PROTOCOL

TITLE:	**AN OPEN-LABEL, PHASE II STUDY OF VEMURAFENIB IN PATIENTS WITH BRAF V600 MUTATION-POSITIVE CANCERS**
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PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	29-Mar-2016 09:47:23

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.

Prior to the closure of the trial, the Sponsor may offer patients who have completed the protocol-mandated minimum 12-month safety follow-up and who continue to benefit from vemurafenib therapy, the opportunity to receive continued vemurafenib via enrolment in the GO28399 extension trial. Should the study be closed due to Sponsor decision, the Sponsor will offer all

patients still receiving vemurafenib therapy the opportunity to receive continued treatment with vemurafenib via enrollment in the GO28399 extension trial at the time of study closure.

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.

Prior to the closure of the trial, the Sponsor may offer patients who have completed the protocol-mandated minimum 12-month safety follow-up and who continue to benefit from vemurafenib therapy, the opportunity to receive continued vemurafenib via enrolment in the GO28399 extension trial. Should the study be closed due to Sponsor decision, the Sponsor will offer all patients still receiving vemurafenib therapy the opportunity to receive continued treatment with vemurafenib via enrollment in the GO28399 extension trial at the time of study closure.

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). For patients with sustained clinical benefit from continued vemurafenib whose visit frequency is lessened to every 2 cycles at Cycle 13 or beyond, dermatology exams may be performed every 16 weeks to coincide with visit cycles.

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). For patients with sustained clinical benefit from continued vemurafenib whose visit frequency is lessened to every 2 cycles at Cycle 13 or beyond, head and neck exams may be performed every 16 weeks to coincide with visit cycles. 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). CT scans are not required at 28 days post-discontinuation visit for patients who have discontinued due to CT-documented progression of disease under study.

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 ECD patients and others who demonstrate sustained clinical benefit and subsequently continued treatment with vemurafenib beyond 12 months, visit frequency may be lessened to every 2 cycles starting from Cycle 13.

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. Note: For patients with sustained clinical benefit from continued vemurafenib whose visit frequency is lessened to every 2 cycles at Cycle 13 or beyond, dermatology exams may be performed every 16 weeks to coincide with visit cycles.
- Head and neck examination (as part of the evaluation for SCC) performed by the treating physician every 12 weeks after starting study drug. Note: For patients with sustained clinical benefit from continued vemurafenib whose visit frequency is lessened to every 2 cycles at Cycle 13 or beyond, head and neck exams may be performed every 16 weeks to coincide with visit cycles.
- 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). CT scans are not required for patients who have discontinued due to CT-documented progression of the disease under study.
- 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), at week 16 and at 9 months (see primary analysis, protocol Section 8.3.2) for expanded cohorts. All cohorts will be analysed at the end of the study.

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.

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). For ECD patients and others who demonstrate sustained clinical benefit and subsequently continued treatment with vemurafenib beyond 12 months, visit frequency may be lessened to every 2 cycles starting from Cycle 13.
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. Prior to the closure of the trial, the Sponsor may offer patients who have completed the protocol-mandated minimum 12-month safety follow-up and who continue to benefit from vemurafenib therapy, the opportunity to receive continued vemurafenib via enrolment in the GO28399 extension trial. Should the study be closed due to Sponsor decision, the Sponsor will offer all patients still receiving vemurafenib therapy the opportunity to receive continued treatment with vemurafenib via enrollment in the GO28399 extension trial at the time of study closure.
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. For patients with sustained clinical benefit from continued vemurafenib whose visit frequency is lessened to every 2 cycles at Cycle 13 or beyond (as per footnote 2), dermatology exams may be performed every 16 weeks to coincide with visit cycles. 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). CT scans not required at 28 days post-discontinuation visit for patients who have discontinued due to CT-documented progression of disease under study.

20. 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). For patients with sustained clinical benefit from continued vemurafenib whose visit frequency is lessened to every 2 cycles at Cycle 13 or beyond (as per footnote 2), head and neck exams may be performed every 16 weeks to coincide with visit cycles.
21. 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. 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). CT scans not required at 28 days post-discontinuation visit for patients who have discontinued due to CT-documented progression of disease under study.
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 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		

	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													
12-lead ECG [10]	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		
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

	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													
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
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										

	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													
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			
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
AKI	Acute kidney injury
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_{0-24h}) 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 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 13).

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 [redacted] 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. A second case of progression of a pre-existing RAS-mutated malignancy (pancreatic adenocarcinoma with KRAS mutation) was reported with vemurafenib in 2014 (81). 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 13).

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 13).

As of Q2 2014, an adverse drug reaction of pancreatitis has been identified in patients being treated with vemurafenib. Seventeen cases of pancreatitis with no strong risk factors or alternative explanations were reported. Eight of the 17 cases were assessed as likely associated with vemurafenib use based on event onset latency and re-challenge/de-challenge information. The clinical presentation including mild to moderate severity was consistent with the clinical picture of drug-induced pancreatitis (81).

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

As of Q3 2015 an adverse drug reaction of acute kidney injury (AKI) including interstitial nephritis following vemurafenib administration has been identified in patients being treated with vemurafenib. The majority of these cases were characterized by mild to moderate increases in serum creatinine (some observed in the setting of dehydration events) with recovery after dose modification. Approximately 2% of cases were biopsy-proven interstitial nephritis and approximately 3% of cases were acute tubular injury/necrosis. No fatal cases were related to acute kidney injury. Renal function should be monitored in patients undergoing vemurafenib treatment. Vemurafenib dose modification guidelines should be utilized when applicable and it is recommended to routinely monitor serum creatinine levels in all patients undergoing vemurafenib therapy.

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

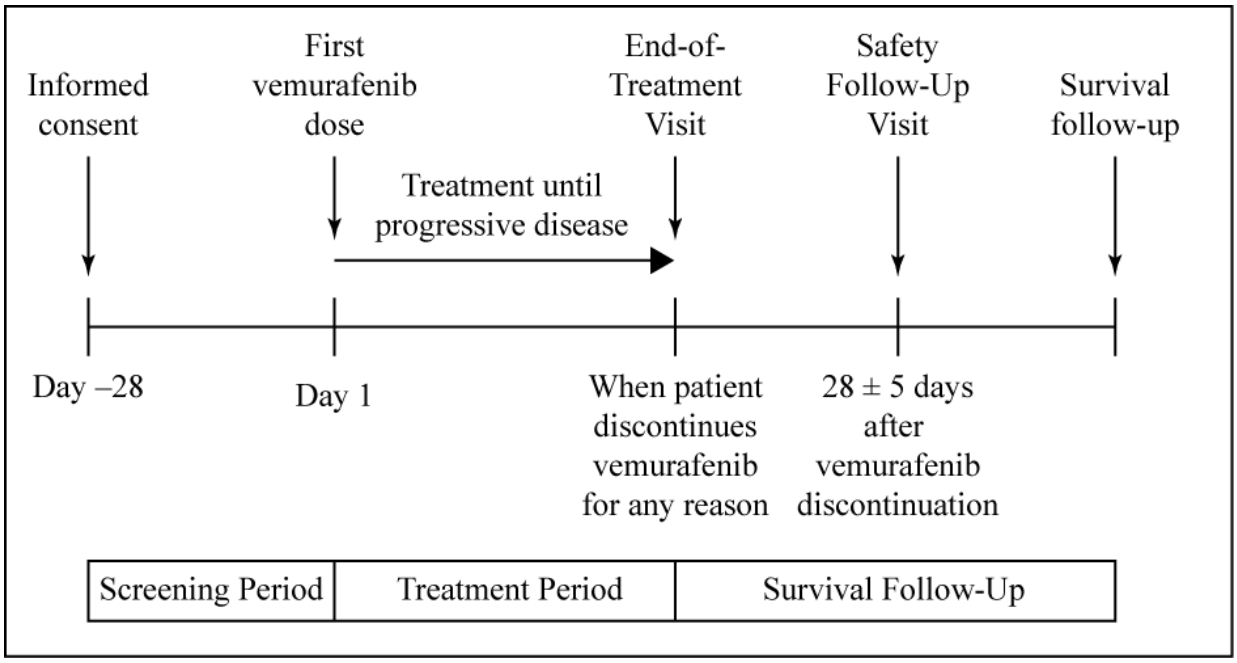
This is an open-label, multicentre, multinational, phase II study exploring the efficacy and safety of vemurafenib in a diverse population of patients with cancers (excluding melanoma and papillary thyroid cancer) known to harbour BRAF V600 mutations and for whom vemurafenib is deemed the best treatment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

Prior to the closure of the trial, the Sponsor may offer patients who have completed the protocol-mandated minimum 12-month safety follow-up and who continue to benefit from vemurafenib therapy, the opportunity to receive continued vemurafenib via enrolment in the GO28399 extension trial. Should the study be closed due to Sponsor decision, the Sponsor will offer all patients still receiving vemurafenib therapy the opportunity to receive continued treatment with vemurafenib via enrollment in the GO28399 extension trial at the time of study closure.

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.

Prior to the closure of the trial, the Sponsor may offer patients who have completed the protocol-mandated minimum 12-month safety follow-up and who continue to benefit from vemurafenib therapy, the opportunity to receive continued vemurafenib via enrolment in the GO28399 extension trial. Should the study be closed due to Sponsor decision, the Sponsor will offer all patients still receiving vemurafenib therapy the opportunity to receive continued treatment with vemurafenib via enrollment in the GO28399 extension trial at the time of study closure.

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

<u>For multiple myeloma only:</u>

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). For ECD patients and others who demonstrate sustained clinical benefit and subsequently continued treatment with vemurafenib beyond 12 months, visit frequency may be lessened to every 2 cycles starting from Cycle 13.
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. Prior to the closure of the trial, the Sponsor may offer patients who have completed the protocol-mandated minimum 12-month safety follow-up and who continue to benefit from vemurafenib therapy, the opportunity to receive continued vemurafenib via enrolment in the GO28399 extension trial. Should the study be closed due to Sponsor decision, the Sponsor will offer all patients still receiving vemurafenib therapy the opportunity to receive continued treatment with vemurafenib via enrollment in the GO28399 extension trial at the time of study closure.
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. For patients with sustained clinical benefit from continued vemurafenib whose visit frequency is lessened to every 2 cycles at Cycle 13 or beyond (as per footnote 2), dermatology exams may be performed every 16 weeks to coincide with visit cycles. 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). CT scans not required at 28 days post-discontinuation visit for patients who have discontinued due to CT-documented progression of disease under study.

20. 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). For patients with sustained clinical benefit from continued vemurafenib whose visit frequency is lessened to every 2 cycles at Cycle 13 or beyond (as per footnote 2), head and neck exams may be performed every 16 weeks to coincide with visit cycles.
21. 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. 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). CT scans not required at 28 days post-discontinuation visit for patients who have discontinued due to CT-documented progression of disease under study.
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			
Follow-up for disease progression																	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													
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 ECD patients and others who demonstrate sustained clinical benefit and subsequently continued treatment with vemurafenib beyond 12 months, visit frequency may be lessened to every 2 cycles starting from Cycle 13.

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. Note: For patients with sustained clinical benefit from continued vemurafenib whose visit frequency is lessened to every 2 cycles at Cycle 13 or beyond, dermatology exams may be performed every 16 weeks to coincide with visit cycles.
- Head and neck examination (as part of the evaluation for SCC) performed by the treating physician every 12 weeks after starting study drug. Note: For patients with sustained clinical benefit from continued vemurafenib whose visit frequency is lessened to every 2 cycles at

Cycle 13 or beyond, head and neck exams may be performed every 16 weeks to coincide with visit cycles.

- 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
- The Sponsor (Roche) recommends that workup of any suspected case of pancreatitis should include serum amylase and lipase testing in addition to other appropriate testing (e.g. CT abdomen).

* 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). CT scans are not required for patients who have discontinued due to CT-documented progression of the disease under study.
- 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). For patients with sustained clinical benefit from continued vemurafenib whose visit frequency is lessened to every 2 cycles at Cycle 13 or beyond, head and neck exams may be performed every 16 weeks to coincide with visit cycles. 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). CT scans are not required at 28 days post-discontinuation visit for patients who have discontinued due to CT-documented progression of disease under study.

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.

Toxicity Grade (CTCAE, v4.0)[a]	Vemurafenib dose changes during current treatment period	Dose adjustments for resumption of treatment
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

Prior to the closure of the trial, the Sponsor may offer patients who have completed the protocol-mandated minimum 12-month safety follow-up and who continue to benefit from vemurafenib therapy, the opportunity to receive continued vemurafenib via enrolment in the GO28399 extension trial. Should the study be closed due to Sponsor decision, the Sponsor will offer all patients still receiving vemurafenib therapy the opportunity to receive continued treatment with vemurafenib via enrollment in the GO28399 extension trial at the time of study closure.

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. Rules for Stage I

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), at week 16 and at 9 months (see primary analysis, Section 8.3.2) for expanded cohorts. All cohorts will be analysed at the end of the study.

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.

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.

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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: 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) o 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 o Bone marrow plasma cell percentage. The absolute percentage must be ≥ 10%[8] o 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

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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.

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