCIST in Listing 16.2.6.13.

The following patients will be considered as responders:

- CR or PR according to RECIST v 1.1
- CMR or PMR according to PERCIST v 1
- Responders based on Multiple assessments

In all other cases, patients are considered non-responders at week 8. Particularly patients who receive study treatment but do not undergo a post-baseline tumor assessment will be counted as non-responders.

Next anticancer therapy after discontinuation of study medication will be listed (Listing 16.2.6.10).

4.6.2 Method of analysis for primary outcome

For patients with solid tumors, responders at Week 8 will be defined based on tumor assessment status of PR or CR at Week 8. For patients with MM, responders at Week 8 will be defined based on tumor assessment status of CR, sCR, VGPR or PR.

If a pre-specified minimal RR will not be achieved in certain cohorts in the first stage of the study in certain cohorts, this cohort will be closed and no further enrolment of patients will be performed for that cohort. However, if a clear clinical benefit has been observed for patients in the cohort, e.g. majority of patients recorded SD at Week 8 and no CR or PR is recorded, then enrolment into Stage II might be allowed for this cohort after discussion with the Sponsor and study Steering Committee. In that case, stage II of that cohort would be handled like "Low response at the end of Stage I" and another 12 patients enrolled, to have 19 patients in total for that cohort.

Only patients with measurable disease at baseline will be included in the analysis of the RR. Patients without a post-baseline tumor assessment will be considered to be non-responders.

The hypotheses for all cohorts for Stage I is:

$H_0: \pi_{N1} < \pi_0$
$H_1: \pi_{N1} \geq \pi_0$

Where: N1 is the percentage of responders within the cohort and $\pi_0 = 15\%$

If H_0 is rejected (and H_1 is accepted), this may result in further patients being enrolled into Stage II of the study based on the number of responders (as of unconfirmed responses at week 8) in Stage I. As this is an early phase II study and cohorts are independent no adjustment will be made for multiplicity.

The number and percentage of responders together with the corresponding Clopper-Pearson 95% confidence interval will be presented for each cohort. In addition, the number and percentage of patients in each response category will also be presented. For cohort 3B confirmed week 8 response rate will be summarised by dose level. All response data including the number of target and non-target lesions will be listed.
Cohort 3b: For this cohort, first, the recommended dose for Stage I/II part should be established based on 3+3 classical design. Then the second part will include a stage I and II parts similar to what is planned for the other cohorts and same statistical hypotheses at Stage I and Stage II will be applied.

The percentage decrease from baseline in sum of diameters at week 8 (Figure 14.2.6.1) and the maximum percentage decrease from baseline (Figure 14.2.6.2) in sum of diameters for target lesions will be plotted in a waterfall plot. Only patients with measurable disease at baseline will be included in the graphical presentation. Bars will be coded according to confirmed and unconfirmed BOR. Maximum % decrease, confirmed BOR and unconfirmed BOR will be listed. All patients, irrespectively of measurable disease at baseline will be listed.

4.6.3 Secondary end-points

4.6.3.1 Progression free survival (PFS)

PFS, measured in days, is defined as the time from the first day of study treatment until the first documented progression of disease or death from any cause, whichever occurs first. PFS for patients who have neither progressed nor died will be censored on the date of last evaluable tumor assessment prior to the data cutoff date. Data for patients who have not died and have no recorded post-baseline tumor assessment will be censored on the date of the first dose of study medication plus 1 day. Patients who die without any recorded post-baseline tumor assessment after receiving the first dose will be considered to have an event on the date of death. Data for patients who are lost to follow-up prior to documented progression will be censored at the last evaluable tumor assessments date which the patient is known to be progression-free prior to the data cut-off date. Patients who die or have progression after two or more consecutive missed visits will be censored at the date of the last evaluable tumor assessment.

PFS will be assessed at SII6A and FA.

For each cohort estimates of the median PFS and the corresponding two-sided 95% CI will be presented along with the estimates for the 25^{th} and 75^{th} percentiles and the associated ranges (minimum, maximum) using the Kaplan-Meier (KM) approach (Table 14.2.2.1, Figure 14.2.1, Listing 16.2.6.11).

4.6.3.2 Time to progression (TTP)

Time to progression is defined as time from the first day of study treatment to the first occurrence of progressive disease. Patients who have not progressed at the time of study completion (including patients who have died before progressive disease) or who are lost to follow-up are censored at the date of the last tumour assessment prior to data cutoff. Patients who have no recorded post-baseline tumor assessment will be censored on the date of the first dose of study medication plus 1 day. Data for patients who are lost to follow-up prior to documented progression will be censored at the last evaluable tumor assessment date which the patient is known to be progression-free prior to data cutoff. Patients who have progression after two or more consecutive missed visits will be censored at the date of the last evaluable tumor assessment.

TTP will be assessed at SII6A and FA.

TTP will be analysed and presented in the same way as PFS (Table 14.2.2.2, Figure 14.2.2, Listing 16.2.6.11).

4.6.3.3 Best overall response (BOR)

BOR is defined as the best response recorded from the first day of study treatment until disease progression/recurrence, death or end of study respectively data cut-off, what ever comes first. Patients with solid tumours are considered responders if they have a tumour assessment status of PR or CR according to RECIST, v1.1. Patients with MM are considered responders if they have a status of CR, sCR, VGPR or PR according to IMWG uniform

response criteria. In the same way as for the primary endpoint RR, response must be confirmed not less than 4 weeks after the criteria for response are first met; only patients with measurable disease at baseline will be included in the analysis of the BOR; patients without a post-baseline tumour assessment will be considered to be non-responders.

The following algorithm describes how best overall response (BOR) is determined from the overall tumor assessments. The hierarchy used to determine best overall response is CR>PR>SD>PD/NE/NA/ND:

- Once a CR is observed (confirmed or unconfirmed) any unequivocal reappearance of disease results in progression. That is, neither a PR nor SD may follow a CR.
- For confirmation of PR:
  - The confirming 2nd PR needs to be consecutive tumor assessments of PR (i.e. if 1 or more SDs occur between the initial and the confirmatory PR, then the BOR will be SD, not PR).
  - A CR will confirm an unconfirmed PR.
- Unconfirmed CR or PR will be defined as a BOR of SD, provided the requirement for at least a 6-week interval since start of treatment has been respected. An unconfirmed CR or PR occurring less than 6 weeks after the start of treatment will be defined as Unevaluable.
- Once a PR is confirmed, the status shall remain PR or improve to CR until criteria for SD or PD are met.

An overall response of progressive disease that was based solely on symptomatic deterioration will not be used in the evaluation of BOR.

Patients who were enrolled and did not receive any study treatment will have a best overall response 'Missing' and will be included as non-responders in the analysis of BOR.

BOR will be assessed at SII6A and FA.

For each cohort, number and percentage of responders in BOR with corresponding Clopper-Pearson 95% confidence intervals and a summary of the number and percentage of patients categorized by confirmed BOR category will also be presented.For cohort 3b BOR will be summarised by dose level.

For patients with solid tumours, these categories are: CR, PR, SD, PD, NE; for MM patients, they are: sCR, CR, VGPR, PR, MR, No change/SD, Plateau, PD, Relapse, Relapse from CR (Tables 14.2.2.3, Listing 16.2.6.12).

The responses by visit will be listed together with BOR (Listings 16.2.6.1.1 and 16.2.6.1.2).

As with response at week 8, in cohort 7, patients with LCH/ECD could be assessed using different methods RECIST v1.1, PERCIST v1.0 or Multiple assessments. The Best overall response summary tables (Table 14.2.2.3) for this cohort will therefore again be split by method and Overall results for this indication will also be put together based on Investigator assessment (responder, non responder). Same rules apply as for response at week 8.

4.6.3.4 Clinical benefit rate (CBR)

Clinical benefit response includes patients whose best response was:

- Confirmed PR (or VGPR) or
- Confirmed CR (or sCR) or

- Stable disease (SD) that have lasted at least 6 weeks.

For the purpose of the stage I analysis clinical benefit response (at week 8) is defined as:

- Unconfirmed PR (or VGPR) or
- Unconfirmed CR (or sCR) or
- Stable disease (SD) that have lasted at least 6 weeks.

In the same way as for the primary endpoint RR and for BOR, response must be confirmed not less than 4 weeks after the criteria for response are first met; only patients with measurable disease at baseline will be included in the analysis of the CBR; patients without a post-baseline tumour assessment will be considered to be CRB non-responders.

CBR will be assessed at SIA, SIIA, SII6A and FA.

For each cohort, CBR with corresponding Clopper-Pearson 95% confidence will also presented (Table 14.2.2.3, Listing 16.2.6.1.1 and 16.2.6.1.2).

4.6.3.5 Time to response (TTR)

Time to response is defined as the time from the first day of study treatment to the first date the response criteria are met, given they were later confirmed. Patients who are not confirmed responders will be censored at the time of their last evaluable tumour assessment. Patients with no tumour assessment after the baseline visit will be censored at the time of the first day of study treatment plus 1 day.

TTR will be assessed at SII6A and FA.

TTR will be analysed and presented in the same way as PFS (Table 14.2.2.4, Figure 14.2.3, Listing 16.2.6.12).

4.6.3.6 Duration of response (DOR)

Duration of response in BOR is defined only for the patients whose confirmed best response is CR or PR, as the time interval between the date of the earliest qualifying response (according to RECIST, v1.1 for patients with solid tumours and according to IMWG uniform response criteria for patients with MM) and the date of PD or death from any cause, whichever occurs first. For patients who are alive without progression following the qualifying response, DOR will be censored on the date of last evaluable tumor assessment or last follow-up for PD before the data cutoff date. Data for patients who are lost to follow-up prior to documented progression will be censored at the last tumor assessment date which the patient is known to be progression-free prior to the data cutoff date.

Note that if an overall assessment of PR occurs before confirmation of CR, the duration of response endpoint will not begin at the time that the BOR of CR is shown but rather at the earlier time point showing PR.

DOR will be assessed at SII6A and FA.

Estimates of the median duration of response and the corresponding two-sided 95% confidence interval will be presented along with the estimates for the 25th and 75th percentiles and the associated ranges (minimum, maximum). The survivor function will be displayed graphically using a Kaplan-Meier curve.

DOR will be analysed and presented in the same way as PFS (Table 14.2.2.5, Figure 14.2.4, Listing 16.2.6.12).

4.6.3.7 Overall survival (OS)

OS (time to death) is defined as time between the first day of study treatment and date of death of any cause. Patients for whom no death is captured on the clinical database are censored at the last date they were known to be alive. Patients with no post baseline information will be censored at the time of first study treatment plus 1 day.

OS will be assessed at FA.

OS will be analysed and presented in the same way as PFS (Table 14.2.2.6, Figure 14.2.5, Listing 16.2.6.11).

4.6.4 Stopping Rules

Stopping Rules for Enrolment and Screening

If no patients are enrolled in the remaining cohorts one year after any of the cohorts has completed enrolment, then enrolment in those remaining cohorts will be stopped (patients already in screening will be allowed to enroll if eligible).

Individual cohorts will stop enrollment once 7 patients with evaluable disease at basleine have been enrolled into that cohort, to allow for the stage I analysis before progressing to stage II.

Rules for Stage I

Enrollment into Stage I will be stopped if the number of (unconfirmed) responders is less than the pre-specified number in table 4 (e.g. if there is none or only one responder out of first seven patients). However if a clear clinical benefit has been observed for patients in the cohort, e.g. the majority of patients recorded SD at Week 8 and no CR or PR is recorded, then enrolment into Stage II might be allowed for this cohort.

If the required response during Stage I or a good clinical benefit is observed for a particular cohort as mentioned above, then additional patients will be enrolled in the second stage of the corresponding cohort, in order to achieve total number of patients required as specified in the Tables 3 and 4 (cf. section Sample Size 3.10).

Cohort 7 will be closed to enrolment when all other cohorts are closed and results are reported, regardless of the number of patients recruited at that time. This cohort may be quite heterogeneous and will be examined primarily to seek efficacy signals in the relatively rare BRAF V600 mutation-positive tumours.

Rules for Stage II

A study treatment will be considered to be efficacious in a cohort in Stage II if

- there is no unacceptable toxicity

and

- the number of responders is equal or above the specified number in the sample size calculations, as presented in Table 4

or

- BOR (confirmed) is higher than 15%.

4.7 Safety Analysis

All safety variables will be summarised for the safety population of each cohort.

For cohort 3b, all safety summaries will be done by dose level and overall column.

4.7.1 Adverse events

Only treatment emergent AEs (AEs occurring on the day of or after first administration of any study treatment) will be included in the AE and SAE summaries. Where an AE start date is partially or fully missing, and it is unclear as to whether the AE is treatment emergent, it will be assumed that it is.

Intensity of all adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events, Version 4.0 (CTCAE, v4.0) on a five-point scale (Grade 1 to 5).

All AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

All adverse events (Table 14.3.1.1) as well as serious adverse events (SAE) (Table 14.3.1.2) will be summarised by presenting the number and percentage of patients having any event, having an event leading to discontinuation of any study drug, by CTC grade, by relationship to any study drug and outcome.

AEs will be summarised separately for each cohort by presenting the number and percentage of patients having any event as well as number of events, by event in each MedDRA system organ class (SOC) and preferred term (PT) for the following subgroups:

- Adverse Events by System Organ Class (SOC) and Preferred Term (PT) (Table 14.3.2.1)
- Adverse Events with CTC Grade 1 or 2 by SOC and PT (Table 14.3.2.2.1)
- Adverse Events with CTC Grade 1 or 2 by CTC Grade, SOC and PT (Table 14.3.2.2.2)
- Adverse Events with CTC Grade 3 or 4 by SOC and PT (Table 14.3.2.3.1)
- Adverse Events with CTC Grade 3 or 4 by CTC Grade, SOC and PT (Table 14.3.2.3.2)
- Serious adverse events by SOC and PT (Table 14.3.2.4)
- AEs leading to study drug interruption by SOC and PT (Table 14.3.2.5)
- AEs leading to study drug discontinuation by SOC and PT (Table 14.3.2.6)
- AEs leading to study drug interruption or discontinuation by SOC and PT (Table 14.3.2.7)
- AEs leading to study drug reduction by SOC and PT (Table 14.3.2.8)
- AEs leading to death by SOC and PT (Table 14.3.2.9)
- Related AEs by SOC and PT (Table 14.3.3.1)
- AEs Related to Vemurafenib by SOC and PT (Table 14.3.3.1.1) (only Cohort 3B)
- AEs Related to Cetuximab by SOC and PT (Table 14.3.3.1.2) (only Cohort 3B)

- AEs Related to Vemurafenib and Cetuximab by SOC and PT (Table 14.3.3.1.3) (only Cohort 3B)
- Related AEs with CTC grade 1 or 2 by SOC and PT (Table 14.3.3.2.1)
- Related AEs with CTC grade 1 or 2 by CTC grade, SOC and PT (Table 14.3.3.2.2)
- Related AEs with CTC grade 3 or 4 by SOC and PT (Table 14.3.3.3.1)
- Related AEs with CTC grade 3 or 4 by CTC grade, SOC and PT (Table 14.3.3.3.2)
- Related Serious Adverse Events (SAEs) by SOC and PT (Table 14.3.3.4)
- Related AEs leading to study drug interruption by SOC and PT (Table 14.3.3.5)
- Related AEs leading to study drug discontinuation by SOC and PT (Table 14.3.3.6)
- Related AEs leading to study drug interruption or discontinuation by SOC and PT (Table 14.3.3.7)
- Related AEs leading to study drug reduction by SOC and PT (Table 14.3.3.8)
- Related AEs leading to death by SOC and PT (Table 14.3.3.9)

A patient with more than one occurrence of the same AE in a particular system organ class respectively preferred term will be counted only once in the total of those experiencing AEs in that particular system organ class. If a patient experiences the same adverse event at more than one CTC grade level, or with more than one relationship to study drug, the most severe rating or the stronger causal relationship to study drug will be given precedence. Any missing CTC grade, causality, or outcome will not be imputed and classed as unknown.

Related refers to those events that there is a reasonable suspected causal relationship to the respective study medication, or with an unknown relationship.

Progression of underlying malignancy will not be reported as an AE if it is clearly consistent with the suspected progression of the underlying cancer; also deaths and hospitalizations solely due to PD may not be reported as SAEs. Clinical symptoms of progression may be reported as AEs if the symptom cannot be determined as exclusively due to the progression of the underlying disease, or does not fit the expected pattern of progression for the disease. If there is any uncertainty about an AE being due only to the disease under study, it will be reported as an AE or SAE.

4.7.1.1 AEs of special interest (AESI)

A summary table of the number and percentage of patients having AEs of special interest and the number of events will be presented by AE of special interest group and preferred term (Table 14.3.4.1).

A summary of the number and percentage of patients in each AE of special interest group and preferred term will also be summarized by NCI CTCAE Grade. Patient having multiple occurrences of AEs in the same AE group will presented only once using the most severe CTC grade (Table 14.3.4.2).

AEs of Special Interest for Statistical Analysis Purposes

The following AE preferred terms are defined as being of special interest for statistical analysis purposes. Terms may be added to the definitions when the data are reviewed prior to analysis. For new primary melanoma and second primary malignancy only cases that are confirmed following medical review will be included.

- cSCC (search terms: bowen's disease, keratoacanthoma, lip neoplasm, lip neoplasm malignant stage unspecified, squamous cell carcinoma of skin, cutaneous squamous cell carcinoma, treatment related secondary malignancy, squamous cell carcinoma in situ of skin, carcinoma in situ of the skin, basal cell carcinoma, neuroendocrine carcinoma of the skin)
- rash (search terms: dermatitis, dermatitis, bullous, dermatitis contact, erythema, folliculitis, generalized erythema, palmar erhytema, plantar erhytema, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash maculovesicular ,vasculitic rash; rash morbilliform, butterfly rash, rash papular, rash paplosquamous , rash pruritic, rash pustular, rash vesicular, dermatitis acneiform, rash generalised, dermatitis exfoliative, skin exfoliation, exfoliative rash, erythema multiforme, dermatitis atopic, drug rash with eosinophilia and systemic symptoms, dermatitis allergic, palmar-plantar erythrodysaesthesia syndrome, urticaria, eczema, eczema numular, erythema nodosus)
- photosensitivity (search terms: photosensitivity allergic reaction, photosensitivity reaction, sunburn, photodermatosis, actinic keratosis, solar dermatitis, xeroderma, actinic cheilitis, solar lentigo)
- liver function abnormalities (search terms: alanine aminotransferase increased, alanine aminotransferase, alanine aminotransferase abnormal, aspartate aminotransferase increased, aspartate aminotransferase, aspartate aminotransferase abnormal, alkaline phosphatase increased, blood alkaline phosphatase increased, blood alkaline phosphatase, blood bilirububin increased, increased bilirubin intermittent, bilirubin unconjugated increased bilirubin conjugated increased, blood bilirubin, bilirubin increased , hyperbilirubinaemia, jaundice, hepatic enzyme increased, blood creatine phosphokinase increased, transaminases, hypertransaminasaemia, transaminase abnormal, hepatotoxicity, drug-induced liver injury, hepatomegaly, cholelithiasis, cholestasis, hepatic function abnormal, hepatitis, hepatocellular injury, cholecystitis, cholecystitis acute, bile duct obstruction, liver disorder, portal vein thrombosis, liver function test abnormal, hepatic failure, granulomatous liver disease, hepatic cirrhosis, hepatic steatosis, hepatitis toxic)
- arthralgia (search terms: arthralgia, swallowed hurting joints, artralgia (shoulder))
- fatigue (search terms: asthenia, fatigue, lethargy, listless, malaise, sluggishness, chronic fatigue syndrome)
- prolongation of cardiac repolarization or arrhythmia (search terms: torsade de pointes/QT prolongation (SMQ): electrocardiogram QT interval abnormal, electrocardiogram QT prolonged, long QT syndrome, long QT syndrome congenital, torsades de pointes, ventricular tachycardia, cardiac arrest, cardiac death, cardiac fibrillation, cardio-respiratory arrest, electrocardiogram QRS complex prolonged, electrocardiogram T wave inversion, conduction disorders, atrial fibrillation, sinus tachycardia, atrial flutter, arrhythmia, supraventricular tachycardia, ventricular extrasystoles, bundle branch block left, cardiac arrest, sinus bradycardia, atrioventricular block, atrioventricular block first degree, bundle branch block right, extrasystoles, atrial tachycardia, bifascicular block, bradyarrhythmia, electrocardiogram QT interval abnormal, electrocardiogram, electrocardiogram repolarisation abnormality, electrocardiogram U-wave abnormality, electrocardiogram U-wave biphasic, loss of consciousness, sudden cardiac death, sudden death, syncope, ventricular arrhythmia, ventricular fibrillation, ventricular) flutter, ventricular tachyarrhythmia, tachyarrhythmia)

- new primary melanoma (search terms:, malignant melanoma, malignant melanoma in situ, dysplastic naevus, superficial spreading melanoma stage I, superficial spreading melanoma stage unspecified, cutaneous metastatic melanoma, melanoma in situ, any term containing "melanoma")
- non-cutaneous SCC (search terms: Search for records where the preferred term (PT) OR the verbatim term contains at least one of the following: 'cancer', 'carcinoma', 'neoplasm' or 'malig'. Exclude records where: PT='basal cell carcinoma', PT contains the text 'skin' or 'cutaneous', Verbatim term contains the text 'skin' or 'cutaneous', squamous cell carcinoma (not specified))
- second primary malignancies (search terms: Malignant Tumours SMQ plus Tumours of Unspecified Malignancy SMQ)
- Pancreatitis (search terms: acute pancreatitis, chronic pancreatities, elevated lipase, elevated amylase)

All AE information collected (AE start and stop dates, initial intensity, most extreme intensity, relationship, outcome, any dose adjustment of any study drug, whether concomitant medication was taken) will be listed. SAE's and non treatment emergent AEs will be identified in the listings. The following listings will be prepared for AEs:

- All AEs (Listing 16.2.7.1.1)
- SAEs (Listing 16.2.7.1.2)
- AEs leading to dose reduction or temporary treatment interruption (Listing 16.2.7.1.3)
- AE leading to permanent treatment discontinuation (Listing 16.2.7.1.4)
- AE leading to death (Listing 16.2.7.1.5)

Time to first incidence (days) and cumulative dose to the first incidence will be summarised at Stage II (Table 14.3.4.3) for the following AEs of special interest for statistical analysis purposes using descriptive statistics:

- cSCC

Estimates of the median time to first incidence and the corresponding two-sided 95% CI will be presented along with the estimates for the 25^{th} and 75^{th} percentiles and the associated ranges (minimum, maximum). The survivor function will be displayed graphically using a KM curve. Patients without an event will be censored on the date of last contact. AEs with missing or partial start dates will be included in the count of events, time to first occurrence will be calculated based on an imputed date: if the day is missing, it will be replaced with the 1st of the month; if the month is missing, it will be replaced with January. If this results in a negative value the date of first dose will be used.

Cumulative dose to the first incidence will be summarised as a continuous variable.

4.7.1.2 Dose limiting toxicities (DLT)

Particularly for Cohort 3b, part 1, i.e. the dose-finding part of the study, the DLTs as defined in Section 3.3.3 will be summarised and listed by dose levels (Table 14.3.5.1**Error! Reference source not found.**, Listing 16.2.7.1.6).

4.7.1.3 Infusion-related AEs during or within 24h after Cetuximab infusion

For Cohort 3b, infusion-related AEs during or within 24h after Cetuximab infusion will be summarised and listed by dose levels and cycle (Table 14.3.5.2, Listing 16.2.7.1.7).

4.7.2 Laboratory findings

Absolute values and changes from baseline of the laboratory parameters will be summarised by visit:

Haematology (Table 14.3.6.1, Listing 16.2.7.3.1):

- Haemoglobin
- Haematocrit
- Platelet count
- White blood cell (WBC) count
- Absolute neutrophil count (ANC)

Biochemistry (Table 14.3.6.3, Listing 16.2.7.3.2):

- Glucose
- C - reactive protein
- Blood Urea Nitrogen (BUN)
- Creatinine
- Creatinine Clearance
- Sodium
- Potassium
- Calcium
- Magnesium
- Bicarbonate (if done in venous blood)
- Total bilirubin (direct/indirect)
- Alkaline phosphatase
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Lipase
- Amylase

For all laboratory parameters, shift tables will be presented comparing NCI-CTC grade at baseline to the worst grade during the treatment period.will be presented (Tables 14.3.6.2 and 14.3.6.4).

At SIA, for each patient, the laboratory values, standardised by upper normal range, at stage II only will also be graphically displayed over time, including some basic demography info of the corresponding patient:

- Figure with the four liver function tests, i.e. AST, ALT, total bilirubin, alkaline phosphatase (Figure 14.3.).
- Figure with creatinine test (Figure 14.3.).

Liver Function Test Abnormalities (Table 14.3.4.4.1 and 14.3.4.4.2)

At Stage II only, the number and percentage of patients who experience worsening of liver function tests (AST, ALT, total bilirubin, direct and indirect bilirubin, alkaline phosphatase) after start of study treatment and the number and percentage of patients who experience worsening of each individual liver function test will be summarized. Worsening is defined as at least one grade increase in lab value on-study compared to the baseline grade

For patients who experienced a worsening, time to first worsening and time to return to baseline grade will be summarized as well as the number of times a worsening occurred (number and percentage of patients). A second, third worsening is counted only after the previous worsening has returned to baseline grade.

The number and percentage of patients who experience worsening of liver function tests (AST, ALT, total bilirubin, alkaline phosphatise) afer start of study treatment willb e summarized. Worsenings of one grade from baseline and worsenings of two or more grades from baseline will be presented.

Patients with at least 2 concurrent liver function test worsenings (AST, ALT, total bilirubin, alkaline phosphatase) will be listed by visit.

Notes:
- All results outside predefined normal ranges will be flagged in the data listings.
- For repeat or unscheduled laboratory assessments, the worst value between the corresponding scheduled visit and before following scheduled visit will be used for summaries.
- Unscheduled assessments with missing assessment date will not be included in summaries.
- Any other laboratory test results will be listed only.

4.7.3 ECG

ECG parameters heart rate, PR interval, QRS duration, QT interval and QTcF interval will be summarised by visit over time (Table 14.3.7.1). ECG findings (normal, abnormal but not clinically relevant and abnormal and clinically relevant) will also be assessed over time (Table 14.3.7.2).

The corrected QT interval QTcF will be derived from QT and RR values, using Fridericia's formula:

QTcF = QT / RR^1/3,

where RR = 60 / heart rate.

The number and percentage of patients whose ECG recordings meet any of the following criteria will be summarised over time (Table 14.3.7.3):

- Absolute QTcF values > 450 msec, > 480 msec and > 500 msec
- Change from baseline in QTcF interval > 30 msec and > 60 msec

The number and percentage of patients who experience QTcF > 500 ms after start of study treatment will be summarised. For those patients time to first elevated result and time to return to baseline (or < 450 ms) will be summarised (Tables 14.3.7.4).

For patients with absolute QTcF > 500 ms, additional summaries and listings will be provided:

- cardiac history (Table 14.3.7.5)
- concomitant medications (Table 14.3.7.6)
- cardiac events

All ECG parameters will also be listed for each assessment (Listing 16.2.7.5).

Note:
- For unscheduled ECG assessments, the worst value between the corresponding scheduled visit and before following scheduled visit will be used for summaries.
- Unscheduled assessments with missing assessment date will not be included in summaries.

4.7.4 Vital signs

Results and change from baseline for vital signs (systolic and diastolic blood pressure, pulse, respiratory rate and temperature) will be summarised by visit (Table 14.3.8, Listing 16.2.7.6).

Note:
- For unscheduled vital sign assessments, the worst value between the corresponding scheduled visit and before following scheduled visit will be used for summaries.
- Unscheduled assessments with missing assessment date will not be included in summaries.

4.7.5 ECOG Performance Status

ECOG performance status (Grade 0 - Grade 5) will be be summarised by visit by presenting the number and percentage of patients in each category (Table 14.3.9, Listing 16.2.7.4). For Stage II and in the final analysis, percentage of patients in each category will be presented graphically with bar charts over time (Figure 14.3.).

Note:
- For unscheduled ECOG assessments, the worst value between the corresponding scheduled visit and before following scheduled visit will be used for summaries.
- Unscheduled assessments with missing assessment date will not be included in summaries.

4.7.6 Dermatology evaluation

Dermatological evaluations will be summarised for each assessment point by

- number and percentage of patients with and without skin lesions (baseline lesions at screening/new lesions at post-screening visits)
- number and percentage of patients with skin lesions at each site (back, torso, breast, leg, arm, face, scalp, neck and other),
- number and percentage of patients with lesions which were biopsied/excised and sent for local pathological evaluation,
- number and percentage of patients by pathology diagnosis (cSCC, cSCC in situ (also known as Bowen's disease), cSCC - Keratoacanthoma type, Actinic keratosis, Basal cell carcinoma, Malignant Melanoma and other),
- number and percentage of patients with biopsied lesions sent to the central laboratory

(Table 14.5.1, Listing 16.2.7.7)

Notes:
- For unscheduled post-baseline dermatological evaluations, the lesions discovered resp. confirmed between two scheduled visits will be attributed to the former scheduled visit for summaries.
- Unscheduled assessments with missing assessment date will not be included in summaries.

4.7.7 Head and Neck Assessment for Squamous Cell Carcinoma (SCC)

Head and neck assessments for SCC will be summarised for each assessment point by

- number and percentage of patients with head and neck exam performed
- number and percentage of patients with suspicion of SCC found
- number and percentage of patients with suspicion confirmed by local pathology laboratory

- number and percentage of patients by outcome diagnosis of local pathology laboratory
- number and percentage of patients with biopsied lesions sent to the central laboratory

(Table 14.5.2, Listing 16.2.7.8)

Notes:
- For unscheduled post-baseline head and neck assessments, the lesions discovered resp. confirmed between two scheduled visits will be attributed to the former scheduled visit for summaries.
- Unscheduled assessments with missing assessment date will not be included in summaries.

4.7.8 Chest CT for Evaluation of SCC

Chest CT for Evaluation of will be summarised for each assessment point by

- number and percentage of patients with a chest CT scan performed
- number and percentage of patients with suspicion of SCC found
- number and percentage of patients with suspicion confirmed by local pathology laboratory
- number and percentage of patients by outcome diagnosis of local pathology laboratory
- number and percentage of patients with biopsied lesions sent to the central laboratory

(Table 14.5.3, Listing 16.2.7.9)

Notes:
- For unscheduled post-baseline head and neck assessments, the lesions discovered resp. confirmed between two scheduled visits will be attributed to the former scheduled visit for summaries.
- Unscheduled assessments with missing assessment date will not be included in summaries.

4.7.9 Pelvic and Anal Examination for SCC

Pelvic and anal examination for SCC will be summarised for each assessment point by

- number and percentage of patients with a pelvic resp. anal examination performed
- number and percentage of patients with suspicion of SCC found
- number and percentage of patients with suspicion confirmed by local pathology laboratory
- number and percentage of patients by outcome diagnosis of local pathology laboratory
- number and percentage of patients with biopsied lesions sent to the central laboratory

(Tables 14.5.4 and 14.5.5, Listings 16.2.7.10 and 16.2.7.11)

4.7.10 Physical examination

Physical examination results at each visit will be listed only (Listing 16.2.7.12).

4.8 Deaths

All cases of death will be summarised by primary cause of death, underlying cause and relationship to study medication and listed, independently whether considered an AE/SAE or not (Table 14.4, Listing 16.2.7.2.1).

Deaths within 30 days of start of treatment, within 28 days and within 60 days after last administration of study drug will be listed separately (Listings 16.2.7.2.2, 16.2.7.2.2, 16.2.7.2.3, 16.2.7.2.4).

Other primary cause of death and other underlying cause will be coded using MedDRA dictionary.

4.9 Concomitant Medication and Medical Procedures

Incidence of prior and concomitant medication will be presented by therapeutic area and preferred drug name (Tables 14.6.1 and 14.6.2, Listing).

Prior medications are those that stopped before the date of first dose of study medication; concomitant medications are all medications taken during the study, including those started before but ongoing at first dose of study medication.

Where a medication end date is partially or fully missing, and it is unclear as to whether the medication is prior or concomitant, it will be assumed that it is concomitant.

Concomitant surgical procedures and concomitant radiotherapy will be listed (Listings 16.2.8.2 and 16.2.8.3) and summarised (Table 14.6.3) by

- number and percentage of patients with radiotherapy.
- number and percentage of patients with a surgical procedure
- number and percentage of patients with a surgical procedure involving either a target or a non-target lesion
- number and percentage of patients with a surgical procedure involving a target lesion
- number and percentage of patients with a surgical procedure involving a non-target lesion
- number and percentage of patients with radiotherapy.

Notes: Medications are coded using WHO Drug dictionary.

4.10 Exposure

Information concerning treatment with Vemurafenib will be summarised for each cohort, presenting (Table 14.7.1)

- cumulative dose
- treatment duration (i.e. including treatment interruption)
- treatment exposure (i.e. excluding treatment interruption)
- average total dose per day including treatment interruptions
- average total dose per day excluding treatment interruptions
- dose intensity

Information concerning treatment modification of Vemurafenib will be summarised for each cohort, presenting (Table 14.7.2)

- patients with at least one dose modification
- reason for dose modification
- patients with at least one dose interruption

- reason for dose interruption
- maximum duration of interruption:
  - as continuous variable
  - by categories (< 1week, 1 week to < 2 weeks, >= 2 weeks)
- last daily dose received.

For cohort 3b, treatment with Cetuximab will be summarised, presenting (Tables 14.7.3)

- cumulative dose
- treatment duration
- number of infusions
- average actual dose delivered per cycle.

Information concerning treatment modification of Cetuximab will be summarised for cohort 3b, presenting (Table 14.7.4)

- patients with at least one temporary infusion interruption
- reason for temporary infusion interruption
- patients with at least one permanent infusion interruption
- reason for permanent infusion interruption
- last Planned Weekly Dose.

Treatment duration refers to days from date of first to date of last administration of study treatment or date of data cut-off (DDMMMYYYY), whatever comes first.

Treatment exposure is the number of days during which patients actually take study treatment; any days without dose taken are not counted.

Dose intensity is defined as:

total actual doses taken / total planned doses * 100%

with

total planned doses = prescribed doses * planned days on treatment

where planned days on treatment are defined as the interval between date of first dose and earliest of (date of last treatment, date of last contact or date of death).

If date of last dose of Vemurafenib is partially missing then the 1st of month will be used unless using the 1st of the month produces a date before date of last administration/interruption (without stop date). In such cases, the date of last administration/start of interruption will be used. If date of last dose is completely missing then the date of Day 1 of last cycle + 15 will be used, last cycle being the last one for which medication as been administered.

If date of last infusion of Cetuximab is partially missing then date of former infusion plus 1 week will used instead.

The following treatment exposure information will be listed:

- For Vemurafenib: duration of exposure, duration of treatment, initial dose, any dose modifications, interruptions or missed doses, together with reasons (Listing 16.2.5.1)

- For Cetuximab: duration of treatment, number of infusions, loading and planned weekly dose, infusion start and stop data-time, infusion duration, actual dose delivered, any dose temporary or permanent infusion interruptions and infusion-related AEs (Listing 16.2.5.2)
- Permanent discontinuations from study medication (Listing 16.2.5.3)

4.11 Adjustment for Covariates

N/A

4.11.1 Centre effects

No assessment of centre effects will be made due to low patient numbers within cohorts.

4.12 Protocol Violations

No per-protocol (PP) population is defined but major protocol violations will be identified, summarised and listed (Table 14.1.2.3, Listing 16.2.4.2.4).

The following are classed as violations but this list may be added to (prior to database lock):

- failure to comply with inclusion/exclusion criteria
- prohibited concomitant medication (e.g., new anti-cancer therapy) received.

4.13 Missing Values – Missing Visits

For partially missing dates for efficacy endpoints, the following imputation rules will be used: if the day of the month is missing, but month and year are known (UN-MMM-YYYY), it will be imputed by the 1st of the month (01-MMM-YYYY). If this implementation rule produces a date before start of treatment, then the date of start of treatment.

In case of missing information for AEs, this will be treated as described in section 4.7.1.

Other missing dates will be used as such.

4.14 Deviations from SAP

Any deviations from the original statistical plan will be described and justified in the final clinical study report, whether written post interim or final analysis.

4.15 Changes in Conduct or Planned Analyses from the Protocol

There have been no changes in analyses from those defined in the protocol.

4.16 Algorithms/SAS Codes

- **Tables that need descriptive statistics – continuous variables:**

```
PROC UNIVARIATE DATA=DSET NOPRINT;
    VAR VAR1 VAR2 VAR3 … VARN;
    BY BYVAR; (optional)
    OUTPUT OUT=OUTNAME
    N=N MEAN=MEAN MIN=MIN MAX=MAX MEDIAN=MEDIAN  STD=STD;
RUN;
```

- **Tables that need frequency counts:**
  PROC FREQ DATA=DSET NOPRINT;
  BY BYVAR; (optional)
  *TABLES VAR1*VAR2;*
  OUTPUT OUT=OUTNAME;
  RUN;

- **Tables that need 95% Clopper Pearson CIs for binomial proportions:**
  PROC FREQ DATA=DSET;
  BY BYVAR; (optional)
  TABLES VAR1 / BINOMIAL ALPHA=0.05;
  RUN;

- **Tables that need life table with estimates of survival, with CIs:**
  PROC LIFETEST DATA=DSET OUTSURV=LIFE METHOD=KM;
  *TIME time to response*censor (0 or 1);*
  ID patient;
  RUN;

5 Tables, Listings and Figures

Outputs will be produced for each cohorts separately indicating the indication studied in the 2nd subtitle respectively.

For cohort 3B, during part 1 of the study (Dose finding), the summaries for the different dose cohorts will be presented as treatment arms in columns, including a total column. Listings of Cohort 3B, during part 1 of the study will be sorted by dose cohort and include the column 'Dose cohort' to indicate which dose cohort the patient was enrolled to.

For Stage I interim analysis, all treated patients will be included in the safety analyses. For the summaries to be performed for the efficacy analysis at week 8 of Stage I, the first 7 patients enrolled into Stage I with measurable disease at baseline will be included. For all listings of efficacy analysis at stage 1, all patients available at that time will be included.

For Cohort 7 (patients with other solid tumours), if there are at least 5 patients in a certain tumour type, number (percentage) of patients will be summarised in frequency tables for RR at Week 8, clinical benefit rate, BOR, AEs and Treatment exposure for these tumour types. In case different tumour types within cohort 7 have less than 7 patients available only listings will be provided. Listings will include a column indicating which 'tumor type' the individual patients were diagnosed with.

In all listings the column 'Stage' will be added indicating if patient was enrolled at Stage I 'I', in between '' or Stage II 'II' respectively.

5.1 Format

All output will be produced using SAS version 9.2 or a later version.

Each output will state the cut-off date respectively and date of extraction from database.

In the top left portion of each table/listing, a *table/listing number* followed by the *title* of the table/listing will be presented. After the title line, optional *sub-title* or *population* information can be presented. Horizontal lines will appear before and after the column heading of the table/listing. *Footnotes* will be put under the main body of text at the bottom of the page.

The *sponsor name*, *protocol number*, programmers User ID, status of the table/listing (i.e. draft or final) and *SAS program name* will appear bottom left in a string and the *page number* will appear on the bottom right corner of each table/listing. The *date and time of creation* of table/listing will appear bottom left under the sponsor name. The source listing number will appear bottom left.

A *landscape layout* is proposed for both table and listing presentations.

The *left* and *right margins* of all tables and listings will be a minimum of 2.1 cm from the left and 1.9cm from the right. The *top and bottom margins* will be a minimum 2.92cm. *Header and footer* will be both 1.27 cm.

There is no special requirement of *font type* and *size*, but an *8-point* font size for tables and *7*or *8-point* for listings is proposed using *Courier New* font. A maximum SAS line size=141 and page size=45 for *8-point* font size, and line size=161 and page size=54 for *7-point* will be used so as to fit on both UK and US paper sizes.

In a listing, in the case that a patient's record has been continued to the next page, an appropriate identification (e.g., the patient ID number) must be presented at the beginning of that page.

5.2 Conventions

Unless otherwise specified, in summary tables of continuous variables, the minimum and maximum values will be displayed to the same number of decimal places as the raw data, the mean and median will be presented to one extra decimal place compared to the raw data, and the standard deviation will be displayed to two extra decimal places compared to the raw data. Wherever possible the data will be decimal aligned.

Unless otherwise specified frequency tabulations will be presented by number and percentage, where the percentage is presented in brackets to 1 decimal place.

All tables will have their source listing referenced in a footnote. In general listings will be sorted by patient ID number with the following exceptions. For patient listings of dose cohort 3b, it will be sorted by dose cohort followed by the patient ID number. For patient listings of cohort 7, it will be sorted by tumor type followed by patient ID number. All outputs have the cut-off date referenced in a footnote. All tables, listings and figures, as applicable, will be converted into Microsoft Word documents and collated into two or three complete documents.

5.3 Tables

All tables below will be presented for all cohorts that enrol at least 7 patients.

For cohorts with less than 7 patients tables are going to be presented according to section 4.1.

Outputs will be produced as indicated below for the respective analyses:

- SIA – Stage I analysis
- SIIA – Stage II analysis after all patients completed 8 weeks
- SIIA – Stage II analysis after all patients completed 6 months
- FA – Final Analysis
- DF – Dose-finding
- Opt. – optional

5.3.1 Demographic and Baseline Information

Demographic and baseline information tables will be produced for the ITT population and in case of cohort where ITT and safety population are different also for safety population.

Table no.	Title	Produced for:
14.1.1	Patient Disposition	SIA, SIIA, SII6A, FA
14.1.2.1	Patient Demography	SIA, SIIA, SII6A, FA
14.1.2.2	Enrolment by Country and Center/Investigator	FA
14.1.2.3	Protocol Violations	SIIA, SII6A, FA
14.1.3.1	Relevant Medical and Surgical History (excluding cancer)	SIIA, SII6A, FA
14.1.3.2	Active Medical and Surgical History (excluding cancer)	SIIA, SII6A, FA
14.1.4.1	Cancer Disease History	SIA, SIIA, SII6A, FA
14.1.4.2	Surgical Resection of Primary Tumour	SIIA, SII6A, FA
14.1.5.1	Prior Systemic Therapies	SIA, SIIA, SII6A, FA
14.1.5.2	Prior Radiotherapy	SIIA, SII6A, FA
14.1.6	Screening Dermatology Evaluation	SIIA, SII6A, FA
14.1.7	BRAF V600 Mutation Type and Test	SIIA, SII6A, FA

5.3.2 Efficacy

Efficacy tables will be produced for the ITT population.

14.2.1.1	Overall Response at Week 8 (unconfirmed)	SIA
14.2.1.1	Overall Response at Week 8 (confirmed)	SIIA, SII6A, FA
14.2.1.1	Overall Response for ECD/LCH patients at Week 8	SIA, SIIA, SII, FA (for LHD/ECD sub-cohort only)
14.2.1.2	Summary of Tumour Response Assessments by	SIA

	Assessment Cycle	
14.2.2.1	Progression Free Survival (PFS)	SII6A, FA
14.2.2.2	Time to progression (TTP)	SII6A, FA
14.2.2.3	Best overall response (BOR) and Clinical benefit rate (CBR)	SII6A, FA
14.2.2.3	Best overall response (BOR) and Clinical benefit rate for ECD/LCH patients (CBR)	SII6A, FA (for LHD/ECD sub-cohort only)
14.2.2.4	Time to response (TTR)	SII6A, FA
14.2.2.5	Duration of response (DOR)	SII6A, FA
14.2.2.6	Overall survival (OS)	FA

5.3.3 Safety

Safety tables will be produced for the safety population.

14.3.1.1	Summary of Adverse Events	DFA, SIA, SIIA, SII6A, FA
14.3.1.2	Summary of Serious Adverse Events	SIIA, SII6A, FA
14.3.2.1	Adverse Events by System Organ Class (SOC) and Preferred Term (PT)	DFA, SIA, SIIA, SII6A, FA
14.3.2.2.1	Adverse Events with CTC Grade 1 or 2 by SOC and PT	SIIA, SII6A, FA
14.3.2.2.2	Adverse Events with CTC Grade 1 or 2 by CTC Grade, SOC and PT	SIIA, SII6A, FA
14.3.2.3.1	Adverse Events with CTC Grade 3 or 4 by SOC and PT	DFA, SIA, SIIA, SII6A, FA
14.3.2.3.2	Adverse Events with CTC Grade 3 or 4 by CTC Grade, SOC and PT	SIA, SIIA, SII6A, FA
14.3.2.4	Serious Adverse Events by SOC and PT	DFA, SIA, SIIA, SII6A, FA
14.3.2.5	Adverse Events leading to Study Drug Interruption by SOC and PT	SIA, SIIA, SII6A, FA
14.3.2.6	Adverse Events leading to Study Drug Discontinuation by SOC and PT	SIA, SIIA, FA
14.3.2.7	Adverse Events leading to Study Drug Interruption or Discontinuation by SOC and PT	DFA, SIA, SIIA, SII6A, FA
14.3.2.8	Adverse Events leading to Study Drug Dose Reduction by SOC and PT	DFA, SIA, SIIA, SII6A, FA
14.3.2.9	AE leading to Death	SIIA, SII6A, FA
14.3.3.1	Related AEs by SOC and PT	SIIA, SII6A, FA
14.3.3.1.1	AEs Related to Vemurafenib by SOC and PT	SIIA, SII6A, FA (only Cohort 3B)
14.3.3.1.2	AEs Related to Cetuximab by SOC and PT	SIIA, SII6A, FA (only Cohort 3B)
14.3.3.1.3	AEs Related to Vemurafenib and Cetuximab by SOC and PT	SIIA, SII6A, FA (only Cohort 3B)
14.3.3.2.1	Related AEs with CTC Grade 1 or 2 by SOC and PT	SIIA, SII6A, FA
14.3.3.2.2	Related AEs with CTC Grade 1 or 2 by CTC Grade, SOC and PT	SIIA, SII6A, FA

14.3.3.3.1	Related AEs with CTC Grade 3 or 4 by SOC and PT	SIA, SIIA, SII6A, FA
14.3.3.3.2	Related AEs with CTC Grade 3 or 4 by CTC Grade, SOC and PT	SIA, SIIA, SII6A, FA
14.3.3.4	Related Serious Adverse Events by SOC and PT	SIA, SIIA, SII6A, FA
14.3.3.5	Related AEs leading to Study Drug Interruption by SOC and PT	SIA, SIIA, SII6A, FA
14.3.3.6	Related AEs leading to Study Drug Discontinuation by SOC and PT	SIA, SIIA, FA
14.3.3.7	Related AEs leading to Study Drug Interruption or Discontinuation by SOC and PT	DFA, SIA, SIIA, SII6A, FA
14.3.3.8	Related AEs leading to Study Drug Dose Reduction by SOC and PT	DFA, SIA, SIIA, SII6A, FA
14.3.3.9	Related AEs leading to Death	SIIA, SII6A, FA
14.3.4.1	Adverse Events of Special Interest by AE of Special Interest Group and PT	SIIA, SII6A, FA
14.3.4.2	Adverse Events of Special Interest by CTC Grade, AE of Special Interest Group and PT	SIIA, SII6A, FA
14.3.4.3	Adverse Events of Special Interest - Time to First Incidence and Cumulative Dose to First Incidence	SIIA, SII6A, FA
14.3.4.4.1	Worsening in Liver Function Tests: One Grade Worsening from Baseline	SIIA, SII6A, FA
14.3.4.4.2	Worsening in Liver Function Tests: Two or More Grades Worsening from Baseline	SIIA, SII6A, FA
14.3.5.1	Dose Limiting Toxicities	DFA, FA
14.3.5.2	Infusion-related adverse events during or within 24h after the Cetuximab infusion	DFA, FA
14.3.6.1	Laboratory Results and Changes from Baseline – Haematology	SIIA, SII6A, FA
14.3.6.2	Laboratory Shift Table of NCI CTC Grades – Haematology	SIIA, SII6A, FA
14.3.6.3	Laboratory Results and Changes from Baseline – Biochemistry	SIIA, SII6A, FA
14.3.6.4	Laboratory Shift Table of NCI CTC Grades – Biochemistry	SIIA, SII6A, FA
14.3.7.1	ECG Results and Change from Baseline over Time	SIIA, SII6A, FA
14.3.7.2	ECG findings over Time	SIIA, SII6A, FA
14.3.7.3	ECG over Time – QTcF	SIA, DFA, SIIA, SII6A, FA
14.3.7.4	QTcF Prolongation (>500 msec)	SIIA, SII6A, FA
14.3.7.5	Cardiac History for Patients with QTcF Prolongation (>500 msec)	SIIA, SII6A, FA
14.3.7.6	Concomitant Medications for Patients with QTcF Prolongation (>500 msec)	SIIA, SII6A, FA
14.3.8	Vital Signs Results and Change from Baseline	SIIA, SII6A, FA
14.3.9	ECOG Performance Status	SIIA, SII6A, FA
14.4	Death Summary	SIIA, SII6A, FA
14.5.1	Dermatology Evaluation	SIIA, SII6A, FA

14.5.2	Head and Neck Assessment for SCC	SIIA, SII6A, FA
14.5.3	Chest CT for Evaluation of SCC	SIIA, SII6A, FA
14.5.4	Pelvic Examination for SCC	SIIA, SII6A, FA
14.5.5	Anal Examination for SCC	SIIA, SII6A, FA

5.3.4 Medications, Concomitant Medical Procedures and Exposure

Following tables will be produced for the safety population.

14.6.1	Prior Medication	SIIA, SII6A, FA
14.6.2	Concomitant Medication	SIIA, SII6A, FA
14.6.3	Concomitant Surgical Procedures and Radiotherapy	SIIA, SII6A, FA
14.7.1	Treatment Exposure Vemurafenib	SIA, SIIA, SII6A, FA
14.7.2	Treatment Modifications of Vemurafenib	SIIA, SII6A, FA
14.7.3	Treatment Exposure Cetuximab	SIA, SIIA, SII6A, FA
14.7.4	Treatment Modifications of Cetuximab	SIIA, SII6A, FA

5.4 Figures

Figure no.	Title	Produced for:
14.2.1	Progression Free Survival (PFS)	SIIA, SII6A, FA
14.2.2	Time to Progression (TTP)	SIIA, SII6A, FA
14.2.3	Time to Response (TTR)	SIIA, SII6A, FA
14.2.4	Duration of Response (DOR)	SIIA, SII6A, FA
14.2.5	Overall Survival (OS)	FA
14.2.6.1	Waterfall Plot of % Change from Baseline in Target Tumor Diameter Sum at Week 8	SIIA, SII6A, FA
14.2.6.2	Waterfall Plot of % Maximal Change from Baseline in Target Tumor Diameter Sum	SIIA, SII6A, FA
14.3.1	Liver Function Tests – Patient Values over Time	SIA, SIIA, SII6A, FA
14.3.2	Creatinine Tests – Patient Values over Time	SIA, SIIA, SII6A, FA
14.3.3	ECOG – Percentage of Patients by Grade over Time	SIIA, SII6A, FA

5.5 Listings

16.2.4.1	Patient Disposition	SIA, SIIA, FA
16.2.4.1.1	Patient Disposition at End of Study Treatment	SIA,SIIA,FA (only 3b)
16.2.4.1.2	Patient Disposition at End of Study	SIA,SIIA,FA (only 3b)
16.2.4.2.1	Inclusion and Exclusion Criteria Questions	SIIA, FA
16.2.4.2.2	Inclusion Criteria – Patient Responses	SIIA, FA
16.2.4.2.3	Exclusion Criteria – Patient Responses	SIIA, FA
16.2.4.2.4	Protocol Violations	SIIA, FA
16.2.4.3	Patient Demography	SIA, SIIA, FA
16.2.4.4.1	Cancer Disease History - <Cohort>	SIA, SIIA, FA

16.2.4.4.2	Surgical Resection of Primary Cancer - <Cohort>	SIA, SIIA, FA
16.2.4.4.3	Screening Dermatology Evaluation	SIIA, FA
16.2.4.5.1	Prior Systemic Therapy	SIA, SIIA, FA
16.2.4.5.2	Prior Radiotherapy	SIA, SIIA, FA
16.2.4.6	Medical and Surgical History	SIIA, FA
16.2.4.7	BRAF V600 Mutation Information	SIIA, FA
16.2.5.1	Administration of Vemurafenib	SIA, SIIA, SII6A, FA
16.2.5.2	Administration of Cetuximab	SIA, SIIA, SII6A, FA
16.2.5.3	Permanent Discontinuations from Study Medication	SIA, SIIA, SII6A, FA
16.2.6.1.1	Response Evaluation (RECIST)	SIA, SIIA, SII6A, FA
16.2.6.1.2	Response Evaluation (IMWG)	SIA, SIIA, SII6A, FA
16.2.6.1.3	Pooled Response Evaluation	SIA, SIIA, SII6A, FA (for LHD/ECD sub-cohort only)
16.2.6.2	Tumor Assessment of Target Lesions	SIA, SIIA, SII6A, FA
16.2.6.3	Tumor Assessment of Non-Target Lesions	SIA, SIIA, SII6A, FA
16.2.6.4	Individual Assessments of Multiple myeloma – Skeletal Survey	SIA, SIIA, SII6A, FA
16.2.6.5	Individual Assessments of Multiple myeloma – Serum Protein Electrophoresis	SIA, SIIA, SII6A, FA
16.2.6.6	Individual Assessments of Multiple myeloma – Urine Protein Electrophoresis	SIA, SIIA, SII6A, FA
16.2.6.7	Individual Assessments of Multiple myeloma – Serum Free Light Chains	SIA, SIIA, SII6A, FA
16.2.6.8	Individual Assessments of Multiple myeloma – Bone Marrow for Histology, Cytogenetics and FISH Mutation Details	SIA, SIIA, SII6A, FA
16.2.6.9	Individual Assessments of Multiple myeloma – Flow Cytometry Evaluation	SIA, SIIA, SII6A, FA
16.2.6.10	Next Anticancer Therapy after Discontinuation of Study Medication	SIA, SIIA, SII6A, FA
16.2.6.11	Disease Progression	SIA, SIIA, SII6A, FA
16.2.6.12	Responder Information	SIA, SIIA, SII6A, FA
16.2.6.13	Tumor Assessment of Lesions via PERCIST	SIA, SIIA, SII6A, FA (for LHD/ECD sub-cohort only)
16.2.6.14	Tumor Assessment of Lesions via Multiple assessments	SIA, SIIA, SII6A, FA (for LHD/ECD sub-cohort only)
16.2.7.1.1	All Adverse Events	SIA, SIIA, SII6A, FA
16.2.7.1.2	Serious Adverse Events	SIA, SIIA, SII6A, FA
16.2.7.1.3	Adverse Events leading to Dose Reduction or Temporary Treatment Interruption	SIA, SIIA, SII6A, FA

16.2.7.1.4	Adverse Events leading to Permanent Treatment Discontinuation	SIA, SIIA, SII6A, FA
16.2.7.1.5	Adverse Events leading to Death	SIIA, SII6A, FA
16.2.7.1.6	Dose Limiting Toxicities	DFA, FA
16.2.7.1.7	Infusion-related AEs during or within 24h after the Cetuximab infusion	DFA, FA
16.2.7.2.1	Deaths	SIA, SIIA, SII6A, FA
16.2.7.2.2	Deaths within 30 days of start of treatment	SIIA, FA
16.2.7.2.3	Deaths within 28 days after last administration of study drug	SIIA, FA
16.2.7.2.4	Deaths within 60 days after last administration of study drug	SIIA, FA
16.2.7.3.1	Laboratory Results - Haematology	SIIA, FA
16.2.7.3.2	Laboratory Results - Biochemistry	SIIA, FA
16.2.7.4	ECOG Performance Status	SIIA, FA
16.2.7.5	ECG Results	SIIA, FA
16.2.7.6	Vital Signs	SIIA, FA
16.2.7.7	Dermatology Evaluation	SIIA, FA
16.2.7.8	Head and Neck Assessment for SCC	SIIA, FA
16.2.7.9	Chest CT for Evaluation of SCC	SIIA, FA
16.2.7.10	Pelvic examination for SCC	SIIA, FA
16.2.7.11	Anal examination for SCC	SIIA, FA
16.2.7.12	Physical examination	SIIA, FA
16.2.8.1	Prior and concomitant medication	SIIA, FA
16.2.8.2	Concomitant Surgical Procedures	SIIA, FA
16.2.8.3	Concomitant Radiotherapy	SIIA, FA

5.6 Appendices

N/A

5.7 References

1. Lin Y, Shih WJ. Adaptive two-stage designs for single-arm phase IIA cancer clinical trials. Biometrics. 2004;60:482-90.
2. NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. See http://evs.nci.nih.gov/ftp1/CTCAE/About.html.

Statistical Analysis Plan

F. HOFFMANN-LA ROCHE LTD

Protocol: MO28072

Treatment: VEMURAFENIB

AN OPEN-LABEL, PHASE II STUDY OF VEMURAFENIB IN PATIENTS WITH BRAF V600 MUTATION-POSITIVE CANCERS

Author(s): Karin Hoffmann

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Contents

Abbreviations

^{18}F-FDG PET	Fluorodeoxyglucose positron emission tomography
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT(SGPT)	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST (SGOT)	Aspartate Aminotransferase
b.i.d	twice daily
BOR	Best Overall Response
BORR	Best Overall Response Rate
BRAF	v-raf murine sarcoma viral oncogene homolog B1
BUN	Blood Urea Nitrogen
CBR	Clinical Bebefir Rate
CI	Confidence Interval
CMR	Complete Metabolic Response
CR	Complete Response
cSCC	Cutaneous Squamous Cell Carcinoma
CT	Computer Tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DFA	Dose Finding Analysis
DOR	Duration of Response
DLT	Dose limiting toxicities
ECD	Erdheim Chester Disease
ECG	Electrocardiogram
ECOG	Eastern Co-operative Oncology Group
eCRF	Electronic Case Report Form
FA	Final Analysis
HEENT	Head, Eyes, Ears, Nose and Throat
IA	Interim Analysis
ID	Identification
IMWG	International Myeloma Working Group
ITT	Intent-to-Treat
KM	Kaplan-Meier
LCH	Langerhans Cell Hystiocytosis
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple Myeloma
MR	Minimal Response
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NE	Non-Evaluable
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease

PERCIST	Positron Emission Response Criteria in Solid Tumors
PFS	Progression-Free Survival
PMD	Partial Metabolic Disease
PMR	Partial Metabolic Response
PR	Partial Response
QTc	Corrected QT Interval
PT	Preferred Term
RR	Response Rate
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Steering Committee
SCC	Squamous Cell Carcinoma
sCR	Stringent Complete Response
SD	Stable Disease or Standard Deviation
SIA	Stage I Analysis
SIIA	Stage II Analysis
SMD	Stable Metabolic Disease
SOC	System Organ Class
TTP	Time to Tumour Progression
TTR	Time to Response
VGPR	Very Good Partial Response
WBC	White Blood Cell

1 Introduction

This document presents the statistical analysis plan (SAP) for Hoffmann-La Roche Ltd, Protocol No. MO28072: An open-label, multicenter, phase II study of vemurafenib in patients with BRAF V600 mutation-positive cancers.

This analysis plan is based on the final protocol version 5 dated 18 March 2014.

This SAP provides the description of the different analyses for the study. The study includes 7 different cohorts, one of them consisting of two sub-cohorts, each which will be reported separately.

For each cohort, in addition to the final analysis, an abbreviated interim analysis (IA) will be carried out when a pre-specified number of patients (cf. sample size section 3.10) will have a minimum of 8 weeks of treatment, develop progressive disease, prematurely withdraw from study, or die, whichever occurs first. The final analysis of each cohort will be done when all patients of the corresponding cohort have finished the study.

For those cohorts that expand into stage II, also a stage II analysis will be performed when all patients enrolled for into stage II of the corresponding cohort will have a minimum of 8 or 16 weeks of treatment – sufficient so that confirmed response at week 8 can be evaluated -, develop progressive disease, withdraw, or are lost tofollow-up, whichever occurs first.

For Cohort 3b only, a dose finding analysis will be carried out to determine the maximum tolerated dose (MTD) and recommended dose for stage I/II of the combination of vemurafenib and cetuximab in BRAF V600-positive metastatic CRC patients.

For Cohort 7, patients with Erdheim Chester disease (ECD) and/or Langerhans Cell Histiocytosis (LCH) are considered a specific cohort and will be analysed specifically according to specific response assessments (cf. Appendix 10 of protocol) .

2 Study Objectives

This is an open-label, multicenter, multinational, phase II study exploring the efficacy and safety of vemurafenib monotherapy in a diverse population of patients with cancers (excluding melanoma and papillary thyroid cancer) known to harbor BRAF V600 mutations.

In the population of colorectal cancer patients, the safety and efficacy of vemurafenib in combination with cetuximab will also be explored in addition to vemurafenib.

The trial will include 7 cohorts and several sub-cohorts of patients with the following cancers:

Cohort 1. Non-small cell lung cancer (NSCLC)

Cohort 2. Ovarian cancer

Cohort 3. Colorectal cancer:

Cohort 3b. Vemurafenib only

Cohort 3b. Combination therapy with vemurafenib and cetuximab

Cohort 4. Cholangiocarcinoma/cancer of the biliary tract

Cohort 5. Breast cancer

Cohort 6. Multiple myeloma (MM)

Cohort 7. Solid tumors other than the above

Cohort 7a. Solid tumors other than the above - ECD and LCH only

For cohort 3b, the study consists of two parts:

- Part 1 is a dose finding phase for vemurafenib in combination with cetuximab (based on a classical 3+3 design)
- Part 2 is investigating the efficacy and safety of the recommended dose for stage I/II of the combination of vemurafenib and cetuximab

As part 2 of cohort 3b with the optimal dose selected is the same stage I/II design as for other cohorts, it is described along them; whilst for part 1, separate subsections are included in where considered necessary for each dose level examined.

The **primary objective** of this trial is to evaluate the efficacy of vemurafenib, in patients with cancers harboring BRAF V600 mutations as response rate (RR) at Week 8 determined by the Investigator using Response Evaluation Criteria In Solid Tumors, Version 1.1 (RECIST, v1.1)* or International Myeloma Working Group (IMWG) uniform response criteria and to identify tumor types for further development.

* Note, see Appendix 9 of protocol for prostate cancer and Appendix 10 of protocol for Erdheim Chester Disease (ECD) and/or Langerhans Cell Hystiocytosis (LCH) response criteria, respectively.

Secondary objectives are as follows:

- To evaluate the safety and tolerability of vemurafenib in this patient population.

- To evaluate in solid tumors and multiple myeloma (MM):
    - Overall response rate (ORR)
    - Clinical benefit rate (CR (or sCR), PR (or VGPR)) and stable disease [SD]
    - Duration of response (DOR)
    - Time to response
    - Time to tumor progression (TTP)
    - Progression free survival (PFS)
    - Overall survival (OS).
- To determine the maximum tolerated dose (MTD) and recommended dose for stage I/II of the combination of vemurafenib and cetuximab in BRAF V600-positive metastatic CRC patients (Cohort 3b only).
- To investigate the safety, tolerability, efficacy of the combination of vemurafenib and cetuximab in BRAF V600-positive metastatic CRC patients (Cohort 3b only).

An **exploratory objective** is to perform concordance testing for the detection of BRAF V600 mutation in tumor samples via either the Roche Companion Diagnostic (CoDx) cobas® 4800 BRAF V600 Test or other acceptable standard methodology.

2.1 Primary endpoint

The primary endpoint is Response Rate (RR) at Week 8, as assessed by the Investigator using RECIST, v1.1 for patients with solid tumors and using IMWG uniform response criteria for patients with MM.

Possible overall response results for Solid Tumours according to RECIST, v1.1, are:

- Complete Response (CR)
- Partial Response (PR)
- Stable Disease (SD)
- Non-CR/Non-PD
- Progressive Disease (PD)
- Non-Evaluable (NE)

Possible overall response results for Multiple myeloma according IMWG uniform response criteria are:

- Stringent Complete Response (sCR)
- Complete Response (CR)
- Very Good Partial Response (VGPR)
- Partial Response (PR)
- Minimal Response (MR)
- No Change/Stable Disease (SD)

- Plateau
- Progressive Disease (PD)
- Relapse
- Relapse from CR

For patients with solid tumors, responders at Week 8 will be defined based on tumor assessment status of PR or CR at Week 8. For patients with MM, responders at Week 8 will be defined based on tumor assessment status of CR, sCR, VGPR or PR at week 8. Only patients with measurable disease at baseline will be included in the analysis of the RR. Patients without a post-baseline tumor assessment will be considered to be non-responders.

For patients with LCH/ECD the tumor response assessment will be based on:

- RECIST v1.1
- PERCIST v1.0
- Multiple assessments (as per protocol depending on involved area of disease)

Best Overall response for PERCIST can be:

- Complete Metabolic Response (CMR)
- Partial Metabolic Response (PMR)
- Stable Metabolic Disease (SMD)
- Progressive Metabolic Disease (PMD)

Patients with a CMR or PMR are considered responders.

Tumour response assessment based on Multiple assessments uses at least one of the following methods to assess Best Overall response:

a. Brain MRI
b. Cardiac MRI (or cardiac echography for patients who cannot undergo MRI and have cardiac involvement)
c. Bone scan
d. ^{18}F-FDG PET
e. CT chest/abdomen/pelvis

Laboratory parameters may also be used.

The patients will be classified as either Reponder or Non responder.

For patients with Multiple myeloma, according IMWG, all response categories require two consecutive assessments.

For solid tumour patients to be assigned a status of partial response (PR) or complete response (CR) (i.e., a responder), changes in tumour measurements must be confirmed by repeat assessments performed at least 4 weeks after the criteria for response are first met, i.e., patients need to have two consecutive assessments of PR or CR to be responders.

The main analysis for the response rate will be based on Adaptive design based on Simon's two stage design for a single proportion; Lin and Shih (2004). Adaptive Two-stage design for Single-Arm Phase II A Cancer Clinical Trials. Biometrics 60, 482-490 (1).

Stage I will be defined as when 7 patients with measurable disease in corresponding cohort (cf. Sample Size section 8.4 of the protocol) will have a minimum of 8 weeks of treatment, and their schedule Tumor assessment reported or develop progressive disease, prematurely withdraw from study, or die, whichever occurs first. Note that for stage I analysis only and for stage I stopping rules, response criteria are based on unconfirmed assessments.

If a pre-specified minimal response rate will not be achieved in certain cohorts in the first stage of the study, the corresponding cohort should not enrol any further patients. However if a clear clinical benefit has been observed for patients in the respective cohort, e.g. majority of patients recorded SD at Week 8 and no CR or PR is recorded, then enrolment into Stage II might be allowed for this cohort. In that case, stage II of that cohort would be handled like "Low response at the end of Stage I" and another 12 patients enrolled, to have 19 patients in total for that cohort.

The final decision about further recruitment into stage II will be taken by the Sponsor in discussion with study Steering Committee (SC).

If further recruitment is approved, enrolment continues into Stage II until a pre-determined number of additional patients is reached. This number depends on the response rate seen after stage I, as detailed in sample size section 3.10 (the exact numbers are found in Table 4).

An exception will be made for Cohort 7 which includes patients with different solid tumor types. For patients with the same tumor type within this cohort a pooled analysis may be performed when at least 5 patients have been enrolled.

The analysis at end of Stage II (for lower or higher desirable confirmed response) for each Cohort will be performed when all patients enrolled in the study will have a minimum of 8 weeks of treatment (including a confirmed response assessment if applicable), develop progressive disease, withdraw, or are lost to follow-up, whichever occurs first.

The final analysis will be done for each cohort after all patients of the respective cohort have finished the study, i.e. have died, been followed up for survival for a minimum of 12 months after the last patient has been enrolled or until all patients have died, withdrawn consent or been lost to follow-up, whichever occurs first.

2.2 Secondary endpoints

Secondary endpoints for each cohort and for patients with solid tumors and MM are as follows:

- Progression free survival (PFS)
- Time to progression (TTP)
- Best overall response (BOR)
- Time to response (TTR)
- Duration of response (DOR)
- Clinical benefit rate (CBR)
- Overall survival (OS)

2.3 Safety endpoints

The safety endpoints for the study are:

- Adverse events (AEs)
- Laboratory parameters
- Exposure to study medication
- Dermatologic evaluations
- Head/neck evaluations
- Chest CT scan
- Pelvic Examination (for women)
- Anal examination
- Vital signs
- Electrocardiogram (ECG)
- ECOG performance status
- Physical examination.

For cohort 3b, dose finding part, only:

- Dose-limiting toxicities

3 Study Design

3.1 Discussion of Study Design

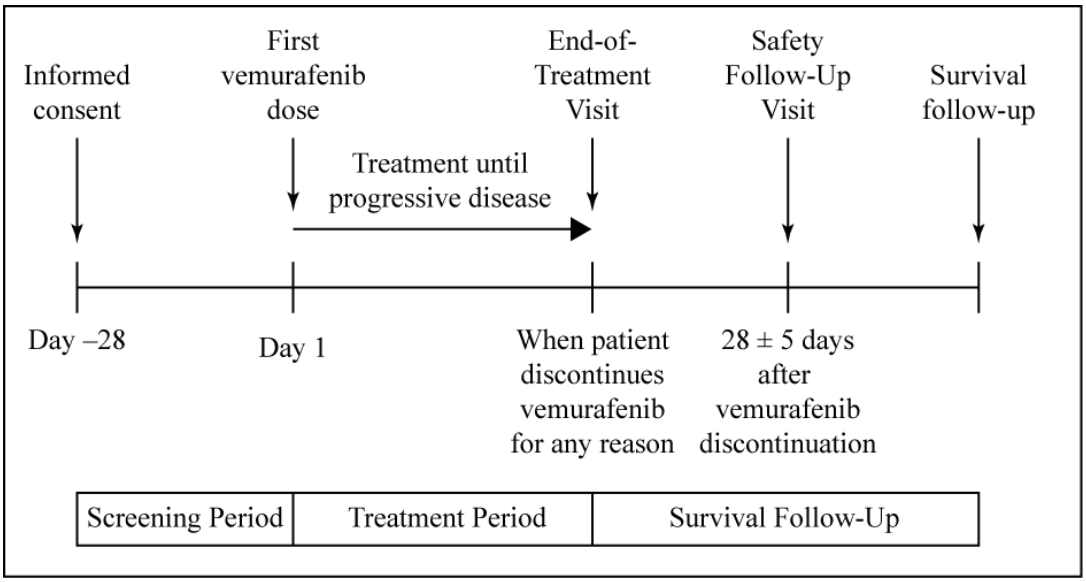
This is an open-label, multicenter, multinational, phase II study exploring the efficacy and safety of vemurafenib in a diverse population of patients with cancers (excluding melanoma and papillary thyroid cancer) known to harbor BRAF V600 mutations and for whom vemurafenib is deemed the best treatment option in the opinion of the Investigator.

In the population of colorectal cancer patients, the safety and efficacy of vemurafenib in combination with cetuximab will also be explored in addition to vemurafenib monotherapy.

Patients with BRAF V600 mutation-positive cancers will be identified through mutation analysis assays as routinely performed at each participating site according to their local procedure. The BRAF V600 mutation identified at the site, as well as the specific BRAF mutation assay that was performed, will be recorded in the electronic case report form (eCRF). The presence of BRAF V600 mutations will be retrospectively confirmed by the cobas® 4800 BRAF V600 Mutation Test.

The trial will consist of a Screening Period (Day –28 to −1), a Treatment Period, an End-of-Treatment Visit occurring when study treatment is discontinued for any reason, a Safety Follow-Up Visit occurring 28 days after the last dose of study treatment and a Survival Follow-Up Period lasting for a minimum of 12 months after enrolment of the last patient to monitor survival status. Day 1 of the study (baseline) is defined as the first day a patient receives study medication. One cycle of therapy is defined as 28 days of treatment.

Figure 1: Study Design



The study includes 7 cohorts of patients with the following cancers:

Cohort 1. Non-small cell lung cancer (NSCLC)

Cohort 2. Ovarian cancer

Cohort 3. Colorectal cancer

Cohort 3a. Vemurafenib only

Cohort 3b. Combination therapy with vemurafenib and cetuximab

Cohort 4. Cholangiocarcinoma/cancer of the biliary tract

Cohort 5. Breast cancer

Cohort 6. Multiple myeloma (MM)

Cohort 7. Solid tumors other than the above

For each of the cohorts, the study is divided into 2 stages. Stage I of the study is completed when 7 patients with measurable disease have been enrolled and completed a minimum of 8 weeks of treatment, developed progressive disease, prematurely withdraw from study, or died, whichever occurs first. Dependent on the RR of patients completing Stage I, more patients may be enrolled to Stage II. An exception to this will be made to cohort 7 as it may not be able to enrol sufficient patients within the different other Solid tumor types which can be combined.

The Cohort 3b is designed to investigate the safety, tolerability, efficacy and to determine the MTD and the recommended dose for stage I/II of the combination of vemurafenib and cetuximab. Therefore, cohort 3b has two parts:

- Part 1 is a dose finding phase of vemurafenib in combination with cetuximab (based on a classical 3+3 design).
- Part 2 is investigating the efficacy and safety of the recommended dose for stage I/II of the combination of vemurafenib and cetuximab; the same Stage I/II design as for the other cohorts will be used.

The decision to carry on enrolment of CRC patients into Cohort 3a (vemurafenib monotherapy) and/or enrol patients into Cohort 3b (combination of vemurafenib and cetuximab) will be based on the stage I analysis for Cohort 3a (vemurafenib monotherapy). This will be decided by the Sponsor in discussion with study Steering Committee.

The decision to continue enrolment in Cohort 3b after the Part I dose escalation phase will be decided by the Sponsor in discussion with study Steering Committee.

Recruitment/enrolment in any of the above cohorts may present some challenges due to the low frequency of BRAF V600 mutations in the specific disease settings. Therefore the following rule on cohort closure will be applied: if no patients are enrolled in the remaining cohorts one year after any of the cohorts has completed enrolment, then enrolment in those remaining cohorts will be stopped.

Within cohort 7 (Other solid tumours), specific sub-cohort can be defined if at least 7 patients of the same tumour type have been enrolled. These sub-cohort will be treated in the same way as the other, predefined cohort, i.e. undergo a stage I analysis followed by stage II in case of

sufficiently promising results. Cohort 7 not part of any sub-cohort will be closed to enrolment when all other cohorts are closed, regardless of the number of patients recruited at that time. This cohort is quite heterogeneous and will be examined primarily to seek efficacy signals in the relatively rare BRAF V600 mutation-positive tumours.

Recruitment into any cohort/indication can be expanded up to a total of 70 patients if a response rate has been demonstrated in Stage II of that cohort as per stopping rules defined in the protocol or a clear clinical benefit for patients is observed. This will be decided by the Sponsor in discussion with study Steering Committee.

3.2 Study Treatment

Patients enrolled in the study receive the following study treatment:

- Cohorts 1 to 7 (except patients in the Cohort 3b):
  - continuous oral dosing of vemurafenib at 960 mg twice daily (b.i.d)
- Cohort 3b:
  - In part 1 vemurafenib and cetuximab at the doses allocated for dose escalation (see section 3.2.1) or
  - In part 2 vemurafenib and cetuximab at the doses recommended for stage I/II during the dose escalation part.

Treatment will continue until the development of progressive disease (as per Investigator assessment), unacceptable toxicity, withdrawal of consent, protocol violation endangering the patient‘s safety, death, reasons deemed critical by the treating physician, or study termination by the Sponsor.

Patients who develop disease progression but, in the opinion of the Investigator, would still benefit from continuing study treatment may continue treatment with study treatment after discussion with the Sponsor.

If recruitment is expanded in any cohort (due to promising efficacy seen in Stage II), patients who are part of this expansion will receive the same treatment as patients who were treated in Stage II of that cohort.

3.2.1 Study Treatment during Dose-finding Part (Cohort 3b only)

For Part 1 of Cohort 3b, the planned dose escalation levels of vemurafenib and cetuximab combination will be as follows:

Dose Level	vemurafenib	cetuximab
1	720 mg b.i.d. starting on Day 2 of cycle 1	Cetuximab: 300 mg/m^2 loading dose on Day 1 of Treatment Phase, then 200 mg/m^2 weekly
2	720 mg b.i.d. starting on Day 2 of cycle 1	Cetuximab: 400 mg/m^2 loading dose on Day 1 of Treatment Phase, then 250 mg/m^2 weekly
3	960 mg b.i.d.	Cetuximab: 400 mg/m^2 loading

	starting on Day 2 of cycle 1	dose on Day 1 of Treatment Phase, then 250 mg/m^2 weekly

If the dose levels above are not tolerated then the following dose levels will be considered as appropriate after discussion between the sponsor and study Steering Committee.

Dose Level	vemurafenib	cetuximab
-1	720 mg b.i.d. starting on Day 2 of cycle 1	Cetuximab: 200 mg/m^2 loading dose on Day 1 of Treatment Phase, then 125 mg/m^2 weekly
-2	720 mg b.i.d. starting on Day 2 of cycle 1	Cetuximab: 300 mg/m^2 loading dose on Day 1 of Treatment Phase, then 250 mg/m^2 weekly
-3	960 mg b.i.d. starting on Day 2 of cycle 1	Cetuximab: 300 mg/m^2 loading dose on Day 1 of Treatment Phase, then 250 mg/m^2 weekly

Once assigned to specific dosages of vemurafenib and cetuximab in combination, each patient will continue to be treated, without interruption throughout the study unless dose modification or interruption is indicated. (Refer to Section 6.3.3 of the protocol for dose modification guidelines for the combination of vemurafenib and cetuximab.)

3.3 Guidelines for Dose-finding Part (Cohort 3b only)

3.3.1 Dose Escalation Guidelines

A minimum of 3 patients initially will be enrolled at the first dose level (Dose level 1 Section 3.2.14.6.2).

The first patient at any dose level will be observed for at least 28 days before the next two patients receive vemurafenib and cetuximab at that dose level.

The dose escalation rules proceed as follows, escalating in cohorts of 3-6 patients per dose level.

For patients treated at the current dose level, the following rules will be applied:

- If at least 2 patients are observed to have a dose-limiting toxicity (DLT) [see section 3.3.3] during the 28 days following the first administration of vemurafenib and cetuximab (DLT assessment period), the MTD will have been exceeded and no further patients will be enrolled at this dose level or at any higher dose level. The prior dose level is defined as the MTD (unless only 3 patients have been treated at that level, in which case it is the tentative MTD).
- If 0 of the 3 patients are observed to have DLT during the DLT assessment period, the dose level is escalated one step for the next cohort of 3 patients, and the process continues as above.
- If exactly 1 of the 3 patients treated shows DLT during the DLT assessment period, 3 additional patients are treated at the current dose level.

If none of these additional 3 patients show DLT during the DLT assessment period, the dose level is escalated for the next cohort of 3 patients, and the process continues as above; otherwise, the prior dose level is defined as the MTD (unless only 3 patients have been treated at that level, in which case it is the tentative MTD).

A tentative MTD becomes the final MTD when a total of 6 patients are treated with less than 2 of them showing DLT.

3.3.2 Recommended dose of vemurafenib and cetuximab

A dose will be considered non-tolerable and dose escalation will cease if 2 or more of up to 6 evaluable patients experience a DLT at a dose level. Once the non-tolerable dose is defined the MTD will be confirmed at the previous dose-level below or a dose between the MTD and the last tolerable dose. Six evaluable patients are required to determine the MTD.

Expected dose levels for the dose escalation are described in Section 3.2.1. The dose escalation guidelines are summarised in Section 3.3.1. Decisions to escalate or de-escalate the doses will be made based on a review of all available safety data both from the study i.e. nature of the DLTs that occurred at one dose level together with all other available data including generally available data on vemurafenib and cetuximab.

The MTD is defined to be the highest dose of vemurafenib in combination with cetuximab which can be given to 6 patients such that less than 2 subjects experience DLT within 28 days (or no more than one-third if there are more than 6 treated patients).

The recommended dose for stage I/II will be based on considerations of the estimated MTD, and on an overall assessment of safety taking into consideration tolerability data from subsequent cycles at all different dose levels tested. The recommended dose for stage I/II will be determined once the MTD is determined by the Sponsor after discussion with the study Steering Committee. The decision to continue enrolment in Cohort 3b after the Part I dose escalation phase will be decided by the Sponsor in discussion with study Steering Committee.

3.3.3 Dose-limiting toxicities

A DLT is defined as a clinically significant adverse event or abnormal laboratory value assessed as unrelated to disease progression, undercurrent illness, or concomitant medications and occurring during the first 4 weeks of treatment with the combination of vemurafenib and cetuximab.

For the purposes of this protocol, the following adverse events determined to be possibly, probably or definitely related to the combination of cetuximab and vemurafenib that occur during the 28 days following the first administration of the combination of vemurafenib and cetuximab at any dose level and that meet any of the following criteria are considered to be DLTs that count for the determination of the MTD.

Toxicity grades are defined in the NCI CTCAE v 4.0 (2).

- Grade $\geq$ 3 non-hematological toxicity (other than untreated nausea, vomiting and diarrhea and excluding alopecia)
- Grade $\geq$ 3 nausea, vomiting or diarrhea refractory to appropriate treatment for at least 2 days
- Grade 4 anemia lasting > 7 consecutive days
- Neutropenia Grade 4 lasting > 7 consecutive days
- Neutropenia Grade 3 or 4 complicated by fever and/or infection (ANC <1.0 x 109/L; fever $\geq 38.5^0$C
- Grade 4 thrombocytopenia lasting >7 consecutive days
- Treatment delay >33% of the scheduled doses over 28 days due to treatment related toxicity

Skin and subcutaneous tissue toxicity is not considered a DLT unless a dose reduction of study treatment is required to permit continuous dosing.

3.4 Study Schedule

The clinical assessments and procedures outlined in **Tables Schedule of Assessments for Cohorts 1, 2, 3a, 4 – 7** and **Schedule of Assessments for Cohort 3b** will be completed for all patients enrolled in the screening and treatment periods. The clinical assessments and procedures described in the End of Treatment Visit will be completed for patients who withdraw from the study during the treatment period.

The visit window for all cycles from cycle 2 onwards is -4/+1 day for all cohorts; with the exception of cohort 3b with a visit window of ± 3 days.

Table 3a.
Schedule of Assessments for Cohorts 1, 2, 3a, 4 – 7 (cohorts with Vemurafenib study treatment only)

	Screening Period [1]	**Treatment Period** [2] **(Allowed visit window: –4 days / +1 day from cycle 2 onwards)**										**End of Treatment Visit** [3]	**Safety-Follow-Up Visit** [4]	**Survival Follow-Up** [5]
Cycle		1		2	3	4	5	6	7	8	9 onwards		Post treatment d/c	Every 3 months
Day	–28 to –1	1	15	29	57	85	113	141	169	197	Every 28 Days		28 (±5) days	
Informed consent [6]	X													
Documentation of BRAF V600 mutation and test performed	X													
Medical history and demographics	X													
Physical examination [7]	X	X	X	X	X	X	X	X	X	X	X	X		
Vital signs [8]	X	X	X	X	X	X	X	X	X	X	X (Q8 weeks)	X		
12-lead ECG [9]	X			X	X	X	X			X	X (Q12 weeks)	X	X	
ECOG performance status	X	X	X	X	X	X	X	X	X	X	X (Q8 weeks)	X		
Hematology [10]	X	X[11]	X	X	X	X	X	X	X	X	X	X		
Biochemistry [12]	X	X[11]	X	X	X	X	X	X	X	X	X	X		
Serum pregnancy test [13]	X													
Solid tumor assessments (CT/MRI) [14]	X				X		X		X		X (every 8 weeks)	X		
Assessments for Multiple Myeloma [15]	X				X[16]	X[16]	X[16]	X[16]	X[16]	X[16]	X[16]	X[16]		
Dermatology evaluation [17]	X			X			X			X	C11 (then Q12	X	X[20]	At 6

	Screening Period [1]	**Treatment Period** [2] **(Allowed visit window: –4 days / +1 day from cycle 2 onwards)**										**End of Treatment Visit** [3]	**Safety-Follow-Up Visit** [4]	**Survival Follow-Up** [5]
Cycle		1		2	3	4	5	6	7	8	9 onwards		Post treatment d/c	Every 3 months
Day	–28 to –1	1	15	29	57	85	113	141	169	197	Every 28 Days		28 (±5) days	
											weeks)			months
Head and neck assessment for SCC [18]	X					X			X		C10 (then Q12 weeks)	X	X[20]	At 6 months
Chest CT for evaluation of SCC [19]	X								X		C13 (then Q6 months)		X[20]	At 6 months
Drug dispensation		X		X	X	X	X	X	X	X	X			
Drug accountability				X	X	X	X	X	X	X	X	X		
Drug Dosing Exception Diary [21]				X	X	X	X	X	X	X	X	X		
Prostate Cancer patients only – PSA Assessment [22]	X				X		X		X		X (Q8 weeks)	X		
Prostate Cancer patients only – Bone Scans [23]	X				X		X		X		X (Q8 weeks)	X		
ECD/LCH patients only – C-reactive protein[27]		X		X	X		X		X		X (Q8 weeks)	X		
ECD/LCH patients only – additional tumor assessments [28]	X				X		X		X		X (Q8 weeks)	X		
Concomitant medications [24]	X						X					X	X	
AEs / SAEs [25]	X						X					X	X	
Vemurafenib administration							X							
Follow-up for disease														X

	Screening Period [1]	**Treatment Period** [2] **(Allowed visit window: –4 days / +1 day from cycle 2 onwards)**										**End of Treatment Visit** [3]	**Safety-Follow-Up Visit** [4]	**Survival Follow-Up** [5]
Cycle		1		2	3	4	5	6	7	8	9 onwards		Post treatment d/c	Every 3 months
Day	–28 to –1	1	15	29	57	85	113	141	169	197	Every 28 Days		28 (±5) days	
progression														
Survival status [5]													X	X
Next anticancer therapy														X
Anal and pelvic exam [26]	**X**												X	

Notes Day 1 = first dose of study drug (vemurafenib)

1. Apart from obtaining written informed consent, no screening procedure may be performed before the patient has been confirmed to be positive for the BRAF V600 mutation. All efforts should be made to collect a tumor sample (formalin-fixed paraffin-embedded tumor tissue [FFPET] or 3-5 serially cut unstained 5-µm sections from one FFPET block) for retrospective confirmation of the BRAF mutation using the cobas 4800 V600 mutation kit. This tumor sample should preferably be from the original specimen used to detect the BRAF mutation. The original tumour block will be returned to the site.
2. Visits during the Treatment Period are to be completed on Day 1, Day 15, Day 29 and every 28 days thereafter until study drug discontinuation. A window of 4 days prior to the scheduled visit date and one day after the scheduled visit date (–4 days / + 1 day) is allowed for each visit from Cycle 2 onwards.
3. The End of Treatment Visit will be performed when the patient discontinues vemurafenib regardless of when it occurs.
4. The Safety Follow-Up Visit will be performed after 28 (±5) days from discontinuation of vemurafenib.
5. The Survival Follow-Up period will last for a minimum of 12 months after the last patient has been enrolled or until all patients have died, withdrawn consent or are lost to follow-up (whichever occurs first).
6. Informed consent must be obtained prior to performing any study procedure including Screening assessments. The date of signature on the informed consent form signifies the beginning of the 28-day Screening Period.
7. Includes the evaluation of the head, eyes, ears, nose, and throat (HEENT); cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal and neurological systems examination; and height (cm) and weight (kg). Height will only be measured during screening.
8. Includes blood pressure, heart rate, temperature and respiratory rate.
9. Includes heart rate, PR interval, QRS duration, QT and QTc intervals and ECG findings.
10. Includes hemoglobin, hematocrit, platelet count, white blood cell count (WBC) and absolute neutrophil count (ANC)
11. Hematology and biochemistry assessments do not need to be repeated on Day 1 if performed within 7 days of first vemurafenib administration. NB: if it is necessary to repeat these blood tests, the results must be known before the patient receives first dose of vemurafenib to ensure that the inclusion and exclusion criteria related to these tests are met.
12. Includes amylase, lipase, glucose, blood urea nitrogen [BUN], creatinine or creatinine clearance, sodium, potassium, calcium, magnesium, bicarbonate ([if routinely performed on venous blood samples],), total bilirubin with fractionation into direct and indirect (if total bilirubin elevated during the study), alkaline phosphatase, AST ([SGOT]], ALT ([SGPT]],
13. Serum pregnancy test to be performed within 7 days prior to first vemurafenib administration for women with childbearing potential.

14. Includes for solid tumour patients only: CT/MRI of the chest, abdomen and pelvis [C/A/P]). The same imaging technique (CT or MRI) should be used for these patients throughout the study. CT/MRI of the brain may also be performed as per standard of care.
15. , Serum protein electrophoresis (SPEP), Urine protein electrophoresis (UPEP), Serum free light chains, 24 hour urine proteins, Bone marrow for histology, cytogenetics and FISH, and flow cytometery with or without biopsy, Beta 2 microglobulin, albumin and lactate dehydrogenase (LDH). A skeletal survey is done during Screening only; thereafter it should be done as per routine clinical practice.
16. Bone marrow assessment only to be done to confirm complete remission after two consecutive immunofluorescence analyses are negative.
17. Performed by a dermatologist. For patients who develop any suspicious new skin lesion during treatment with vemurafenib. Further confirmation by a designated central pathology laboratory. Only required at the End of Treatment visit if not performed in the previous 12 weeks. Should be done at Safety Follow-up visit at 28 days (±5 days) and at 6 months following study drug discontinuation or until initiation of another anti-neoplastic therapy.
18. Performed by the treating physician as part of the evaluation for SCC. Should also be done at Safety Follow-up visit at 28 days (±5 days) and at 6 months following study drug discontinuation or until initiation of another anti-neoplastic therapy.
19. CT of the chest for the evaluation of noncutaneous SCC (for all patients, solid tumors and MM). For patients with solid tumours, the routinely scheduled radiographic assessment for tumor burden may be used (if available) as the chest CT for the evaluation of noncutaneous SCC while the patient is taking vemurafenib.
20. Must be performed at this visit and 6 months following study drug discontinuation or until initiation of another anti-neoplastic therapy.
21. Patients will keep a diary to record ONLY those occasions when a vemurafenib dose was missed (morning or evening, each day of treatment). The patient will bring this diary with him/her to each study visit to allow missed doses to be recorded by the Investigator.
22. See Appendix 9
23. See Appendix 9 for further details. Bone scans to be performed every 8 weeks or as per institution standard of care, but at a minimum every 16 weeks and at the end of study.
24. All concomitant medications during the study started within 14 days prior to the screening visit and up to the end of study visit must be recorded.
25. During screening AEs are not recorded in the eCRF unless they are SAEs which are related to protocol-mandated procedures. ALL AEs (including SAEs) must be recorded from the time of first vemurafenib administration. After the last dose of vemurafenib any new, AEs should be reported up to 28 days after last dose. The Sponsor should be notified if the Investigator becomes aware of any SAE or non-serious AEs of special interest occurring after the end of the adverse event reporting period, regardless of causality.
26. Pelvic examinations for women (with special attention to cervix) and anal examinations for all patients will be performed at screening and at the Safety follow-up visit for evaluation of SCC. The pelvic examination should include a complete external and internal examination (internal examination of uterine cervix may include a Pap smear, which would be a decision of the investigator). The anal examination should include external examination, digital anorectal examination and anoscopy or proctoscopy. However, if in opinion of the investigator the presence of "abnormal lesions including SCC" can be excluded by the external inspection and the manual examination, this is acceptable. However, if the presence of a lesion is suspected, an anoscopy or proctoscopy are recommended.
27. See Appendix 10 for further details.
28. Baseline tumor assessments must include CT/MRI of the chest, abdomen and pelvis (C/A/P) and any additional assessment as clinically relevant as described in Appendix 10 to define baseline extent of disease (brain MRI, cardiac MRI/echo, bone scan, ^{18}F-FDG PET). For patients with baseline measurable disease according to RECIST v1.1, the following tumor assessments will consist of the same method(s) used at baseline to determine measurable disease (CT/MRI of [C/A/P], brain MRI, cardiac MRI). For all other patients the following tumor assessments will consist of the same method/s used at baseline that have defined the area involved by the disease (brain MRI, cardiac MRI/echo, bone scan, ^{18}F-FDG PET, CT chest/abdomen/pelvis) as described in Appendix 10

Table 3b.
Schedule of Assessments for Cohort 3b (colorectal cohort with Vemurafenib and Cetuximab study treatment)

	Screening Period [1]	**Treatment Period** [2] **(Allowed visit window: ± 1 day starting on Day 8 of Cycle 1 and onwards)**													**End of Treatment Visit** [3]	**Safety-Follow-Up Visit** [4]	**Survival Follow-Up** [5]
Cycle (C)		1					2				3 onwards						
Study Day	–28 to –1	1	2	8	15	22	29	36	43	50						Post treatment d/c	Every 3 months
Cycle Day		1	2	8	15	22	1	8	15	22	1	8	15	22		28 (±5) days	
Informed consent [6]	X																
Documentation of BRAF V600 mutation and test performed	X																
Medical history and demographics	X																
Physical examination [7]	X	X		X	X	X	X	X	X	X	X		X		X		
Vital signs [8]	X	X		X	X	X	X	X	X	X	X		X		X		
12-lead ECG [9]	X						X				X + C4 and C5 (then Q12 weeks)				X	X	
ECOG performance status	X	X		X	X	X	X	X	X	X	X		X		X		
Hematology [10]	X	X[11]		X	X	X	X	X	X	X	X		X		X		
Biochemistry [12]	X	X[11]		X	X	X	X	X	X	X	X		X		X		
Serum pregnancy test [13]	X																
Tumor assessments (CT/MRI) [14]	X										X (Q8 weeks)				X		
Dermatology evaluation [15]	X						X				C5 (then Q12 weeks)				X	X[18]	At 6 months
Head and neck	X										C4 (then				X	X[18]	At 6 months

	Screening Period [1]	**Treatment Period** [2] **(Allowed visit window: ± 1 day starting on Day 8 of Cycle 1 and onwards)**													**End of Treatment Visit** [3]	**Safety-Follow-Up Visit** [4]	**Survival Follow-Up** [5]
Cycle (C)		1					2				3 onwards						
Study Day	–28 to –1	1	2	8	15	22	29	36	43	50						Post treatment d/c	Every 3 months
Cycle Day		1	2	8	15	22	1	8	15	22	1	8	15	22		28 (±5) days	
assessment for SCC [16]											Q12 weeks)						
Chest CT for evaluation of SCC [17]	X										C7 (then Q6 months)					X[18]	At 6 months
Vemurafenib dispensation (**Part 1**)			X[19]				X		X		X (Q4 weeks)						
Vemurafenib dispensation (**Part 2**)		X					X		X		X (Q4 weeks)						
Vemurafenib accountability							X		X		X (Q4 weeks)				X		
Vemurafenib Dosing Exception Diary [20]				X	X	X	X	X	X	X	X (Q4 weeks)				X		
DLTs [21]				X	X	X	X										
Concomitant medications [22]	X	X													X	X	
AEs / SAEs [23]	X	X													X	X	
Cetuximab administration		X		X	X	X	X	X	X	X	X	X	X	X			
Follow-up for disease progression																	X
Survival status [5]																X	X
Next anticancer therapy																	X
Anal and pelvic exam[24]	X															X	

Notes Day 1 = first dose of study drug

1. Apart from obtaining written informed consent, no screening procedure may be performed before the patient has been confirmed to be positive for the BRAF V600 mutation. All efforts should be made to collect a tumor sample (formalin-fixed paraffin-embedded tumor tissue [FFPET] or 3-5 serially cut unstained 5-µm sections from one FFPET block) for retrospective confirmation of the BRAF mutation using the cobas 4800 V600 mutation kit. This tumor sample should preferably be from the original specimen used to detect the BRAF mutation. The original tumour block will be returned to the site.
2. Visits during the Treatment Period are to be completed on Day 1, Day 8, Day 15, Day 22, Day 29 and every 14 days thereafter until study drug discontinuation. A visit window of ± 1 day will apply starting on Day 8 of Cycle 1 and onwards.
3. The End of Treatment Visit will be performed when the patient discontinues study medication regardless of when it occurs.
4. The Safety Follow-Up Visit will be performed after 28 (±5) days from discontinuation of study medication
5. The Survival Follow-Up period will last for a minimum of 12 months after the last patient has been enrolled or until all patients have died, withdrawn consent or are lost to follow-up (whichever occurs first).
6. Informed consent must be obtained prior to performing any study procedure including Screening assessments. The date of signature on the informed consent form signifies the beginning of the 28-day Screening Period.
7. Includes the evaluation of the head, eyes, ears, nose, and throat (HEENT); cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal and neurological systems examination; and height (cm) and weight (kg). Height will only be measured during screening.
8. Includes blood pressure, heart rate, temperature and respiratory rate.
9. Includes heart rate, PR interval, QRS duration, QT and QTc intervals and ECG findings.
10. Includes hemoglobin, hematocrit, platelet count, white blood cell count (WBC) and absolute neutrophil count (ANC)
11. Hematology and biochemistry assessments must be done on Day 1, prior to cetuximab administration.
12. Includes amylase, lipase, glucose, blood urea nitrogen [BUN], creatinine or creatinine clearance, sodium, potassium, calcium, magnesium, bicarbonate ([if routinely performed on venous blood samples],), total bilirubin with fractionation into direct and indirect (if total bilirubin elevated during the study), alkaline phosphatase, AST ([SGOT]], ALT ([SGPT]]
13. Serum pregnancy test to be performed within 7 days prior to first vemurafenib administration for women with childbearing potential.
14. CT/MRI of the chest, abdomen and pelvis [C/A/P]). The same imaging technique (CT or MRI) should be used for these patients throughout the study. CT/MRI of the brain may also be performed as per standard of care.
15. Performed by a dermatologist. For patients who develop any suspicious new skin lesion during treatment with study medication. Further confirmation by a designated central pathology laboratory. Only required at the End of Treatment visit if not performed in the previous 12 weeks. Should be done at Safety Follow-up visit at 28 days (±5 days) and at 6 months following study drug discontinuation or until initiation of another anti-neoplastic therapy.
16. Performed by the treating physician as part of the evaluation for SCC. Should be done at Safety Follow-up visit at 28 days (±5 days) and at 6 months following study drug discontinuation or until initiation of another anti-neoplastic therapy.
17. CT of the chest for the evaluation of noncutaneous SCC. The routinely scheduled radiographic assessment for tumor burden may be used (if available) as the chest CT for the evaluation of noncutaneous SCC while the patient is taking study medication.
18. Must be performed at this visit and 6 months following study drug discontinuation or until initiation of another anti-neoplastic therapy.
19. For patients in Part I of Cohort 3b, vemurafenib will start on Day 2 of Cycle 1 (administered while in hospital).
20. Patients will keep a diary to record ONLY those occasions when a vemurafenib dose was missed (morning or evening, each day of treatment). The patient will bring this diary with him/her to each study visit to allow missed doses to be recorded by the Investigator.
21. Only for patients enrolled in the Part 1 of Cohort 3b (the dose-escalation part of the study)
22. All concomitant medications during the study started within 14 days prior to the screening visit and up to the end of study visit must be recorded.

23. During screening AEs are not recorded in the eCRF unless they are SAEs which are related to protocol-mandated procedures. ALL AEs (including SAEs) must be recorded from the time of first study drug administration. After the last dose of study medication any new AEs should be reported up to 28 days after last dose. The Sponsor should be notified if the Investigator becomes aware of any SAE or non-serious AEs of special interest occurring after the end of the adverse event reporting period, regardless of causality.
24. Pelvic examinations for women (with special attention to cervix) and anal examinations for all patients will be performed at screening and at the Safety follow-up visit for evaluation of SCC. The pelvic examination should include a complete external and internal examination (internal examination of uterine cervix may include a Pap smear, which would be a decision of the investigator). The anal examination should include external examination, digital anorectal examination and anoscopy or proctoscopy. However, if in opinion of the investigator the presence of "abnormal lesions including SCC" can be excluded by the external inspection and the manual examination, this is acceptable. However, if the presence of a lesion is suspected, an anoscopy or proctoscopy are recommended.

3.5 Concomitant Medication

At study initiation, patients should continue with their concomitant medications, as prescribed by their physician, with the exception of study precluded medications (see below).

Due to the underlying illness and the frequency of co-existent medical conditions in this patient population, all concomitant medication or treatment required by the patient will be at the discretion of the treating physician. In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the patient are allowed, provided their use is documented in the patient records and on the eCRF.

For Cohort 3b only, prior to the first infusion of cetuximab, patients must receive premedication with an antihistamine and a corticosteroid. This premedication is recommended prior to all subsequent infusions.

See Appendix 9 of protocol for more details for prostate cancer patients.

The following medications and treatments are not allowed while the patient is on the study:

- Other anti-cancer therapies (except cetuximab for patients in Cohort 3b)
- Concomitant alternative therapies and herbal preparations
- Radiotherapy for the treatment of disease during the study; the exception will be limited field radiotherapy for palliative bone pain due to pre-existing bone metastasis if not considered a target lesion for RECIST assessments

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

All other medications (over the counter or prescription only medication) are permitted during this study at the discretion of the Investigator.

3.6 Study Analysis Populations

The main analysis population for the efficacy analysis will be the intent-to-treat (ITT) population, which will include all patients enrolled in the study irrespective of whether they have received study medication or not. ITT1, ITT2, ITT3a to ITT6 will correspond to the ITT population for each cohort (Cohort 1 to Cohort 6, respectively).

The per-protocol (PP) population will not be defined due to the small number of patients per cohort, but protocol deviations will be listed, (including patients with non-measurable disease at baseline) (see section 4.12).

The safety populations SP1, SP2, SP3a to SP6 will correspond to the safety populations for Cohort 1 to Cohort 6, respectively, and will include, for each cohort, all patients who have received at least one dose of study medication.

Cohort 7 (patients with other solid tumour) will include patients with different tumour types and therefore different safety/ITT populations may be defined given at least 5 patients in one indication. In case there are less than 5 patients in each indication, it will be listed together indicating tumour type into a column.

For Stage I interim analysis, all treated patients will be included in the safety analyses. For all summaries to be performed for the efficacy analysis at week 8 of Stage I, the first 7 patients enrolled into Stage I with measurable disease at baseline will be included. For all listings of efficacy analysis at stage 1, all patients available at that time will be included.

3.7 Withdrawn Patients

The following patients will be replaced:

- patients who never received study treatment as per protocol
- patients who did not have measurable disease at baseline

3.8 Randomisation

This is an open label study that includes different cohorts and randomization is not applicable.

3.9 Blinding

This is an open label study. There is no blinding of study treatment.

3.10 Sample Size

The sample size estimation is based on the method of Lin and Shih (1).

There will be up to 170 patients enrolled in this study for the Stage I/II analysis (see Table 3).

There will be 7 cohorts with patients with different indications, and two sub-cohorts with patients with colorectal cancer, one treated only with vemurafenib while other treated with vemurafenib and cetuximab.

Cohorts (except Cohort 3b) will have a minimum of 13 and a maximum of 19 patients at Stage II (depending on results in Stage I).

Cohort 3b will have a dose escalation phase based on a classical 3+3 design and will enrol a maximum of 18 patients. Cohort of patients with recommended dose will be expanded to 7 patients as per rule of Stage I design. Then a further 6 or 12 patients will be enrolled to a maximum of 13 or 19 patients will be enrolled depending on the results for stage I (see Table 3). The maximum number of patients for this cohort might be up to 37 patients.

A proportion of 15% is chosen for a low response, based on present knowledge.

If the number of responders is 2, 3, or 4 out of 7 patients of the corresponding cohort in Stage I, then the study medication is possibly efficacious for that cohort and further data at stage II will be collected based on the "low desirable response at Stage II" Sample Size estimation, i.e., an additional 12 patients will be enrolled in order to have a total of 19 patients for that cohort. Recruitment into cohort will be stopped if the number of responders is less than the pre-specified number in Table 4 (e.g. if there is none or only one responder out of first seven patients). However if a clear clinical benefit has been observed for patients in the cohort (e.g. majority of patients recorded SD at Week 8 and no CR or PR is recorded), then enrolment into Stage II will be allowed for this cohort after discussion with the Sponsor and study Steering Committee.

If there are 5 or more responders out of 7, then further data will be collected based on "high desirable response at Stage II" Sample Size estimation, i.e., an additional 6 patients will be enrolled in order to have a total of 13 patients for that cohort.

Assuming RRs as specified in the hypothesis testing as of section 3.2.1, a power of 80% for high desirable response and 70% for low desirable response and two-sided alpha of 0.1, the number of patients required in each cohort is presented in Table 3:

Table 3: Sample Size for Each Cohort

	Dose Finding*	**At the end of Stage Two**	
		Low desirable response	**High desirable response**
NSCLC		19	13
Ovarian cancer		19	13
Colorectal cancer (Cohort 3a vemurafenib only)		19	13
Colorectal cancer (Cohort 3b vemurafenib and cetuximab)	3+3 Design up to 18	19	13
Cholangiocarcinoma/cancer of biliary tract		19	13
Breast cancer		19	13
MM		19	13
Other tumors(cohort 7)**		19	13
Total number for the whole study	**up to 170 patients**		

* Cohort 3b Part 1 only

** The n's presented are for each individual tumor types with enough patients available to follow the 2 stage study design.

Details regarding Stage I and number of responders are displayed in Table 4:

Table 4: Sample Size for Each Cohort and Each Stage

	Stage (Two-Stage Design)		**Total Number of Patients in Each Cohort**	**Two-Sided Alpha Level / Power**
	Stage I	**Stage II [a]**		
All Cohorts				
Low response at the end of Stage I				
Number of patients	7	19	19	10% / 70%
Number of responders [b]	≥ 2 and ≤ 4	≥ 5		
High response at the end of Stage I				
Number of patients	7	13	13	10% / 80%
Number of responders [b]	≥ 5	≥ 6		

The sample size was estimated using the method of Lin and Shih (1) and corresponding SAS program.

[a] This column displays the maximum number of patients required for each cohort and the number of responders that should be present at the end of Stage II in order to declare efficacious treatment.

[b] Number of patients needed to respond in order to continue into Stage II or have a positive result at the end of the trial.

Recruitment into any cohort/indication can be expanded up to a total of 70 patients if a response rate has been demonstrated in Stage II of that cohort as per stopping rules defined in the protocol or a clear clinical benefit for patients is observed. This will be decided by the Sponsor in discussion with study Steering Committee. The maximum number of patients in this study is therefore 490 (7 cohorts at 70 patients each).

4 Statistical Methodology

4.1 Planned Analyses

The following reporting events are planned in this study for each cohort:

- Stage I analysis (unconfirmed 8 week response available for 7 pats) (SIA)
- Stage II analysis (confirmed 8 week response available for up to 19 pts) in case Stage II is reached (SIIA)
- Additional analysis might be carried out, when last patient in corresponding cohort has been on treatment for at least 6 months, developped progressive disease, withdrew consent or is lost to follow-up, whichever occurs first (AM6A)
- For expanded Cohort 1 (NSCLC), the primary analysis will occur once all patients have at least 9 months of treatment, or the patient developped progressive disease, withdrew consent, or is lost to follow-up, whichever occurs first. (Note: this analysis is not part of this document.)
- Final Analysis (FA)
- Dose Finding Analysis (only cohort 3b) (DFA)

4.2 Statistical Analyses

Statistical analyses will be performed for each cohort separately.

For the Stage II respectively final analyses, baseline characteristics and the efficacy endpoints will be summarised using the ITT populations, whilst safety variables will be summarised for the safety populations. For the cohorts, where corresponding ITT and safety populations are different, the baseline characteristics will be also summarised for the safety population.

Generally, summary statistics will be presented for continuous variables, by way of n, mean, standard deviation (SD), median, minimum and maximum and by way of group frequencies and percentages for categories of categorical variables.

Percentages will be calculated using the total patients within the respective cohort. Number and percentage of responders will be presented together with their corresponding Clopper-Pearson 95% confidence intervals.

For time to event type variables and as indicated in corresponding sections below, 95% confidence interval and Kaplan-Meier (KM) estimates will be calculated.

Due to the expected heterogenious indications in Cohort 7 (patients with other solid tumours) may not be summarised. If there are at least 5 patients in a certain tumour type, number (percentage) of patients will be summarised in frequency tables for RR at Week 8, clinical benefit rate, BOR, AEs and Treatment exposure for these tumour types. Listings will include same information as for other cohorts.

For cohort 7, the decision about further enrolment into stage II will be made for each type of tumour separately. For example, if seven patients of the same tumour type are enrolled in Stage I, then Stage I stopping rules may be applied for these patients.

4.3 Interim Analysis

Each cohort will be analysed for efficacy at the end of Stage I (SIA) and, in case enrolment continues, at Stage II when confirmed week 8 response rate can be assessed (SIIA).

Potentially when last patient in corresponding cohort has been on treatment for at least 6 months, developped progressive disease, withdrew consent or is lost to follow-up, whichever occurs first, (AM6A)

Cohort 3b, the additional dose-finding Part 1 will be analysed separately (DFA) as explained in section 3.3.

No additional interim analysis for efficacy is planned in this study other than that.

4.4 Disposition of Patients

The number of screen failures, reason for screening failure, the number of patients enrolled, number and percentage in each analysis population, the reasons for discontinuation of treatment, time on treatment and the reasons for discontinuation of study will be presented (Table 14.1.1, Listing 16.2.4.1).

Time on treatment (date of last dose - date of first dose + 1) will be summarised separately for each study treatment using KM approach. Patients who withdrew will be counted as patients with events while patients who did not withdraw will be censored on the date of last study drug intake prior to cut-off date. If date of last study drug intake is partially missing then the 1st of month will be used unless using the 1st of the month produces a date before date of last former study drug intake or interruption (without stop date). In such cases, the date of last study drug intake/start of interruption will be used. If date of last dose is completely missing then the date of last study drug intake + 15 will be used.

- Date of 1st study drug intake = Day 1 of cycle.

4.5 Demographic, Baseline Information and Medical History

Following information will be summarised for each cohort, in the cases where applicable specific to each cohort:

- Demography including: gender, age, age group (<65 and >=65), race, ethnicity, smoking history, height and weight (Table 14.1.2.1, Listing 16.2.4.3)
- Patients by centre (Table 14.1.2.2, Listing 16.2.4.3)
- Cancer disease history including: number and percentage of patients by origin of primary tumour, histological tumour type and grade, stage at diagnosis and current stage (Table 14.1.4.1, Listing 16.2.4.4.1)
- Surgical resection of primary tumour including (not for cohort 6): number and percentage of patients with surgical resection of primary tumour and by type/location of resection (Table 14.1.4.2, Listing 16.2.4.4.2)
- Screening dermatology evaluation including: number and percentage of patients with any history and number and percentage of patients with a history of any of following risk factors: Sorafenib, photochemotherapy for psoriasis, chronic sun exposure, tanning beds, immunosuppresion, prior actinic keratosis, prior keratocanthoma, prior squamous cell carcinoma, prior malignant melanoma and other risk factors for cutaneous squamous cell carcinoma (Table 14.1.6, Listing 16.2.4.4.3)

- Prior systemic therapies including: number of systemic agents, number and percentage of patients previously treated with at least one systemic agent and number and percentage of patients treated with each systemic agent displayed by therapeutic class and preferred term (Table 14.1.5.1, Listing 16.2.4.5.1)
- Prior radiotherapies including: number and percentage of patients previously treated with radiotherapy and by purpose (Table 14.1.5.2, Listing 16.2.4.5.2)
- Relevant Medical and Surgical History (excluding cancer): number of clinically significant diseases, number and percentage of patients with at least one clinically significant disease and number and percentage of patients with each disease displayed by body system and preferred term for diagnosis (Table 14.1.3.1, Listing 16.2.4.6)
- Active Medical and Surgical History (excluding cancer): number of clinically significant diseases, number and percentage of patients with at least one clinically significant disease and number and percentage of patients with each disease displayed by body system and preferred term for diagnosis (Table 14.1.3.2, Listing 16.2.4.6)
- BRAF V600 Mutation Information at baseline (Table 14.1.7, Listing 16.2.4.7)

Notes:

Age will be calculated as the integer ((Date of Consent – Date of Birth) / 365.25). If the day of birth is missing, it will be replaced with the 1st of the month; if the month of birth is missing, it will be replaced with January. Age will be presented/summarised as a whole number.

Female reproduction status will be listed as part of the demography listing (Listing 16.2.4.3)

The diagnosis of the medical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

4.6 Efficacy Analysis

The efficacy parameters will be summarised for the ITT population of each cohort and presented in tables, figures and listings at different times of analysis (StageI, Stage II, 6 month on treatment Stage II analysis, Final Analysis) given there are at least 7 patients available as detailed in the following sections.

In addition for cohort 3B, response rate and best overall response rate (BORR) will be summarised by dose group.

4.6.1 Primary endpoint

Response rate (unconfirmed) at week 8 is the primary endpoint for the statistical analysis of Stage I.

For the Stage II analyses and the final analysis, confirmed response rate at week 8 is the primary endpoint.

A patient is assigned a confirmed 8 week response in case of a response assessment of either CR or PR at week 8 and at a second assessment at least 4 weeks (28 days) afterwards which confirms it. In all other cases, patients are considered non-responders at week 8. Particularly patients who receive study treatment but do not undergo a post-baseline tumor assessment will be counted as non-responders.

Unconfirmed (Stage I) respectively confirmed response (Stage II, final analysis) will be displayed in corresponding versions of Table 14.2.1.1.

Listings for overall response (Listing 16.2.6.1.1) as well as for individual assessments of target (Listing 16.2.6.1.2) and non-target lesions (Listing 16.2.6.1.3), in case of solid tumour cancers, will be provided.

Listings for overall response (Listing 16.2.6.2.1) as well as for individual assessment of Multiple myeloma (Listing 16.2.6.2.2 to 16.2.6.2.7) will be provided.

In cohort 7, patients with LCH/ECD the tumor response assessment can be based on RECIST v1.1, PERCIST v1.0 or Multiple assessments. The overall response summary table (Table **Error! Reference source not found.**) will therefore be split by method and overall results for this indication will also be put together based on Investigator assessment (responder, non responder). The pooled overall response evaluations will be displayed in Listing 16.2.6.3.1 and the lesion evaluation via PERCIST in Listing **Error! Reference source not found.**.

The following patients will be considered as responders:

- CR or PR according to RECIST v 1.1
- CMR or PMR according to PERCIST v 1
- Responders based on Overall Response according to Multiple assessments

In all other cases, patients are considered non-responders at week 8. Particularly patients who receive study treatment but do not undergo a post-baseline tumor assessment will be counted as non-responders.

Next anticancer therapy after discontinuation of study medication will be listed (Listing 16.2.6.).

4.6.2 Method of analysis for primary outcome

For patients with solid tumors, responders at Week 8 will be defined based on tumor assessment status of PR or CR at Week 8. For patients with MM, responders at Week 8 will be defined based on tumor assessment status of CR, sCR, VGPR or PR.

If a pre-specified minimal RR will not be achieved in certain cohorts in the first stage of the study in certain cohorts, this cohort will be closed and no further enrolment of patients will be performed for that cohort. However, if a clear clinical benefit has been observed for patients in the cohort, e.g. majority of patients recorded SD at Week 8 and no CR or PR is recorded, then enrolment into Stage II might be allowed for this cohort after discussion with the Sponsor and study Steering Committee. In that case, stage II of that cohort would be handled like “Low response at the end of Stage I” and another 12 patients enrolled, to have 19 patients in total for that cohort.

Only patients with measurable disease at baseline will be included in the analysis of the RR. Patients without a post-baseline tumor assessment will be considered to be non-responders.

The hypotheses for all cohorts for Stage I is:

$H_0: \pi_{N1} < \pi_0$
$H_1: \pi_{N1} \geq \pi_0$

Where: N1 is the percentage of responders within the cohort and $\pi_0 = 15\%$

If H_0 is rejected (and H_1 is accepted), this may result in further patients being enrolled into Stage II of the study based on the number of responders (as of unconfirmed responses at week 8) in Stage I. As this is an early phase II study and cohorts are independent no adjustment will be made for multiplicity.

The number and percentage of responders together with the corresponding Clopper-Pearson 95% confidence interval will be presented for each cohort. In addition, the number and percentage of patients in each response category will also be presented. For cohort 3B confirmed week 8 response rate will be summarised by dose level. All response data including the number of target and non-target lesions will be listed.
Cohort 3b: For this cohort, first, the recommended dose for Stage I/II part should be established based on 3+3 classical design. Then the second part will include a stage I and II parts similar to what is planned for the other cohorts and same statistical hypotheses at Stage I and Stage II will be applied.

The percentage decrease from baseline in sum of diameters at week 8 (Figure 14.2.6.1) and the maximum percentage decrease from baseline (Figure 14.2.6.2.1) in sum of diameters for target lesions will be plotted in a waterfall plot. Only patients with measurable disease at baseline will be included in the graphical presentation. Bars will be coded according to confirmed and unconfirmed BOR. Maximum % decrease, confirmed BOR and unconfirmed BOR will be listed. All patients, irrespectively of measurable disease at baseline will be listed.

4.6.3 Secondary end-points

4.6.3.1 Progression free survival (PFS)

PFS, measured in days, is defined as the time from the first day of study treatment until the first documented progression of disease or death from any cause, whichever occurs first. PFS for patients who have neither progressed nor died will be censored on the date of last evaluable tumor assessment prior to the data cutoff date. Data for patients who have not died and have no recorded post-baseline tumor assessment will be censored on the date of the first dose of study medication plus 1 day. Patients who die without any recorded post-baseline tumor assessment after receiving the first dose will be considered to have an event on the date of death. Data for patients who are lost to follow-up prior to documented progression will be censored at the last evaluable tumor assessments date which the patient is known to be progression-free prior to the data cut-off date. Patients who die or have progression after two or more consecutive missed visits will be censored at the date of the last evaluable tumor assessment.

PFS will be assessed at SIIA and FA.

For each cohort estimates of the median PFS and the corresponding two-sided 95% CI will be presented along with the estimates for the 25^{th} and 75^{th} percentiles and the associated ranges (minimum, maximum) using the Kaplan-Meier (KM) approach (Table 14.2.2.1, Figure 14.2.1, Listing 16.2.6.).

4.6.3.2 Time to progression (TTP)

Time to progression is defined as time from the first day of study treatment to the first occurrence of progressive disease. Patients who have not progressed at the time of study completion (including patients who have died before progressive disease) or who are lost to follow-up are censored at the date of the last tumour assessment prior to data cutoff. Patients who have no recorded post-baseline tumor assessment will be censored on the date of the first dose of study medication plus 1 day. Data for patients who are lost to follow-up prior to documented progression will be censored at the last evaluable tumor assessment date which the patient is known to be progression-free prior to data cutoff. Patients who have progression after two or more consecutive missed visits will be censored at the date of the last evaluable tumor assessment.

TTP will be assessed at SIIA and FA.

TTP will be analysed and presented in the same way as PFS (Table 14.2.2.2, Figure 14.2.2, Listing 16.2.6.).

4.6.3.3 Best overall response (BOR)

BOR is defined as the best response recorded from the first day of study treatment until disease progression/recurrence, death or end of study respectively data cut-off, what ever comes first. Patients with solid tumours are considered responders if they have a tumour assessment status of PR or CR according to RECIST, v1.1. Patients with MM are considered responders if they have a status of CR, sCR, VGPR or PR according to IMWG uniform response criteria. In the same way as for the primary endpoint RR, response must be confirmed not less than 4 weeks after the criteria for response are first met; only patients with measurable disease at baseline will be included in the analysis of the BOR; patients without a post-baseline tumour assessment will be considered to be non-responders.

The following algorithm describes how best overall response (BOR) is determined from the overall tumor assessments. The hierarchy used to determine best overall response is CR>PR>SD>PD/NE/NA/ND:

- Once a CR is observed (confirmed or unconfirmed) any unequivocal reappearance of disease results in progression. That is, neither a PR nor SD may follow a CR.
- For confirmation of PR:
  - The confirming 2nd PR needs to be consecutive tumor assessments of PR (i.e. if 1 or more SDs occur between the initial and the confirmatory PR, then the BOR will be SD, not PR).
  - A CR will confirm an unconfirmed PR.
- Unconfirmed CR or PR will be defined as a BOR of SD, provided the requirement for at least a 6-week interval since start of treatment has been respected. An unconfirmed CR or PR occurring less than 6 weeks after the start of treatment will be defined as Unevaluable.
- Once a PR is confirmed, the status shall remain PR or improve to CR until criteria for SD or PD are met.

An overall response of progressive disease that was based solely on symptomatic deterioration will not be used in the evaluation of BOR.

Patients who were enrolled and did not receive any study treatment will have a best overall response 'Missing' and will be included as non-responders in the analysis of BOR.

BOR will be assessed at SIIA and FA.

For each cohort, number and percentage of responders in BOR with corresponding Clopper-Pearson 95% confidence intervals and a summary of the number and percentage of patients categorized by confirmed BOR category will also be presented.For cohort 3b BOR will be summarised by dose level.

For patients with solid tumours, these categories are: CR, PR, SD, PD, NE; for MM patients, they are: sCR, CR, VGPR, PR, MR, No change/SD, Plateau, PD, Relapse, Relapse from CR (Tables 14.2.2.3, Listing **Error! Reference source not found.**).

The responses by visit will be listed together with BOR (Listings 16.2.6.1.1 and 16.2.6.2.1).

As with response at week 8, in cohort 7, patients with LCH/ECD could be assessed using different methods RECIST v1.1, PERCIST v1.0 or Overall Response according to Multiple assessments. Same rules apply as for response at week 8.

4.6.3.4 Clinical benefit rate (CBR)

Clinical benefit response includes patients whose best response was:

- Confirmed PR (or VGPR) or
- Confirmed CR (or sCR) or
- Stable disease (SD) that have lasted at least 6 weeks.

For the purpose of the stage I analysis clinical benefit response (at week 8) is defined as:

- Unconfirmed PR (or VGPR) or
- Unconfirmed CR (or sCR) or
- Stable disease (SD) that have lasted at least 6 weeks.

In the same way as for the primary endpoint RR and for BOR, response must be confirmed not less than 4 weeks after the criteria for response are first met; only patients with measurable disease at baseline will be included in the analysis of the CBR; patients without a post-baseline tumour assessment will be considered to be CRB non-responders.

CBR will be assessed at SIA, SIIA and FA.

For each cohort, CBR with corresponding Clopper-Pearson 95% confidence will also presented (Table 14.2.2.3, Listing 16.2.6.1.1 and 16.2.6.2.1).

For patients with LCH/ECD, the same rules for response categories apply as for response at week 8.

4.6.3.5 Time to response (TTR)

Time to response is defined as the time from the first day of study treatment to the first date the response criteria are met, given they were later confirmed. Patients who are not confirmed responders will be censored at the time of their last evaluable tumour assessment. Patients with no tumour assessment after the baseline visit will be censored at the time of the first day of study treatment plus 1 day.

TTR will be assessed at SIIA and FA, if there are any responses.

TTR will be analysed and presented in the same way as PFS (Table 14.2.2.4, Figure 14.2.3, Listing **Error! Reference source not found.**).

For patients with LCH/ECD, the same rules for response categories apply as for response at week 8.

4.6.3.6 Duration of response (DOR)

Duration of response in BOR is defined only for the patients whose confirmed best response is CR or PR, as the time interval between the date of the earliest qualifying response (according to RECIST, v1.1 for patients with solid tumours and according to IMWG uniform response criteria for patients with MM) and the date of PD or death from any cause, whichever occurs first. For patients who are alive without progression following the qualifying response, DOR will be censored on the date of last evaluable tumor assessment or last follow-up for PD before the data cutoff date. Data for patients who are lost to follow-up prior to documented progression will be censored at the last tumor assessment date which the patient is known to be progression-free prior to the data cutoff date.

Note that if an overall assessment of PR occurs before confirmation of CR, the duration of response endpoint will not begin at the time that the BOR of CR is shown but rather at the earlier time point showing PR.

DOR will be assessed at SIIA and FA, if there are any responses.

Estimates of the median duration of response and the corresponding two-sided 95% confidence interval will be presented along with the estimates for the 25th and 75th percentiles and the associated ranges (minimum, maximum). The survivor function will be displayed graphically using a Kaplan-Meier curve.

DOR will be analysed and presented in the same way as PFS (Table 14.2.2.5, Figure 14.2.4, Listing **Error! Reference source not found.**).

For patients with LCH/ECD, the same rules for response categories apply as for response at week 8.

4.6.3.7 Overall survival (OS)

OS (time to death) is defined as time between the first day of study treatment and date of death of any cause. Patients for whom no death is captured on the clinical database are censored at the last date they were known to be alive. Patients with no post baseline information will be censored at the time of first study treatment plus 1 day.

OS will be assessed at FA.

OS will be analysed and presented in the same way as PFS (Table 14.2.2.6, Figure 14.2.5, Listing 16.2.6.).

4.6.4 Stopping Rules

Stopping Rules for Enrolment and Screening

If no patients are enrolled in the remaining cohorts one year after any of the cohorts has completed enrolment, then enrolment in those remaining cohorts will be stopped (patients already in screening will be allowed to enroll if eligible).

Individual cohorts will stop enrollment once 7 patients with evaluable disease at basleine have been enrolled into that cohort, to allow for the stage I analysis before progressing to stage II.

Rules for Stage I

Enrollment into Stage I will be stopped if the number of (unconfirmed) responders is less than the pre-specified number in table 4 (e.g. if there is none or only one responder out of first seven patients). However if a clear clinical benefit has been observed for patients in the cohort, e.g. the majority of patients recorded SD at Week 8 and no CR or PR is recorded, then enrolment into Stage II might be allowed for this cohort.

If the required response during Stage I or a good clinical benefit is observed for a particular cohort as mentioned above, then additional patients will be enrolled in the second stage of the corresponding cohort, in order to achieve total number of patients required as specified in the Tables 3 and 4 (cf. section Sample Size 3.10).

Cohort 7 will be closed to enrolment when all other cohorts are closed and results are reported, regardless of the number of patients recruited at that time. This cohort may be quite heterogeneous and will be examined primarily to seek efficacy signals in the relatively rare BRAF V600 mutation-positive tumours.

Rules for Stage II

A study treatment will be considered to be efficacious in a cohort in Stage II if

- there is no unacceptable toxicity

and

- the number of responders is equal or above the specified number in the sample size calculations, as presented in Table 4

or

- BOR (confirmed) is higher than 15%.

Cohort Expansion

There will be no formal statistical hypothesis tested as part of the expansion cohort analysis. The analysis of the expanded cohort will allow estimation of RR with increased precision and more insight concerning the safety profile.

4.7 Safety Analysis

All safety variables will be summarised for the safety population of each cohort.

For cohort 3b, all safety summaries will be done by dose level and overall column.

4.7.1 Adverse events

Only treatment emergent AEs (AEs occurring on the day of or after first administration of any study treatment) will be included in the AE and SAE summaries. Where an AE start date is partially or fully missing, and it is unclear as to whether the AE is treatment emergent, it will be assumed that it is.

Intensity of all adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events, Version 4.0 (CTCAE, v4.0) on a five-point scale (Grade 1 to 5).

All AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

All adverse events (Table 14.3.1.1) as well as serious adverse events (SAE) (Table 14.3.1.2) will be summarised by presenting the number and percentage of patients having any event, having an event leading to discontinuation of any study drug, by CTC grade, by relationship to any study drug and outcome.

AEs will be summarised separately for each cohort by presenting the number and percentage of patients having any event as well as number of events, by event in each MedDRA system organ class (SOC) and preferred term (PT) for the following subgroups:

- Adverse Events by System Organ Class (SOC) and Preferred Term (PT) (Table 14.3.2.1)
- Adverse Events with CTC Grade 1 or 2 by SOC and PT (Table 14.3.2.2.1)
- Adverse Events with CTC Grade 1 or 2 by CTC Grade, SOC and PT (Table 14.3.2.2.2)
- Adverse Events with CTC Grade 3 or 4 by SOC and PT (Table 14.3.2.3.1)
- Adverse Events with CTC Grade 3 or 4 by CTC Grade, SOC and PT (Table 14.3.2.3.2)
- Serious adverse events by SOC and PT (Table 14.3.2.4)
- AEs leading to study drug interruption by SOC and PT (Table 14.3.2.5)
- AEs leading to study drug discontinuation by SOC and PT (Table 14.3.2.6)
- AEs leading to study drug interruption or discontinuation by SOC and PT (Table 14.3.2.7)
- AEs leading to study drug reduction by SOC and PT (Table 14.3.2.8)
- AEs leading to death by SOC and PT (Table 14.3.2.9)
- Related AEs by SOC and PT (Table 14.3.3.1)
- AEs Related to Vemurafenib by SOC and PT (Table 14.3.3.1.1) (only Cohort 3B)
- AEs Related to Cetuximab by SOC and PT (Table 14.3.3.1.2) (only Cohort 3B)

- AEs Related to Vemurafenib and Cetuximab by SOC and PT (Table 14.3.3.1.3) (only Cohort 3B)
- Related AEs with CTC grade 1 or 2 by SOC and PT (Table 14.3.3.2.1)
- Related AEs with CTC grade 1 or 2 by CTC grade, SOC and PT (Table 14.3.3.2.2)
- Related AEs with CTC grade 3 or 4 by SOC and PT (Table 14.3.3.3.1)
- Related AEs with CTC grade 3 or 4 by CTC grade, SOC and PT (Table 14.3.3.3.2)
- Related Serious Adverse Events (SAEs) by SOC and PT (Table 14.3.3.4)
- Related AEs leading to study drug interruption by SOC and PT (Table 14.3.3.5)
- Related AEs leading to study drug discontinuation by SOC and PT (Table 14.3.3.6)
- Related AEs leading to study drug interruption or discontinuation by SOC and PT (Table 14.3.3.7)
- Related AEs leading to study drug reduction by SOC and PT (Table 14.3.3.8)
- Related AEs leading to death by SOC and PT (Table 14.3.3.9)

A patient with more than one occurrence of the same AE in a particular system organ class respectively preferred term will be counted only once in the total of those experiencing AEs in that particular system organ class. If a patient experiences the same adverse event at more than one CTC grade level, or with more than one relationship to study drug, the most severe rating or the stronger causal relationship to study drug will be given precedence. Any missing CTC grade, causality, or outcome will not be imputed and classed as unknown.

Related refers to those events that there is a reasonable suspected causal relationship to the respective study medication, or with an unknown relationship.

Progression of underlying malignancy will not be reported as an AE if it is clearly consistent with the suspected progression of the underlying cancer; also deaths and hospitalizations solely due to PD may not be reported as SAEs. Clinical symptoms of progression may be reported as AEs if the symptom cannot be determined as exclusively due to the progression of the underlying disease, or does not fit the expected pattern of progression for the disease. If there is any uncertainty about an AE being due only to the disease under study, it will be reported as an AE or SAE.

4.7.1.1 AEs of special interest (AESI)

A summary table of the number and percentage of patients having AEs of special interest and the number of events will be presented by AE of special interest group and preferred term (Table 14.3.4.1).

A summary of the number and percentage of patients in each AE of special interest group and preferred term will also be summarized by NCI CTCAE Grade. Patient having multiple occurrences of AEs in the same AE group will presented only once using the most severe CTC grade (Table 14.3.4.2).

AEs of Special Interest for Statistical Analysis Purposes

The following AE preferred terms are defined as being of special interest for statistical analysis purposes. Terms may be added to the definitions when the data are reviewed prior to analysis. For new primary melanoma and second primary malignancy only cases that are confirmed following medical review will be included.

- cSCC (search terms: bowen's disease, keratoacanthoma, lip neoplasm, lip neoplasm malignant stage unspecified, squamous cell carcinoma of skin, cutaneous squamous cell carcinoma, treatment related secondary malignancy, squamous cell carcinoma in situ of skin, carcinoma in situ of the skin, basal cell carcinoma, neuroendocrine carcinoma of the skin)
- rash (search terms: dermatitis, dermatitis, bullous, dermatitis contact, erythema, folliculitis, generalized erythema, palmar erhytema, plantar erhytema, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash maculovesicular ,vasculitic rash; rash morbilliform, butterfly rash, rash papular, rash paplosquamous , rash pruritic, rash pustular, rash vesicular, dermatitis acneiform, rash generalised, dermatitis exfoliative, skin exfoliation, exfoliative rash, erythema multiforme, dermatitis atopic, drug rash with eosinophilia and systemic symptoms, dermatitis allergic, palmar-plantar erythrodysaesthesia syndrome, urticaria, eczema, eczema numular, erythema nodosus)
- photosensitivity (search terms: photosensitivity allergic reaction, photosensitivity reaction, sunburn, photodermatosis, actinic keratosis, solar dermatitis, xeroderma, actinic cheilitis, solar lentigo)
- liver function abnormalities (search terms: alanine aminotransferase increased, alanine aminotransferase, alanine aminotransferase abnormal, aspartate aminotransferase increased, aspartate aminotransferase, aspartate aminotransferase abnormal, alkaline phosphatase increased, blood alkaline phosphatase increased, blood alkaline phosphatase, blood bilirububin increased, increased bilirubin intermittent, bilirubin unconjugated increased bilirubin conjugated increased, blood bilirubin, bilirubin increased , hyperbilirubinaemia, jaundice, hepatic enzyme increased, blood creatine phosphokinase increased, transaminases, hypertransaminasaemia, transaminase abnormal, hepatotoxicity, drug-induced liver injury, hepatomegaly, cholelithiasis, cholestasis, hepatic function abnormal, hepatitis, hepatocellular injury, cholecystitis, cholecystitis acute, bile duct obstruction, liver disorder, portal vein thrombosis, liver function test abnormal, hepatic failure, granulomatous liver disease, hepatic cirrhosis, hepatic steatosis, hepatitis toxic)
- arthralgia (search terms: arthralgia, swallowed hurting joints, artralgia (shoulder))
- fatigue (search terms: asthenia, fatigue, lethargy, listless, malaise, sluggishness, chronic fatigue syndrome)
- prolongation of cardiac repolarization or arrhythmia (search terms: torsade de pointes/QT prolongation (SMQ): electrocardiogram QT interval abnormal, electrocardiogram QT prolonged, long QT syndrome, long QT syndrome congenital, torsades de pointes, ventricular tachycardia, cardiac arrest, cardiac death, cardiac fibrillation, cardio-respiratory arrest, electrocardiogram QRS complex prolonged, electrocardiogram T wave inversion, conduction disorders, atrial fibrillation, sinus tachycardia, atrial flutter, arrhythmia, supraventricular tachycardia, ventricular extrasystoles, bundle branch block left, cardiac arrest, sinus bradycardia, atrioventricular block, atrioventricular block first degree, bundle branch block right, extrasystoles, atrial tachycardia, bifascicular block, bradyarrhythmia, electrocardiogram QT interval abnormal, electrocardiogram, electrocardiogram repolarisation abnormality, electrocardiogram U-wave abnormality, electrocardiogram U-wave biphasic, loss of consciousness, sudden cardiac death, sudden death, syncope, ventricular arrhythmia, ventricular fibrillation, ventricular) flutter, ventricular tachyarrhythmia, tachyarrhythmia)

- new primary melanoma (search terms:, malignant melanoma, malignant melanoma in situ, dysplastic naevus, superficial spreading melanoma stage I, superficial spreading melanoma stage unspecified, cutaneous metastatic melanoma, melanoma in situ, any term containing "melanoma")
- non-cutaneous SCC (search terms: Search for records where the preferred term (PT) OR the verbatim term contains at least one of the following: 'cancer', 'carcinoma', 'neoplasm' or 'malig'. Exclude records where: PT='basal cell carcinoma', PT contains the text 'skin' or 'cutaneous', Verbatim term contains the text 'skin' or 'cutaneous', squamous cell carcinoma (not specified))
- second primary malignancies (search terms: Malignant Tumours SMQ plus Tumours of Unspecified Malignancy SMQ)
- Pancreatitis (search terms: acute pancreatitis, chronic pancreatities, elevated lipase, elevated amylase)

All AE information collected (AE start and stop dates, initial intensity, most extreme intensity, relationship, outcome, any dose adjustment of any study drug, whether concomitant medication was taken) will be listed. SAE's and non treatment emergent AEs will be identified in the listings. The following listings will be prepared for AEs:

- All AEs (Listing 16.2.7.1.1)
- SAEs (Listing 16.2.7.1.2)
- AEs leading to dose reduction or temporary treatment interruption (Listing 16.2.7.1.3)
- AE leading to permanent treatment discontinuation (Listing 16.2.7.1.4)
- AE leading to death (Listing 16.2.7.1.5)

Time to first incidence (days) and cumulative dose to the first incidence will be summarised at Stage II (Table 14.3.4.3) for the following AEs of special interest for statistical analysis purposes using descriptive statistics:

- cSCC

Estimates of the median time to first incidence and the corresponding two-sided 95% CI will be presented along with the estimates for the 25th and 75th percentiles and the associated ranges (minimum, maximum). The survivor function will be displayed graphically using a KM curve. Patients without an event will be censored on the date of last contact. AEs with missing or partial start dates will be included in the count of events, time to first occurrence will be calculated based on an imputed date: if the day is missing, it will be replaced with the 1st of the month; if the month is missing, it will be replaced with January. If this results in a negative value the date of first dose will be used.

Cumulative dose to the first incidence will be summarised as a continuous variable.

4.7.1.2 Dose limiting toxicities (DLT)

Particularly for Cohort 3b, part 1, i.e. the dose-finding part of the study, the DLTs as defined in Section 3.3.3 will be summarised and listed by dose levels (Table 14.3.5.1**Error! Reference source not found.**, Listing 16.2.7.1.6).

4.7.1.3 Infusion-related AEs during or within 24h after Cetuximab infusion

For Cohort 3b, infusion-related AEs during or within 24h after Cetuximab infusion will be summarised and listed by dose levels and cycle (Table 14.3.5.2, Listing 16.2.7.1.7).

4.7.2 Laboratory findings

Absolute values and changes from baseline of the laboratory parameters will be summarised by visit:

Haematology (Table 14.3.6.1, Listing 16.2.7.3.1):

- Haemoglobin
- Haematocrit
- Platelet count
- White blood cell (WBC) count
- Absolute neutrophil count (ANC)

Biochemistry (Table 14.3.6.3, Listing 16.2.7.3.2):

- Glucose
- C - reactive protein
- Blood Urea Nitrogen (BUN)
- Creatinine
- Creatinine Clearance
- Sodium
- Potassium
- Calcium
- Magnesium
- Bicarbonate (if done in venous blood)
- Total bilirubin (direct/indirect)
- Alkaline phosphatase
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Lipase
- Amylase

For all laboratory parameters, shift tables will be presented comparing NCI-CTC grade at baseline to the worst grade during the treatment period.will be presented (Tables 14.3.6.2 and 14.3.6.4).

At SIA, for each patient, the laboratory values, standardised by upper normal range, at stage II only will also be graphically displayed over time, including some basic demography info of the corresponding patient:

- Figure with the four liver function tests, i.e. AST, ALT, total bilirubin, alkaline phosphatase (Figure **Error! Reference source not found.**).
- Figure with creatinine test (Figure **Error! Reference source not found.**).

Liver Function Test Abnormalities (Table 14.3.4.4.1 and 14.3.4.4.2)

At Stage II only, the number and percentage of patients who experience worsening of liver function tests (AST, ALT, total bilirubin, direct and indirect bilirubin, alkaline phosphatase) after start of study treatment and the number and percentage of patients who experience worsening of each individual liver function test will be summarized. Worsening is defined as at least one grade increase in lab value on-study compared to the baseline grade

For patients who experienced a worsening, time to first worsening and time to return to baseline grade will be summarized as well as the number of times a worsening occurred (number and percentage of patients). A second, third worsening is counted only after the previous worsening has returned to baseline grade.

The number and percentage of patients who experience worsening of liver function tests (AST, ALT, total bilirubin, alkaline phosphatise) afer start of study treatment willb e summarized. Worsenings of one grade from baseline and worsenings of two or more grades from baseline will be presented.

Patients with at least 2 concurrent liver function test worsenings (AST, ALT, total bilirubin, alkaline phosphatase) will be listed by visit.

Notes:
- All results outside predefined normal ranges will be flagged in the data listings.
- For repeat or unscheduled laboratory assessments, the worst value between the corresponding scheduled visit and before following scheduled visit will be used for summaries.
- Unscheduled assessments with missing assessment date will not be included in summaries.
- Any other laboratory test results will be listed only.

4.7.3 ECG

ECG parameters heart rate, PR interval, QRS duration, QT interval and QTcF interval will be summarised by visit over time (Table 14.3.7.1). ECG findings (normal, abnormal but not clinically relevant and abnormal and clinically relevant) will also be assessed over time (Table 14.3.7.2).

The corrected QT interval QTcF will be derived from QT and RR values, using Fridericia's formula:

QTcF = QT / RR^1/3,

where RR = 60 / heart rate.

The number and percentage of patients whose ECG recordings meet any of the following criteria will be summarised over time (Table 14.3.7.3):

- Absolute QTcF values > 450 msec, > 480 msec and > 500 msec
- Change from baseline in QTcF interval > 30 msec and > 60 msec

The number and percentage of patients who experience QTcF > 500 ms after start of study treatment will be summarised. For those patients time to first elevated result and time to return to baseline (or < 450 ms) will be summarised (Tables 14.3.7.4).

For patients with absolute QTcF > 500 ms, additional summaries and listings will be provided:

- cardiac history (Table 14.3.7.5)
- concomitant medications (Table 14.3.7.6)
- cardiac events

All ECG parameters will also be listed for each assessment (Listing 16.2.7.5).

Note:
- For unscheduled ECG assessments, the worst value between the corresponding scheduled visit and before following scheduled visit will be used for summaries.
- Unscheduled assessments with missing assessment date will not be included in summaries.

4.7.4 Vital signs

Results and change from baseline for vital signs (systolic and diastolic blood pressure, pulse, respiratory rate and temperature) will be summarised by visit (Table 14.3.8, Listing 16.2.7.6).

Note:
- For unscheduled vital sign assessments, the worst value between the corresponding scheduled visit and before following scheduled visit will be used for summaries.
- Unscheduled assessments with missing assessment date will not be included in summaries.

4.7.5 ECOG Performance Status

ECOG performance status (Grade 0 - Grade 5) will be be summarised by visit by presenting the number and percentage of patients in each category (Table 14.3.9, Listing 16.2.7.4). For Stage II and in the final analysis, percentage of patients in each category will be presented graphically with bar charts over time (Figure 14.3).

Note:
- For unscheduled ECOG assessments, the worst value between the corresponding scheduled visit and before following scheduled visit will be used for summaries.
- Unscheduled assessments with missing assessment date will not be included in summaries.

4.7.6 Dermatology evaluation

Dermatological evaluations will be summarised for each assessment point by

- number and percentage of patients with and without skin lesions (baseline lesions at screening/new lesions at post-screening visits)
- number and percentage of patients with skin lesions at each site (back, torso, breast, leg, arm, face, scalp, neck and other),
- number and percentage of patients with lesions which were biopsied/excised and sent for local pathological evaluation,
- number and percentage of patients by pathology diagnosis (cSCC, cSCC in situ (also known as Bowen's disease), cSCC - Keratoacanthoma type, Actinic keratosis, Basal cell carcinoma, Malignant Melanoma and other),
- number and percentage of patients with biopsied lesions sent to the central laboratory

(Table 14.5.1, Listing 16.2.7.7)

Notes:
- For unscheduled post-baseline dermatological evaluations, the lesions discovered resp. confirmed between two scheduled visits will be attributed to the former scheduled visit for summaries.
- Unscheduled assessments with missing assessment date will not be included in summaries.

4.7.7 Head and Neck Assessment for Squamous Cell Carcinoma (SCC)

Head and neck assessments for SCC will be summarised for each assessment point by

- number and percentage of patients with head and neck exam performed
- number and percentage of patients with suspicion of SCC found
- number and percentage of patients with suspicion confirmed by local pathology laboratory

- number and percentage of patients by outcome diagnosis of local pathology laboratory
- number and percentage of patients with biopsied lesions sent to the central laboratory

(Table 14.5.2, Listing 16.2.7.8)

Notes:
- For unscheduled post-baseline head and neck assessments, the lesions discovered resp. confirmed between two scheduled visits will be attributed to the former scheduled visit for summaries.
- Unscheduled assessments with missing assessment date will not be included in summaries.

4.7.8 Chest CT for Evaluation of SCC

Chest CT for Evaluation of will be summarised for each assessment point by

- number and percentage of patients with a chest CT scan performed
- number and percentage of patients with suspicion of SCC found
- number and percentage of patients with suspicion confirmed by local pathology laboratory
- number and percentage of patients by outcome diagnosis of local pathology laboratory
- number and percentage of patients with biopsied lesions sent to the central laboratory

(Table 14.5.3, Listing 16.2.7.9)

Notes:
- For unscheduled post-baseline head and neck assessments, the lesions discovered resp. confirmed between two scheduled visits will be attributed to the former scheduled visit for summaries.
- Unscheduled assessments with missing assessment date will not be included in summaries.

4.7.9 Pelvic and Anal Examination for SCC

Pelvic and anal examination for SCC will be summarised for each assessment point by

- number and percentage of patients with a pelvic resp. anal examination performed
- number and percentage of patients with suspicion of SCC found
- number and percentage of patients with suspicion confirmed by local pathology laboratory
- number and percentage of patients by outcome diagnosis of local pathology laboratory
- number and percentage of patients with biopsied lesions sent to the central laboratory

(Tables 14.5.4 and 14.5.5, Listings 16.2.7.10 and 16.2.7.11)

4.7.10 Physical examination

Physical examination results at each visit will be listed only (Listing 16.2.7.12).

4.8 Deaths

All cases of death will be summarised by primary cause of death, underlying cause and relationship to study medication and listed, independently whether considered an AE/SAE or not (Table 14.4, Listing 16.2.7.2.1).

Deaths within 30 days of start of treatment, within 28 days and within 60 days after last administration of study drug will be listed separately (Listings 16.2.7.2.2, 16.2.7.2.2, 16.2.7.2.3, 16.2.7.2.4).

Other primary cause of death and other underlying cause will be coded using MedDRA dictionary.

4.9 Concomitant Medication and Medical Procedures

Incidence of prior and concomitant medication will be presented by therapeutic area and preferred drug name (Tables 14.6.1 and 14.6.2, Listing).

Prior medications are those that stopped before the date of first dose of study medication; concomitant medications are all medications taken during the study, including those started before but ongoing at first dose of study medication.

Where a medication end date is partially or fully missing, and it is unclear as to whether the medication is prior or concomitant, it will be assumed that it is concomitant.

Concomitant surgical procedures and concomitant radiotherapy will be listed (Listings 16.2.8.2 and 16.2.8.3) and summarised (Table 14.6.3) by

- number and percentage of patients with radiotherapy.
- number and percentage of patients with a surgical procedure
- number and percentage of patients with a surgical procedure involving either a target or a non-target lesion
- number and percentage of patients with a surgical procedure involving a target lesion
- number and percentage of patients with a surgical procedure involving a non-target lesion
- number and percentage of patients with radiotherapy.

Notes: Medications are coded using WHO Drug dictionary.

4.10 Exposure

Information concerning treatment with Vemurafenib will be summarised for each cohort, presenting (Table 14.7.1)

- cumulative dose
- treatment duration (i.e. including treatment interruption)
- treatment exposure (i.e. excluding treatment interruption)
- average total dose per day including treatment interruptions
- average total dose per day excluding treatment interruptions
- dose intensity

Information concerning treatment modification of Vemurafenib will be summarised for each cohort, presenting (Table 14.7.2)

- patients with at least one dose modification
- reason for dose modification
- patients with at least one dose interruption

- reason for dose interruption
- maximum duration of interruption:
  - as continuous variable
  - by categories (< 1week, 1 week to < 2 weeks, >= 2 weeks)
- last daily dose received.

For cohort 3b, treatment with Cetuximab will be summarised, presenting (Tables 14.7.3)

- cumulative dose
- treatment duration
- number of infusions
- average actual dose delivered per cycle.

Information concerning treatment modification of Cetuximab will be summarised for cohort 3b, presenting (Table 14.7.4)

- patients with at least one temporary infusion interruption
- reason for temporary infusion interruption
- patients with at least one permanent infusion interruption
- reason for permanent infusion interruption
- last Planned Weekly Dose.

Treatment duration refers to days from date of first to date of last administration of study treatment or date of data cut-off (DDMMMYYYY), whatever comes first.

Treatment exposure is the number of days during which patients actually take study treatment; any days without dose taken are not counted.

Dose intensity is defined as:

total actual doses taken / total planned doses * 100%

with

total planned doses = prescribed doses * planned days on treatment

where planned days on treatment are defined as the interval between date of first dose and earliest of (date of last treatment, date of last contact or date of death).

If date of last dose of Vemurafenib is partially missing then the 1st of month will be used unless using the 1st of the month produces a date before date of last administration/interruption (without stop date). In such cases, the date of last administration/start of interruption will be used. If date of last dose is completely missing then the date of Day 1 of last cycle + 15 will be used, last cycle being the last one for which medication as been administered.

If date of last infusion of Cetuximab is partially missing then date of former infusion plus 1 week will used instead.

The following treatment exposure information will be listed:

- For Vemurafenib: duration of exposure, duration of treatment, initial dose, any dose modifications, interruptions or missed doses, together with reasons (Listing 16.2.5.1)

- For Cetuximab: duration of treatment, number of infusions, loading and planned weekly dose, infusion start and stop data-time, infusion duration, actual dose delivered, any dose temporary or permanent infusion interruptions and infusion-related AEs (Listing 16.2.5.2)
- Permanent discontinuations from study medication (Listing 16.2.5.3)

4.11 Adjustment for Covariates

N/A

4.11.1 Centre effects

No assessment of centre effects will be made due to low patient numbers within cohorts.

4.12 Protocol Violations

No per-protocol (PP) population is defined but major protocol violations will be identified, summarised and listed (Table 14.1.2.3, Listing 16.2.4.2.4).

The following are classed as violations but this list may be added to (prior to database lock):

- failure to comply with inclusion/exclusion criteria
- prohibited concomitant medication (e.g., new anti-cancer therapy) received.

4.13 Missing Values – Missing Visits

For partially missing dates for efficacy endpoints, the following imputation rules will be used: if the day of the month is missing, but month and year are known (UN-MMM-YYYY), it will be imputed by the 1st of the month (01-MMM-YYYY). If this implementation rule produces a date before start of treatment, then the date of start of treatment.

In case of missing information for AEs, this will be treated as described in section 4.7.1.

Other missing dates will be used as such.

4.14 Deviations from SAP

Any deviations from the original statistical plan will be described and justified in the final clinical study report, whether written post interim or final analysis.

4.15 Changes in Conduct or Planned Analyses from the Protocol

There have been no changes in analyses from those defined in the protocol.

4.16 Algorithms/SAS Codes

- **Tables that need descriptive statistics – continuous variables:**

```
PROC UNIVARIATE DATA=DSET NOPRINT;
    VAR VAR1 VAR2 VAR3 … VARN;
    BY BYVAR; (optional)
    OUTPUT OUT=OUTNAME
    N=N MEAN=MEAN MIN=MIN MAX=MAX MEDIAN=MEDIAN  STD=STD;
RUN;
```

- **Tables that need frequency counts:**
  PROC FREQ DATA=DSET NOPRINT;
  BY BYVAR; (optional)
  *TABLES VAR1*VAR2;*
  OUTPUT OUT=OUTNAME;
  RUN;

- **Tables that need 95% Clopper Pearson CIs for binomial proportions:**
  PROC FREQ DATA=DSET;
  BY BYVAR; (optional)
  TABLES VAR1 / BINOMIAL ALPHA=0.05;
  RUN;

- **Tables that need life table with estimates of survival, with CIs:**
  PROC LIFETEST DATA=DSET OUTSURV=LIFE METHOD=KM;
  *TIME time to response*censor (0 or 1);*
  ID patient;
  RUN;

5 Tables, Listings and Figures

Outputs will be produced for each cohorts separately indicating the indication studied in the 2nd subtitle respectively.

For cohort 3B, during part 1 of the study (Dose finding), the summaries for the different dose cohorts will be presented as treatment arms in columns, including a total column. Listings of Cohort 3B, during part 1 of the study will be sorted by dose cohort and include the column 'Dose cohort' to indicate which dose cohort the patient was enrolled to.

For Stage I interim analysis, all treated patients will be included in the safety analyses. For the summaries to be performed for the efficacy analysis at week 8 of Stage I, the first 7 patients enrolled into Stage I with measurable disease at baseline will be included. For all listings of efficacy analysis at stage 1, all patients available at that time will be included.

For Cohort 7 (patients with other solid tumours), if there are at least 5 patients in a certain tumour type, number (percentage) of patients will be summarised in frequency tables for RR at Week 8, clinical benefit rate, BOR, AEs and Treatment exposure for these tumour types. In case different tumour types within cohort 7 have less than 7 patients available only listings will be provided. Listings will include a column indicating which 'tumor type' the individual patients were diagnosed with.

In all listings the column 'Stage' will be added indicating if patient was enrolled at Stage I 'I', in between '' or Stage II 'II' respectively.

5.1 Format

All output will be produced using SAS version 9.2 or a later version.

Each output will state the cut-off date respectively and date of extraction from database.

In the top left portion of each table/listing, a *table/listing number* followed by the *title* of the table/listing will be presented. After the title line, optional *sub-title* or *population* information can be presented. Horizontal lines will appear before and after the column heading of the table/listing. *Footnotes* will be put under the main body of text at the bottom of the page.

The *sponsor name*, *protocol number*, programmers User ID, status of the table/listing (i.e. draft or final) and *SAS program name* will appear bottom left in a string and the *page number* will appear on the bottom right corner of each table/listing. The *date and time of creation* of table/listing will appear bottom left under the sponsor name. The source listing number will appear bottom left.

A *landscape layout* is proposed for both table and listing presentations.

The *left* and *right margins* of all tables and listings will be a minimum of 2.1 cm from the left and 1.9cm from the right. The *top and bottom margins* will be a minimum 2.92cm. *Header and footer* will be both 1.27 cm.

There is no special requirement of *font type* and *size*, but an *8-point* font size for tables and *7*or *8-point* for listings is proposed using *Courier New* font. A maximum SAS line size=141 and page size=45 for *8-point* font size, and line size=161 and page size=54 for *7-point* will be used so as to fit on both UK and US paper sizes.

In a listing, in the case that a patient's record has been continued to the next page, an appropriate identification (e.g., the patient ID number) must be presented at the beginning of that page.

5.2 Conventions

Unless otherwise specified, in summary tables of continuous variables, the minimum and maximum values will be displayed to the same number of decimal places as the raw data, the mean and median will be presented to one extra decimal place compared to the raw data, and the standard deviation will be displayed to two extra decimal places compared to the raw data. Wherever possible the data will be decimal aligned.

Unless otherwise specified frequency tabulations will be presented by number and percentage, where the percentage is presented in brackets to 1 decimal place.

All tables will have their source listing referenced in a footnote. In general listings will be sorted by patient ID number with the following exceptions. For patient listings of dose cohort 3b, it will be sorted by dose cohort followed by the patient ID number. For patient listings of cohort 7, it will be sorted by tumor type followed by patient ID number. All outputs have the cut-off date referenced in a footnote. All tables, listings and figures, as applicable, will be converted into Microsoft Word documents and collated into two or three complete documents.

5.3 Tables

All tables below will be presented for all cohorts that enrol at least 7 patients.

For cohorts with less than 7 patients tables are going to be presented according to section 4.1.

Outputs will be produced as indicated below for the respective analyses:

- SIA – Stage I analysis
- SIIA – Stage II analysis after all patients have confirmed week 8 assessment
- FA – Final Analysis
- DFA – Dose-finding Analysis
- Opt. – optional

5.3.1 Demographic and Baseline Information

Demographic and baseline information tables will be produced for the ITT population and in case of cohort where ITT and safety population are different also for safety population.

Table no.	Title	Produced for:
14.1.1	Patient Disposition	SIA, SIIA, FA
14.1.2.1	Patient Demography	SIA, SIIA,
14.1.2.2	Enrolment by Country and Center/Investigator	FA
14.1.2.3	Protocol Violations	FA
14.1.3.1	Active Relevant Medical and Surgical History (excluding cancer)	SIIA, FA
14.1.3.2	Past Medical and Surgical History (excluding cancer)	SIIA, FA
14.1.4.1	Cancer Disease History	SIA, SIIA, FA
14.1.4.2	Surgical Resection of Primary Tumour	SIA, SIIA, FA
14.1.4.3	Bone Marrow Transplants	SIIA, FA
14.1.5.1	Prior Systemic Therapies	SIA, SIIA, FA
14.1.5.2	Prior Radiotherapy	SIIA, FA
14.1.5.3	Number of Prior Systemic Therapies	SIIA, FA
14.1.6	Screening Dermatology Evaluation	SIIA, FA
14.1.7	BRAF V600 Mutation Type and Test	SIIA, FA

5.3.2 Efficacy

Efficacy tables will be produced for the ITT population.

14.2.1.1.1	Overall Response based on RECIST at Week 8 (unconfirmed)	SIA (not for MM cohort)
14.2.1.1.2	Overall Response based on RECIST at Week 8 (confirmed)	SIIA, FA (not for MM cohort)
14.2.1.1.3	Summary of Tumour Response Assessments based on RECIST by Assessment Cycle	SIA SIIA, FA (not for MM cohort)
14.2.1.2.1	Overall Response based on IMWG at Week 8 (unconfirmed)	SIA (for MM cohort only)
14.2.1.2.2	Overall Response based on IMWG at Week 8	SIIA, FA (for

	(confirmed)	MM cohort only)
14.2.1.2.3	Summary of Tumour Response Assessments based on IMWG by Assessment Cycle	SIA SIIA, FA (for MM cohort only)
14.2.1.3.1	Response based on PERCIST at Week 8 (unconfirmed)	SIA (for LHD/ECD sub-cohort only)
14.2.1.3.2	Response based on PERCIST at Week 8 (confirmed)	SIIA, FA (for LHD/ECD sub-cohort only)
14.2.1.3.3	Summary of Response based on PERCIST by Assessment Cycle	SIA SIIA, FA (for LHD/ECD sub-cohort only)
14.2.1.4.1	Overall Response based on all non-RECIST based Assessments at Week 8 (unconfirmed)	SIA (for LHD/ECD sub-cohort only)
14.2.1.4.2	Overall Response based on all non-RECIST based Assessments at Week 8 at Week 8 (confirmed)	SIIA, FA (for LHD/ECD sub-cohort only)
14.2.1.4.3	Summary of Overall Response based on all non-RECIST based Assessments by Assessment Cycle	SIA SIIA,FA (for LHD/ECD sub-cohort only)
14.2.2.1.1	Progression Free Survival (PFS) based on RECIST	SIIA, FA (not for MM cohort)
14.2.2.1.2	Progression Free Survival (PFS) based on IMWG	SIIA, FA (for MM cohort only)
14.2.2.1.3	Progression Free Survival (PFS) based on Overall Response (based on all non-RECIST based Assessments)	SIIA, FA (for LHD/ECD sub-cohort only)
14.2.2.2.1	Time to progression (TTP) based on RECIST	SIIA, FA (not for MM cohort)
14.2.2.2.2	Time to progression (TTP) based on IMWG	SIIA, FA (for MM cohort only)
14.2.2.2.3	Time to progression (TTP) based on Overall Response (based on all non-RECIST based Assessments)	SIIA, FA (for LHD/ECD sub-cohort only)
14.2.2.3.1	Best overall response (BOR) and Clinical benefit rate (CBR) based on RECIST	SIIA,FA (not for MM cohort)
14.2.2.3.2	Best overall response (BOR) and Clinical benefit rate (CBR) based on IMWG	SIIA,FA (for MM cohort only)
14.2.2.3.3	Best overall response (BOR) and Clinical benefit rate (CBR) based on Overall Response (based on all non-RECIST based Assessments)	SIIA,FA (for LHD/ECD sub-cohort only)
14.2.2.4.1	Time to response (TTR) based on RECIST	FA
14.2.2.4.2	Time to response (TTR) based on IMWG	FA
14.2.2.4.3	Time to response (TTR) based based on Overall Response (all non-RECIST Evaluations)	FA
14.2.2.5.1	Duration of response (DOR) based on RECIST	FA
14.2.2.5.2	Duration of response (DOR) based on IMWG	FA

14.2.2.5.3	Duration of response (DOR) based based on Overall Response (all non-RECIST Evaluations)	FA
14.2.2.6	Overall survival (OS)	FA

5.3.3 Safety

Safety tables will be produced for the safety population.

14.3.1.1	Summary of Adverse Events	DFA, SIA, SIIA,FA
14.3.1.2	Summary of Serious Adverse Events	SIA, SIIA,FA
14.3.2.1	Adverse Events by System Organ Class (SOC) and Preferred Term (PT)	DFA, SIA, SIIA,FA
14.3.2.2.1	Adverse Events with CTC Grade 1 or 2 by SOC and PT	SIA, SIIA,FA
14.3.2.2.2	Adverse Events with CTC Grade 1 or 2 by CTC Grade, SOC and PT	SIA, SIIA,FA
14.3.2.3.1	Adverse Events with CTC Grade 3 or 4 by SOC and PT	DFA, SIA, SIIA,FA
14.3.2.3.2	Adverse Events with CTC Grade 3 or 4 by CTC Grade, SOC and PT	SIA, SIIA,FA
14.3.2.4	Serious Adverse Events by SOC and PT	DFA, SIA, SIIA,FA
14.3.2.5	Adverse Events leading to Study Drug Interruption by SOC and PT	SIA, SIIA,FA
14.3.2.6	Adverse Events leading to Study Drug Discontinuation by SOC and PT	SIA, SIIA, FA
14.3.2.7	Adverse Events leading to Study Drug Interruption or Discontinuation by SOC and PT	DFA, SIA, SIIA,FA
14.3.2.8	Adverse Events leading to Study Drug Dose Reduction by SOC and PT	DFA, SIA, SIIA,FA
14.3.2.9	AE leading to Death	SIIA,FA
14.3.3.1	Related AEs by SOC and PT	SIA, SIIA,FA (all cohorts but 3B)
14.3.3.1.1	AEs Related to Vemurafenib by SOC and PT	SIA, SIIA,FA (only Cohort 3B)
14.3.3.1.2	AEs Related to Cetuximab by SOC and PT	SIA, SIIA,FA (only Cohort 3B)
14.3.3.1.3	AEs Related to either Vemurafenib or Cetuximab by SOC and PT	SIIA,FA (only Cohort 3B)
14.3.3.2.1	Related AEs with CTC Grade 1 or 2 by SOC and PT	SIA, SIIA,FA
14.3.3.2.2	Related AEs with CTC Grade 1 or 2 by CTC Grade, SOC and PT	SIA, SIIA,FA
14.3.3.3.1	Related AEs with CTC Grade 3 or 4 by SOC and PT	SIA, SIIA,FA
14.3.3.3.2	Related AEs with CTC Grade 3 or 4 by CTC Grade, SOC and PT	SIA, SIIA,FA
14.3.3.4	Related Serious Adverse Events by SOC and PT	SIA, SIIA,FA
14.3.3.5	Related AEs leading to Study Drug Interruption by SOC and PT	SIA, SIIA,FA

14.3.3.6	Related AEs leading to Study Drug Discontinuation by SOC and PT	SIA, SIIA, FA
14.3.3.7	Related AEs leading to Study Drug Interruption or Discontinuation by SOC and PT	DFA, SIA, SIIA,FA
14.3.3.8	Related AEs leading to Study Drug Dose Reduction by SOC and PT	DFA, SIA, SIIA,FA
14.3.3.9	Related AEs leading to Death	SIA, SIIA,FA
14.3.4.1	Adverse Events of Special Interest by AE of Special Interest Group and PT	SIIA,FA
14.3.4.2	Adverse Events of Special Interest by CTC Grade, AE of Special Interest Group and PT	SIIA,FA
14.3.4.3	Adverse Events of Special Interest - Time to First Incidence and Cumulative Dose to First Incidence	SIIA,FA
14.3.5.1	Dose Limiting Toxicities	DFA, SIA, FA (only Cohort 3B)
14.3.5.2	Infusion-related adverse events during or within 24h after the Cetuximab infusion	DFA, SIA, FA (only Cohort 3B)
14.3.6.1	Laboratory Results and Changes from Baseline – Haematology	SIIA,FA
14.3.6.2	Laboratory Shift Table of NCI CTC Grades – Haematology	SIIA,FA
14.3.6.3	Laboratory Results and Changes from Baseline – Biochemistry	SIIA,FA
14.3.6.4	Laboratory Shift Table of NCI CTC Grades – Biochemistry	SIIA,FA
14.3.6.5	Worsening in Liver Function Tests: One Grade Worsening from Baseline	SIIA,FA
14.3.6.6	Worsening in Liver Function Tests: Two or More Grades Worsening from Baseline	SIIA,FA
14.3.7.1	ECG Results and Change from Baseline over Time	SIIA,FA
14.3.7.2	ECG findings over Time	SIIA,FA
14.3.7.3	ECG over Time – QTcF	SIA, DFA, SIIA,FA
14.3.7.4	QTcF Prolongation (>500 msec)	SIIA,FA
14.3.7.5	Cardiac History for Patients with QTcF Prolongation (>500 msec)	SIIA,FA
14.3.7.6	Concomitant Medications for Patients with QTcF Prolongation (>500 msec)	SIIA,FA
14.3.8	Vital Signs Results and Change from Baseline	SIIA,FA
14.3.9	ECOG Performance Status	SIIA,FA
14.4	Death Summary	SIIA,FA
14.5.1	Dermatology Evaluation	SIIA,FA
14.5.2	Head and Neck Assessment for SCC	SIIA,FA
14.5.3	Chest CT for Evaluation of SCC	SIIA,FA
14.5.4	Pelvic Examination for SCC	SIIA,FA
14.5.5	Anal Examination for SCC	SIIA,FA

5.3.4 Medications, Concomitant Medical Procedures and Exposure

Following tables will be produced for the safety population.

14.6.1	Prior Medication	SIIA,FA
14.6.2	Concomitant Medication	SIIA,FA
14.6.3	Concomitant Surgical Procedures and Radiotherapy	SIIA,FA
14.7.1	Treatment Exposure Vemurafenib	SIA, SIIA,FA
14.7.2	Treatment Modifications of Vemurafenib	SIIA,FA
14.7.3	Treatment Exposure Cetuximab	SIA, SIIA,FA (only Cohort 3B)
14.7.4	Treatment Modifications of Cetuximab	SIIA,FA (only Cohort 3B)

5.4 Figures

Figure no.	Title	Produced for:
14.2.1	Progression Free Survival (PFS)	SIIA,FA
14.2.2	Time to Progression (TTP)	SIIA,FA
14.2.3	Time to Response (TTR)	SIIA,FA
14.2.4	Duration of Response (DOR)	SIIA,FA
14.2.5	Overall Survival (OS)	FA
14.2.6.1.1	Waterfall Plot of % Change from Baseline in Target Tumor Diameter Sum at Week 8 by assigned Overall Response at Week 8	SIA, SIIA,FA (all cohorts but 6)
14.2.6.2.1	Waterfall Plot of % Maximal Change from Baseline in Target Tumor Diameter Sum by Best Overall Response	SIIA,FA (all cohorts but 6)
14.2.7	Swimmer Plot	SIA, SIIA,FA
14.3	ECOG – Percentage of Patients by Grade over Time	SIIA,FA

5.5 Listings

16.2.4.1	Patient Disposition	SIA, SIIA, FA (all cohorts but 3B)
16.2.4.1.1	Patient Disposition at End of Study Treatment	SIA,SIIA,FA (only Cohort 3b)
16.2.4.1.2	Patient Disposition at End of Study	SIA,SIIA,FA (only Cohort 3b)
16.2.4.1.3	Patient with Other Solid Organ Cancer - Tumour Types	SIA,SIIA,FA (only Cohort 7 Other)
16.2.4.2.1	Inclusion and Exclusion Criteria Questions	SIA,SIIA, FA
16.2.4.2.2	Inclusion Criteria – Patient Responses	SIA,SIIA, FA
16.2.4.2.3	Exclusion Criteria – Patient Responses	SIA,SIIA, FA
16.2.4.2.4	Protocol Violations	SIIA, FA
16.2.4.3	Patient Demography	SIA, SIIA, FA
16.2.4.4.1	Cancer Disease History - <Cohort>	SIA, SIIA, FA
16.2.4.4.2	Surgical Resection of Primary Cancer - <Cohort>	SIA, SIIA, FA

16.2.4.4.3	Screening Dermatology Evaluation	SIA, SIIA, FA
16.2.4.5.1	Prior Systemic Therapy	SIA, SIIA, FA
16.2.4.5.2	Prior Radiotherapy	SIA, SIIA, FA
16.2.4.6	Medical History	SIA, SIIA, FA
16.2.4.7	BRAF V600 Mutation Information	SIA, SIIA, FA
16.2.4.8	Measurable Disease Assessment at Baseline	SIA, SIIA, FA
16.2.5.1	Administration of Vemurafenib	SIA, SIIA,FA
16.2.5.2	Administration of Cetuximab	SIA, SIIA,FA (only Cohort 3B)
16.2.5.3	Permanent Discontinuations from Study Medication	SIA, SIIA,FA
16.2.6.1.1	Response Evaluation (RECIST)	SIA, SIIA,FA (all Cohorts but 6)
16.2.6.1.2	Tumor Assessment of Target Lesions	SIA, SIIA,FA (all Cohorts but 6)
16.2.6.1.3	Tumor Assessment of Non-Target Lesions	SIA, SIIA,FA (all Cohorts but 6)
16.2.6.1.4	Percentage change from Baseline for Target Lesions at week 8 and week 16	SIA, SIIA,FA (all Cohorts but 6)
16.2.6.1.5	Maximal Percentage Change from Baseline for Target Lesions and Target, Non-Target and Overall Response at MPCBL and Best Overall Response	SIA, SIIA,FA (all Cohorts but 6)
16.2.6.1.6	Responder Information according to RECIST	SIA, SIIA,FA (all Cohorts but 6)
16.2.6.2.1	Response Evaluation (IMWG)	SIA, SIIA,FA (only Cohort 6)
16.2.6.2.2	Individual Assessments of Multiple myeloma – Skeletal Survey	SIA, SIIA,FA (only Cohort 6)
16.2.6.2.3	Individual Assessments of Multiple myeloma – Serum Protein Electrophoresis	SIA, SIIA,FA (only Cohort 6)
16.2.6.2.4	Individual Assessments of Multiple myeloma – Urine Protein Electrophoresis	SIA, SIIA,FA (only Cohort 6)
16.2.6.2.5	Individual Assessments of Multiple myeloma – Serum Free Light Chains	SIA, SIIA,FA (only Cohort 6)
16.2.6.2.6	Individual Assessments of Multiple myeloma – Bone Marrow for Histology, Cytogenetics and FISH Mutation Details	SIA, SIIA,FA (only Cohort 6)
16.2.6.2.7	Individual Assessments of Multiple myeloma – Flow Cytometry Evaluation	SIA, SIIA,FA (only Cohort 6)
16.2.6.3.1	Tumour Assessment of Lesions via PERCIST	SIA, SIIA,FA (only Cohort 7 LHD/ECD sub-cohort)
16.2.6.3.2	Response Evaluation (PERCIST)	SIA, SIIA,FA (only Cohort 7 LHD/ECD sub-cohort)
16.2.6.3.3	Bone Scan (ECD/LCH only)	SIA, SIIA,FA (only Cohort 7 LHD/ECD sub-cohort)

16.2.6.3.4	Disease Not Measurable by RECIST 1.1 - CT/MRI	SIA, SIIA,FA (only Cohort 7 LHD/ECD sub-cohort)
16.2.6.3.5	Disease Not Measurable by RECIST 1.1 - Cardiac MRI/Cardiac Echo	SIA, SIIA,FA (only Cohort 7 LHD/ECD sub-cohort)
16.2.6.3.6	Disease Not Measurable by RECIST 1.1 - Aortic Thickening	SIA, SIIA,FA (only Cohort 7 LHD/ECD sub-cohort)
16.2.6.3.7	Disease Not Measurable by RECIST 1.1 - Perinephric Stranding	SIA, SIIA,FA (only Cohort 7 LHD/ECD sub-cohort)
16.2.6.3.8	Disease Not Measurable by RECIST 1.1 - Overall Response	SIA, SIIA,FA (only Cohort 7 LHD/ECD sub-cohort)
16.2.6.4	Next Anticancer Therapy after Discontinuation of Study Medication	SIA, SIIA,FA
16.2.6.5	Disease Progression	SIA, SIIA,FA
16.2.7.1.1	All Adverse Events	SIA, SIIA,FA
16.2.7.1.2	Serious Adverse Events	SIA, SIIA,FA
16.2.7.1.3	Adverse Events leading to Dose Reduction or Temporary Treatment Interruption	SIA, SIIA,FA
16.2.7.1.4	Adverse Events leading to Permanent Treatment Discontinuation	SIA, SIIA,FA
16.2.7.1.5	Adverse Events leading to Death	SIA, SIIA,FA
16.2.7.1.6	Dose Limiting Toxicities	DFA, SIA, SIIA, FA (only Cohort 3B)
16.2.7.1.7	Infusion-related AEs during or within 24h after the Cetuximab infusion	DFA, SIA, SIIA, FA (only Cohort 3B)
16.2.7.2.1	Deaths	SIA, SIIA,FA
16.2.7.2.2	Deaths within 30 days of start of treatment	SIA, SIIA, FA
16.2.7.2.3	Deaths within 28 days after last administration of study drug	SIA, SIIA, FA
16.2.7.2.4	Deaths within 60 days after last administration of study drug	SIA, SIIA, FA
16.2.7.3.1	Laboratory Results - Haematology	SIA, SIIA, FA
16.2.7.3.2	Laboratory Results - Biochemistry	SIA, SIIA, FA
16.2.7.4	ECOG Performance Status	SIA, SIIA, FA
16.2.7.5	ECG Results	SIA, SIIA, FA
16.2.7.6	Vital Signs	SIA, SIIA, FA
16.2.7.7	Dermatology Evaluation	SIA, SIIA, FA
16.2.7.8.1	Head and Neck Assessment for SCC	SIA, SIIA, FA
16.2.7.8.2	Head and Neck Assessment for SCC- Diagnosis	SIA, SIIA, FA
16.2.7.9	Chest CT for Evaluation of SCC	SIA, SIIA, FA
16.2.7.10	Pelvic examination for SCC	SIA, SIIA, FA
16.2.7.11	Anal examination for SCC	SIA, SIIA, FA
16.2.7.12	Physical examination	SIA, SIIA, FA
16.2.8.1	Prior and concomitant medication	SIA, SIIA, FA
16.2.8.2	Concomitant Surgical Procedures	SIA, SIIA, FA

16.2.8.3	Concomitant Radiotherapy	SIA, SIIA, FA

Note: Tables, listings and figures will follow the format of: **MO28072 Final Version 2 of Shells 3Dec2014.**

5.6 Appendices

N/A

5.7 References

1. Lin Y, Shih WJ. Adaptive two-stage designs for single-arm phase IIA cancer clinical trials. Biometrics. 2004;60:482-90.
2. NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. See http://evs.nci.nih.gov/ftp1/CTCAE/About.html.

Two final SAP versions have been written to date for this study.

SAP Version 1 was based on the final protocol version 3 dated 12 June 2013.

On 03 December 2014, a second SAP version was finalized to mainly align with subsequent Protocol amendments (based on Protocol version 4, 18 March 2014.).

Changes to statistical analyses are summarized within the protocols.