CONFIDENTIAL PROTOCOL

RT & Combi in metastatic melanoma
CombiRT (02.14 / GSK PROTOCOL ID: 201303)

An open-label, single-arm, phase I/II, multicentre study to evaluate the safety and efficacy of the combination of dabrafenib, trametinib and palliative radiotherapy in patients with unresectable (stage IIIc) and metastatic (stage IV) BRAF V600E/K mutation-positive cutaneous melanoma.

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This is an independent investigator initiated co-operative group trial, sponsored by MASC Trials.

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1 ABBREVIATIONS

AE	Adverse event
ALT	Alanine transaminase
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
BAL	Bronchoalveolar lavage
BED	Biological effective dose
BID	Twice daily
BOR	Best overall response
BP	Blood pressure
C	Celsius
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
cuSCC	Cutaneous Squamous Cell Carcinoma
DBP	Diastolic blood pressure
DLT	Dose limiting toxicity
DMSO	Dimethyl sulfoxide
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
F	Fahrenheit
FDA	Food & Drug Administration
FDG PET	Fluorodeoxyglucose positron emission tomography
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
GSK	GlaxoSmithKline
Gy	Gray – unit of radiation dose delivery
HCG	Human chorionic gonadotropin
HFSR	Hand-foot Skin Reactions
Hg	Mercury
HIV	Human immunodeficiency virus
HPMC	Hydroxypropyl methyl cellulose
HREC	Human research ethics committees
HRT	Hormone replacement therapy
IB	Investigator Brochure
ICF	Informed consent form
ICH GCP	International Conference on Harmonisation of Good Clinical Practice
ID	Identification
IHC	Immunohistochemistry
INR	International Normalised Ratio
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IV	Intravenous
Kg	Kilogram
LDH	Lactate dehydrogenase
LFTs	Liver function tests

LLN	Lower limit of normal
LVEF	Left ventricular ejection fraction
MAPK	Mitogen-activated protein kinase
MASC Trials	Melanoma and Skin Cancer Trials
Mg	Milligram
Ml	Millilitre
Mm	Millimeter
mmHg	Millimetres mercury
Msec	Milliseconds
MRI	Magnetic resonance imaging
MSDS	Material Safety Data Sheets
MTD	Maximum tolerated dose
NSAIDS	Non-steroidal anti-inflammatory drugs
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NA	Not applicable
NE	Not evaluable
OR	Overall response
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progressive disease
PFS	Progression Free Survival
PTT	Partial thromboplastin time
PR	Partial response
PT	Prothrombin time
QTcB	QT interval on electrocardiogram corrected using the Bazett's formula
RAP	Reporting and analysis plan
RECIST	Response Evaluation Criteria In Solid Tumours
RPED	Retinal pigment epithelial detachment
RVO	Retinal vein occlusion
RT	Radiotherapy
SAE	Serious adverse event
SD	Stable disease
SBP	Systolic blood pressure
SPF	Sun protection factor
SOM	Study Operations Manual
TGA	Therapeutic Goods Administration
TLD	Thermoluminescent dosimeter
TMC	Trial Management Committee
ULN	Upper Limit of Normal
VAS	Visual analog scale
WBC	White blood count
WOCBP	Women of child bearing potential
%	Percent
#	Fractionation

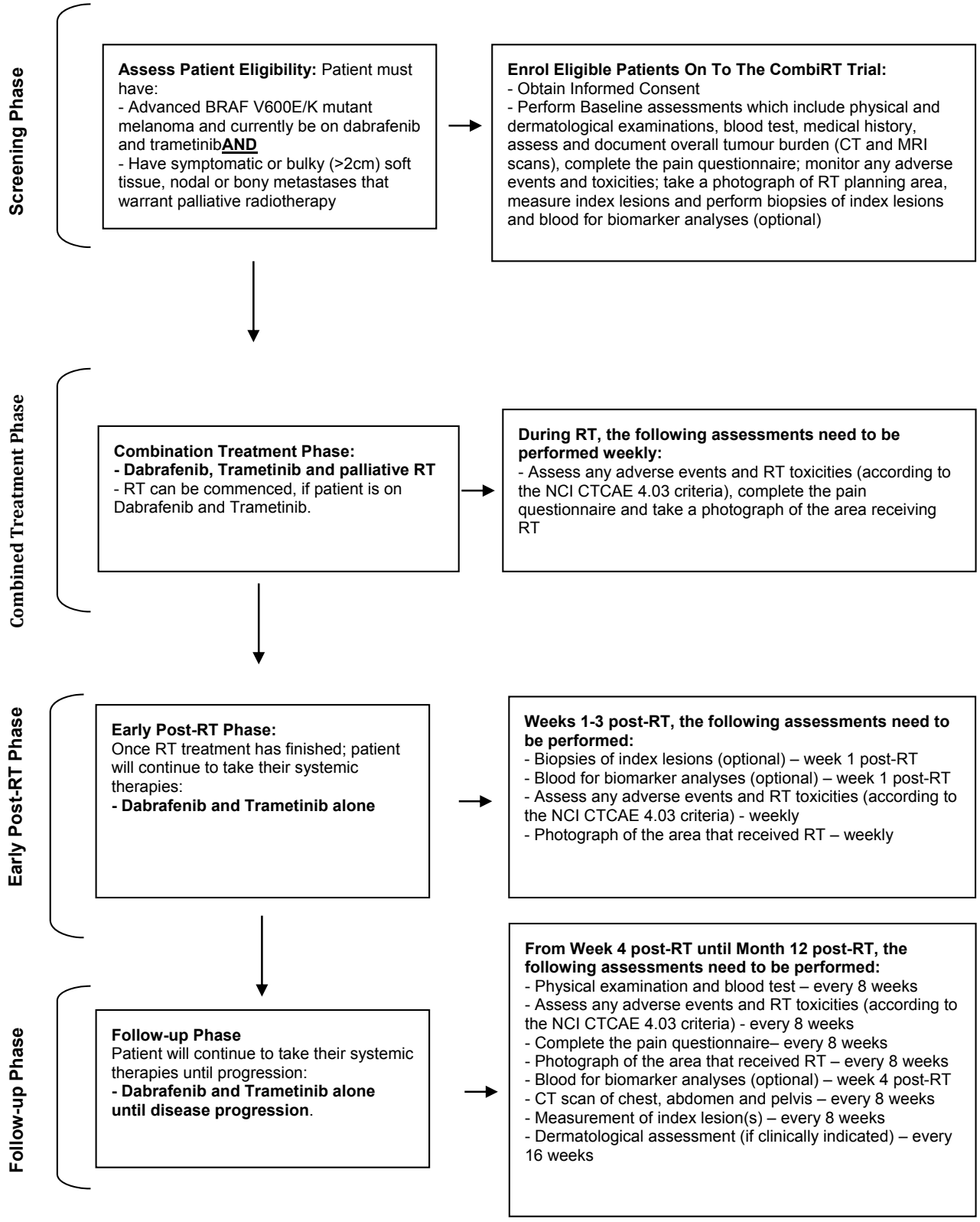
2 STUDY SUMMARY

Title:	An open-label, single-arm, phase I/II, multicentre study to evaluate the safety and efficacy of the combination of dabrafenib, trametinib and palliative radiotherapy in patients with unresectable (stage IIIc) and metastatic (stage IV) BRAF V600E/K mutation-positive cutaneous melanoma.
Dosing:	Dabrafenib will be administered at standard dose of 150mg twice daily. Trametinib will be administered at standard dose of 2mg once daily. For patients needing RT to bony, soft tissue or nodal metastases, the following dose levels for palliative RT are shown as below: • Level 1: 20 Gy in 5 fractions, to any locations • Level 2a: 30 Gy in 10 fractions, with no abdominal viscera directly exposed to RT • Level 2b: 30 Gy in 10 fractions, with abdominal viscera directly exposed to RT • Level 3a: 40 Gy in 16 fractions, with no abdominal viscera directly exposed to RT • Level 3b: 40 Gy in 16 fractions, with abdominal viscera directly exposed to RT Radiotherapy dose will be escalated to the next dose level if 0 out of 3 patients at the current dose level experiences dose limiting toxicity (DLT). If 2 or more patients experience DLT, de-escalate to dose level below. If 1 patient experiences DLT, treat 3 more patients at the current dose level. If 1 of 6 experiences DLT, escalate to the next dose level. If 2 or more of 6 experiences DLT, de-escalate to dose level below. The clinician may use their discretion in prescribing the palliative radiotherapy dose when a lower dose level is preferred (for up to 6 trial participants), but only when the prescribed dose level has already been deemed safe by the TMC and/or DSMC.
Sample size:	Up to 30 subjects
Subject participation duration:	12 months
Trial accrual & completion time estimation:	It is anticipated that 12 months will be required to complete accrual and the study will take 24 months to complete.
Population:	Patients with BRAF V600E/K mutation-positive advanced stage melanoma, who have symptomatic or bulky (>2cm)

	soft tissue, nodal or bony metastases that warrant palliative RT.
Description of agent or intervention:	This is a prospective study combining dabrafenib, trametinib and palliative RT.
Objectives:	**Primary:** ▪ To evaluate the safety and tolerability of the combination of dabrafenib, trametinib and palliative RT to extra-cranial sites, in patients with BRAF V600E/K mutation-positive advanced stage melanoma, as assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.033 (NCI CTCAE 4.03) **Secondary:** ▪ To assess patients' pain using the visual analog scale (VAS). ▪ To assess progression free survival (PFS) and overall survival (OS). ▪ To evaluate local tumour response and the time to local progression in the irradiated index lesion(s). (Only if these lesions are measurable by RECIST 1.1 criteria.)
Description of study design:	Phase I/II prospective study examining the toxicity of palliative RT concurrently with dabrafenib and trametinib. Eligible subjects are patients who are taking dabrafenib and trametinib, as the current standard management for advanced stage melanoma. Patients may receive dabrafenib and trametinib via PBS authority approval for supply of medication. Palliative RT will be delivered to symptomatic or bulky (>2cm) soft tissue, nodal or bony metastases concurrently with dabrafenib and trametinib. Up to 3 areas of disease can be irradiated at the same time. Following RT, dabrafenib and trametinib alone will be continued until disease progression according to RECIST 1.1 criteria. Further palliative RT to the same lesion(s) or other symptomatic or bulky (>2cm) lesion(s) are permitted on the study. The dose fractionation is at the discretion of the treating radiation oncologist, but the accumulative dose to the normal tissue and organ should be kept within a safe limit. Further RT should not be carried out concurrently with dabrafenib and trametinib. Any and all RT related toxicities will be documented from the commencement of the RT; including weekly during RT, weekly post-RT for 4 weeks, and then every 8 weeks until study completion. Overall disease response and local treatment response in the index lesions will be measured on the restaging CT

	scan, at week 4 post-RT and then every 8 weeks until study completion. For the translational sub-study, patients will be consented separately by their local institution to allow core biopsy to be performed on the irradiated tumour. Tumour biopsies are optional for patients and will be managed in accordance with the policy and procedures at each participating site. Tumour tissue will be collected at baseline and post-RT to assess for biomarkers that correlate with tumour response to treatment.
Summary of Statistical Methods	As this is an early phase study to assess safety and efficacy, which would then be evaluated in larger (appropriated powered) future studies, a phase I study design is selected with the goal to enrolling a maximum sample size of 30 patients. Safety and efficacy analyses will be performed at study completion.

Figure 1 Schema



**See also Table 19 - study timeline table for further clarification*

3 INTRODUCTION

3.1 Background

Cutaneous melanoma is the most aggressive form of all skin cancers. Worldwide, it is currently expected that approximately 132,000 people will be diagnosed with melanoma each year and some 37,000 people are expected to die of the disease annually. The median survival time for patients with Stage IV melanoma remains short at approximately 6 months with 26% of subjects alive at 1-year [Korn, 2008]; the estimated 5-year survival rate is <10% [Huncharek, 2001]. Median progression free survival (PFS) is also short at 1.7 months and only 14.5% of subjects are progression-free at 6 months [Korn, 2008].

The RAS/RAF/MEK/ERK pathway is a critical proliferation pathway in many human cancers. This pathway can be constitutively activated by alteration in specific proteins, including BRAF, which phosphorylates MEK on two regulatory serine residues. Over 45 cancer-associated mutations have been identified in BRAF [Wellbrock, 2004]. BRAF mutations have been identified in up to 60% of melanoma tumours [Davis, 2002]. In melanoma, more than 80% of the BRAF mutations cause a substitution of the amino acid glutamate (E) for valine (V) at position 600 (V600E) of the BRAF protein, whereas approximately 3-20% of melanoma mutations are a substitution of lysine (K) for valine at position 600 (V600K) [Gorden, 2003; Houben, 2004; Kirschner, 2005; Kumar, 2003; Libra, 2005; Omholt, 2003]. Both mutations cause constitutive activation of BRAF, which in turn activates the MAP kinase pathway.

The first BRAF inhibitor approved for treatment of unresectable or metastatic melanoma with BRAF V600E mutation was vemurafenib. This was based on an improvement in overall survival compared to chemotherapy [Chapman, 2011]. Dabrafenib is another potent and selective RAF kinase inhibitor of mutant forms BRAFV600E, BRAFV600K and BRAFV600D. The mode of action of dabrafenib is consistent with competitive inhibition of adenosine triphosphate (ATP) binding. Recently, the FDA approved dabrafenib for the treatment of unresectable or metastatic melanoma with V600 BRAF mutation, based on a phase III randomized controlled trial showing a median progression free survival improvement from 2.7 months for dacarbazine, to 5.1 months for dabrafenib [Hauschild, 2012].

Trametinib is a reversible, highly selective, allosteric inhibitor of MEK1 and MEK2. As BRAF and MEK are in the same pathway, and because MEK is a substrate of activated BRAF, inhibiting both BRAF and MEK rather than individually could provide more effective pathway inhibition. In addition, there is preclinical evidence to suggest that BRAF inhibitor can paradoxically activate mitogen-activated protein kinase (MAPK) pathway in BRAF wild-type cells with preexisting RAS mutation [Hatzivassiliou, 2010]. Inhibiting MEK along with BRAF can potentially reduce the paradoxical activation of the MAPK pathway and BRAF wild-type tumour growth.

The clinical data from phase I/II studies for the combination of dabrafenib and trametinib demonstrated an acceptable safety profile, with a higher incidence of pyrexia and chills, and a lower incidence of squamous cell carcinoma and hyperkeratosis which is likely to be due to reduced paradoxical MAPK pathway activation. The phase I/II study also demonstrated higher clinical activity of the combination treatment relative to dabrafenib monotherapy. In the phase II study, the median PFS for patients who received the full-dose combination was 9.4 months, as compared with 5.8 months with dabrafenib monotherapy [Flaherty, 2012]. As a result, in January 2014, the FDA has approved trametinib for use in combination with dabrafenib for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations. This accelerated approval is contingent on the results of the ongoing Phase III trial, which is designed to evaluate the clinical benefit of the combination in this patient population.

Disease in clinically significant sites such as brain, bone, lymph nodes and soft tissue, may also benefit from local palliative RT. RT has been under-utilised for the treatment of melanoma, partly because of the misconception that melanoma is a universally radioresistant tumour. Preclinical studies have demonstrated that melanoma display a large variety of radiosensitivity, ranging from highly radiosensitive to moderately or highly radioresistant [Sambade, 2011]. Recent randomised controlled trial showed that adjuvant nodal irradiation significantly reduced the risk of regional recurrence after lymph node dissection [Burmeister, 2012], again confirming the efficacy of RT in the treatment of melanoma. Palliative RT often achieves good palliation of symptomatic metastatic disease, studies have shown a 39% and 68-84% incidence of significant symptomatic relief of intracranial and extracranial metastases [Konefal, 1988; Olivier, 2007].

3.2 Scientific Rationale

To date, the safety and efficacy of the combination of dabrafenib, trametinib and radiotherapy has not been prospectively evaluated in the clinical setting. Due to concerns about potential interactions, current clinical studies involving dabrafenib and/or trametinib mandates that patients cease the drug at least 24 hours prior to the first fraction of radiotherapy, and dabrafenib and/or trametinib can only be resumed 24 hours after the last fraction of radiotherapy. Anecdotally, following cessation of BRAF and/or MEK inhibitors, rapid pace of disease progression can occur. Therefore patients are potentially at risk of disease progression outside radiotherapy field during the break from dabrafenib and/or trametinib. Safety of dabrafenib, trametinib and radiotherapy combination should be evaluated in the clinical setting as a priority.

Furthermore, preclinical study on melanoma cell lines by Sambade et al. has demonstrated potential synergistic effect by combining BRAF inhibitor and radiation [Sambade, 2011]. In this study, the combination of PLX-4032 (vemurafenib) and radiation resulted in significantly more cell kill than either agent alone. The mean radiation enhancement ratio of PLX-4032 is estimated at 9.7, meaning the PLX-4032 and radiation combination achieved 9.7 times the cell kill produced by radiation alone. Sambade et al. also demonstrated that the PLX-4032 did not sensitize BRAF wild type cell lines to radiation. This study showed that radiosensitising effect of BRAF inhibitor occurred at higher dose/fraction than standard fractionation of 2Gy/fraction. Palliative radiotherapy typically use dose per fraction between 2.4-8 Gy / fraction, therefore the synergistic effect may be more pronounced in the palliative radiotherapy setting.

Despite the potential synergy, the BRAF inhibitor and radiotherapy combination has only been tested in melanoma cell lines, there are currently no prospective trial data available to confirm the safety and synergistic effect of this combination. Furthermore, the radiation-induced-malignancy effect may cause accelerated development of non-melanomatous skin cancers induced by BRAF inhibitor monotherapy. Given that MEK inhibitor has been shown to reduce the risk of secondary skin cancers caused by BRAF inhibitor, it is then logical to evaluate the safety and efficacy of the addition of radiotherapy onto the dabrafenib and trametinib combination.

Several case reports have demonstrated increased skin toxicity from the combination of BRAF inhibitors and RT [Satzger, 2013; Peters, 2013; Anker, 2013; Pulvirenti, 2014]. The case report by Anker et al. also reported increased in-field liver toxicity in the patient treated by the combination of vemurafenib and RT. On the other hand, another case series by Rompoti et al. showed only minimal acute toxicity for five patients who received the combination of BRAF inhibitor and brain radiotherapy [Rompoti, 2013]. Phosphorylated histone H2AX repair foci were measured in peripheral blood lymphocytes for two of the five patients, no evidence of impaired repair of DNA double-strand breaks was observed to suggest any increased normal tissue radiosensitivity. Given these conflicting case reports, our prospective study designed to evaluate the safety and tolerability of BRAF, MEK inhibitors and RT is necessary.

4 STUDY GOALS AND OBJECTIVES

4.1 Study goal

The study will examine the safety and tolerability of combining dabrafenib, trametinib and RT for treatment of extra-cranial disease in patients with unresectable or metastatic melanoma.

4.2 Study Objectives

Primary objective:

- To establish a toxicity profile for patients receiving dabrafenib and trametinib in combination with RT.

Secondary objectives:

- To assess patients' pain using a visual analog scale.
- To assess overall disease response by measuring progression free survival and overall survival.
- To evaluate local treatment response and the time to local progression in the irradiated index lesion(s).

Translational objective (optional):

- Tumour tissue and serum will be collected at baseline and at week 1 post-RT. Biomarkers will be evaluated to correlate with tumour response and normal tissue toxicity.

5 ETHICAL CONSIDERATIONS

5.1 Good Clinical Practice and Responsibilities of the Principal Investigator each site

The study will be performed in accordance with the CPMP/ICH Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) in Australia and applicable guidelines in participating sites overseas.

The study protocol, including the final version of the participant information and informed consent form to be used, must be approved by the Trial Management Committee and a constituted Human Research Ethics Committee (HREC) prior to enrolment of any patients into the study. The opinion of the HREC should be dated and given in writing. It is the responsibility of the PI at each site to forward a copy of the approval from the HREC clearly identifying the protocol submitted for review and a copy of the approved participant information sheet and consent form to the Trial Coordinating Centre prior to entry of patients.

The investigator is responsible for ensuring that written informed consent by the patient is obtained before study entry. The investigator is responsible for informing the Trial Coordinating centre and the HREC of any SAEs and/or major amendments to the protocol as per local requirements.

The investigator is responsible for ensuring that all regulatory requirements are followed.

The investigator is required to ensure compliance with the protocol in its entirety. It is the responsibility of the investigator to maintain adequate and accurate CRFs.

International centres: International centres must abide by their own laws and regulations. It is the responsibility of the local PI to forward a copy of the necessary approvals for this study to MASC Trials ahead of site initiation. Any correspondence relating to the approval of protocol amendments and ongoing study reports must also be provided to MASC Trials on request.

6 INVESTIGATIONAL PLAN

6.1 Study design & duration

This is an investigator-driven prospective study in patients with advanced Stage IIIC and IV melanoma who are receiving palliative RT to symptomatic or bulky (> 2cm) soft tissue, nodal or bony metastases, concurrently with dabrafenib and trametinib systemic therapy. Patients may receive dabrafenib and trametinib via PBS authority approval for supply of medication.
Up to 3 areas of disease can be irradiated at the same time. Palliative RT should be commenced concurrently with dabrafenib and trametinib.

Acute and late toxicities, local and overall tumour response, progression free survival and overall survival will be assessed, in addition to the translational component.

The translational sub-study is being run in parallel with the clinical trial. Optional tumour biopsies from the irradiated index lesion(s) will be collected from patients at baseline and after the RT course. Serum will be collected at different time points of the trial. The aim is to analyse both serum and tumour biomarkers that may correlate with treatment response.

Systemic therapies will be administered according to the dosing guidelines; i.e.
- Dabrafenib will be administered at standard dose of 150mg twice daily;
- Trametinib will be administered at standard dose of 2mg once daily.

In order to evaluate response, patients with metastases present in different body systems are eligible to participate in the trial, including up to 3 sites of palliative RT that can be given concurrently.

For patients needing RT to bony, soft tissue or nodal metastases, the following dose levels for palliative RT are shown as below, with a phase I 3+3 study design:

Level 1: 20 Gy in 5 fractions, to any locations
Level 2a: 30 Gy in 10 fractions, with no abdominal viscera directly exposed to RT
Level 2b: 30 Gy in 10 fractions, with abdominal viscera directly exposed to RT
Level 3a: 40 Gy in 16 fractions, with no abdominal viscera directly exposed to RT
Level 3b: 40 Gy in 16 fractions, with abdominal viscera directly exposed to RT

Radiotherapy dose will be escalated to the next dose level if 0 out of 3 patients at the current dose level experiences dose limiting toxicity (DLT). If 2 or more patients experience DLT, de-escalate to dose level below. If 1 patient experiences DLT, treat 3 more patients at the current dose level. If 1 of 6 experiences DLT, escalate to the next dose level. If 2 or more of 6 experiences DLT, de-escalate to dose level below.

The clinician may use their discretion in prescribing the palliative radiotherapy dose when a lower dose level is preferred (for up to 6 trial participants), but only when the prescribed dose level has already been deemed safe by the TMC and/or DSMC.

The duration of dabrafenib and trametinib prior to commencing the trial will be documented at the time of study enrolment. The timing of the RT will be classified as upfront, at nadir or at local disease advancement.

- The timing of RT is considered upfront, if it is delivered within 4 weeks of commencing dabrafenib and trametinib.

- If RT is delivered for symptom-relief at any time after 4 weeks of dabrafenib and trametinib, such as to relieve pain from a bony metastases (not a measurable by RECIST 1.1 criteria), the RT is considered to be delivered "at local disease advancement".

- If RT is delivered to the metastatic lesions which are measurable by RECIST 1.1 criteria, i.e. the index lesion(s), and the RT is delivered at any time after 4 weeks of dabrafenib and trametinib, then the timing of RT is classified as either "at nadir" or "at local disease advancement".

    - The timing of RT is considered at nadir, if the index lesion has recorded the smallest sum of diameters since dabrafenib and trametinib started, and has not advanced locally as defined by at least a 20% increase in the smallest sum of the diameters.

    - The RT is delivered at local disease advancement, when the sum of diameters for the index lesion has increased by at least 20% from the smallest sum of the diameters recorded.

The protocol is divided into four phases:

- **Screening phase:** This establishes eligibility, informed consent and the documentation of baseline assessments to include optional biopsy of index lesion(s), blood samples and clinical, photographical and radiological evaluation of the tumour.
  To minimise the impact of the tumour biopsy on the measurement of the index lesion or the patient's assessment of pain, only one core biopsy will be taken from the index lesion(s).

- **Radiation therapy phase:** Begins once the patient commences RT concurrently with dabrafenib and trametinib and the start of documentation of adverse events including toxicity assessment, assessment of patients' pain, and photographs of the irradiated area (to be taken weekly during radiotherapy).

- **Early post-RT phase:** For the first 3 weeks post RT, the assessment of patients' pain, adverse events and toxicity assessment and clinical photograph of the irradiated area will continue to be taken weekly. Optional biopsy of index lesion(s) will be taken during the first post-RT week. To minimise the impact of the tumour biopsy on the measurement of the index lesion or the patient's assessment of pain, only one core biopsy will be taken from the index lesion(s). Blood will be taken during the first post-RT week and the fourth post-RT week for serum storage.

- **Follow-up phase:** Follow-up CT scan for disease response assessment will be performed at week 4 post-RT and then every 8 weeks until study completion. Measurement of index lesion(s), as well as overall disease response by RECIST 1.1 criteria will be performed at week 4 post-RT and then every 8 weeks until study completion. Assessment of patients' pain, adverse events and toxicity assessment and clinical photograph of the irradiated area will continue to be taken every 8 weeks. Dermatological examination will be performed if clinically indicated. Blood will be taken every 8 weeks for serum storage.

Following RT, dabrafenib and trametinib will be continued until there is evidence of overall disease progression according to RECIST 1.1 criteria.

Further palliative RT to the same lesion(s) or other symptomatic or bulky (>2cm) lesion(s) are permitted on the study. The dose fractionation is at the discretion of the treating radiation oncologist, but the accumulative dose to the normal tissue and organ should be kept within safe limit. For example, the maximum accumulated dose to the spinal cord, at equivalent 2 Gy fractions using a α/β ratio of 1, should not exceed 45Gy, i.e. EQD2 $\leq$ 45Gy. The Trial Coordinating Centre should be notified of any further RT required.

If resection of the index lesion(s) or re-irradiation to the index lesion(s) is planned, then measurement of the index lesion(s) should be performed within 14 days prior to the surgical excision or re-irradiation. The interval between initial course of RT and re-irradiation to index lesion(s) should be at least 4 weeks.

It is anticipated that 12 months will be required to complete accrual.

The completion of the study will occur when one of following has occurred in each patient:

- Completion of 12 months of post-RT follow up,
- Withdrawal from the study,
- Lost to follow-up,
- Death.

In the phase II study [Flaherty KT, 2012] on patients receiving dabrafenib and trametinib, the median PFS for patients who received the full-dose dabrafenib and trametinib combination was 9.4 months. Therefore at the time of study completion, it is expected that the vast majority of the patients on the study would have developed disease progression according to the RECIST 1.1 criteria.

6.1.1 Dose limiting toxicity for RT

Any adverse event should be differentiated by the treating physician as to whether it is solely related to RT, solely related to systemic treatment, related to both treatments, or not related to the study treatment. Toxicity related to RT usually occurs within the RT field or in the vicinity of the RT field, e.g. within 5cm distance from the edge of the radiotherapy field.

Dose limiting toxicity for RT will be evaluated weekly during RT and up to 4 weeks post-RT. DLT includes CTCAE Grade 4 radiation dermatitis or any other CTCAE Grade 3 or above toxicity which are either “solely related to RT” or “related to both treatments”.

CTC Grade 3 radiation dermatitis defined as moist desquamation in areas other than skin folds and creases, and bleeding induced by minor trauma or abrasion, can occur with moderate to high dose palliative RT, e.g. 40Gy in 16 fraction.

Any suspicion of possible DLT should be reported to the Trial Coordinating Centre (MASC Trials) within 24 hours of its detection. The RT for this patient should be stopped once a “possible DLT” is reported. Discussion between the physician who reported the possible DLT, the principle investigator at the local site, and the study chair will take place within 3 days of receiving the report. After which the study chair will immediately determine whether the toxicity represents a DLT. If the toxicity is not a DLT, RT can be resumed, and the toxicity should be managed in accordance to the recommendations.

Tolerability of the combination systemic therapy with palliative RT will be reviewed in a scheduled interim analysis. This analysis will be reviewed for the first 3 patients (20Gy in 5 fractions) when all three patients have completed their RT and are at least 4 weeks post RT. The data from these first 3 patients once they have completed at least 4 weeks post-RT are part of a scheduled interim analysis which is designed to review the safety tolerability, adverse event and toxicity profile. As a general rule, at any dose level when 2 or more patients have encountered DLT, the dose escalation should be stopped at that point.

A report will be produced from the data which will be reviewed and analyzed by the Study Chair, independent Data Safety Monitoring Committee (DSMC) and the Trial Management Committee (TMC). Any relevant issues will be escalated for consideration to the pharmaceutical company.

During the study, each study site will be informed of any pertinent information relating to RT dose levels and safety profile.

Given the safety concern of RT exposure of abdominal viscera, due to one reported case of excess liver toxicity occurring with palliative RT concurrent with BRAF inhibitor [Anker, 2013], patients are divided into the following study sub-cohorts:

1. Patients whose abdominal or pelvic viscera are not directly exposed to RT, i.e. not within the RT field, which means the maximum dose received by abdominal viscera are less than 50% of the prescribed dose. This sub-cohort would include patients receiving palliative RT to head and neck, limbs, thoracic spine or ribs, mediastinal or hilar lymph nodes, axillary or supraclavicular lymph nodes.

2. Patients whose abdominal viscera are directly exposed to RT, i.e. within the RT field, which means part of abdominal viscera such as small bowel or liver are receiving at least 50% of the prescribed dose. This sub-cohort would include patients receiving palliative RT to lumbosacral spine or bony pelvis, para-aortic or pelvic lymph nodes, or inguinal lymph nodes where part of abdominal viscera is within RT fields.

6.2 Study population and expected sample size

Patients with BRAF V600E/K mutation-positive advanced stage melanoma who have been commenced on dabrafenib and trametinib, and who have symptomatic or bulky (>2cm) soft tissue, nodal or bony metastases that warrant palliative radiotherapy (RT) are suitable for this study.

Planned enrolment: In total, up to 30 patients will be enrolled in the study.

If the highest dose levels for palliative RT (i.e. 40Gy in 16 fractions) are reached, and no DLT was experienced by any of the patients treated at the highest dose level within 4 weeks from the RT, or only 1 of 6 patients treated by the highest dose level experienced DLT within 4 weeks from the RT, patient enrollment can be ceased at this point. All enrolled patients will continue to be followed up according to the Schedule of Assessments (Table 19) until study completion.

However, if the above scenario occurs within 12 months after the enrolment of the first patient, the investigators may continue to enroll patients in this study up to 12 months from the enrolment of the first patient, or up to 30 patients in total, whichever occurs earlier. The palliative RT dose used in these additional patients can be any of the dose fractionation regimen used in the dose escalation levels, i.e. 20Gy/5#, 30Gy/10#, 40Gy/16#, at the discretion of the treating physician.

If the study accrues slowly, and the required number of patients in each of the metastatic anatomical cohorts and the total number of patients is not reached 24 months after the enrolment of the first patient, then enrolment will be stopped early at that point and the last patient will be followed up until the completion of the study (as defined in Section 6.3). The final data analysis will then be performed on the existing patients enrolled in the study.

6.2.1 Inclusion Criteria

Subjects eligible for enrolment in the study must meet all of the following criteria:

1. ≥18 years of age.
2. Signed written informed consent.
3. Histologically confirmed cutaneous melanoma that is either Stage IIIC (unresectable) or Stage IV (metastatic), and determined to be BRAF V600E/K mutation-positive as determined by a BRAF mutation assay.

Note: For Stage IIIC disease, the decision that the disease is unresectable should be formally endorsed by the melanoma multidisciplinary tumour board of the local institution.

4. Symptomatic or bulky (greater than 2 cm in diameter) soft tissue, nodal or bony metastases requiring palliative RT.
5. Have measurable disease according to RECIST 1.1 criteria.
   Note: patients with bony metastases that are not measurable by RECIST 1.1 criteria are allowed in this study.
6. All anti-cancer treatment-related toxicities (except alopecia and laboratory values as listed on Table 1) must be less than or equal to (≤) Grade 1 according to the Common Terminology Criteria for Adverse Events version 4 (CTCAE version 4.03; NCI, 2009) at the time of study enrolment.
7. Able to swallow and retain oral medication and must not have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels.
8. Women of childbearing potential must have a negative serum pregnancy test within 7 days prior to enrolment and agree to use effective contraception, as defined in Section 6.2.3.1, from 14 days prior to enrolment throughout the treatment period, and for 4 months after the last dose of study treatment.
9. An Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2 [Oken, 1982]. Refer to Appendix 1 for details.

6.2.2 Exclusion Criteria

Subjects meeting any of the following criteria must not be enrolled in the study:

1. Concurrent treatment with Ipilimumab or any other anti-CTLA-4 monoclonal antibody therapy.
2. Concurrent treatment with anti-PD-1 or anti-PD-L1 monoclonal antibody therapy.
3. Known ocular or primary mucosal melanoma.
4. Four (4) or more lesions requiring palliative RT at the time of study enrolment.
5. Symptomatic brain metastases or those treated < 3 months previously
6. Clear evidence of widespread systemic disease progression on dabrafenib and trametinib.
7. Concurrent systemic anti-cancer treatment (chemotherapy, immunotherapy, biologic therapy, vaccine therapy, or investigational treatment)
   Note: Tamoxifen and aromatase inhibitors are allowed in the adjuvant setting of breast cancer within the last 4 weeks.
8. Current use of a prohibited medication as described in Section 8.2.
9. Active malignancy other than disease under study with exceptions below, or any malignancy with confirmed activating RAS mutation.
   Note: Prospective RAS testing is not required. However, if the results of previous RAS testing are known, they must be used in assessing eligibility.
   Excluding: Non-melanoma skin cancers (basal cell carcinoma and squamous cell carcinoma) and carcinoma in situ of the cervix.
10. Any serious or unstable pre-existing medical conditions (aside from malignancy exceptions specified above), psychiatric disorders, or other conditions that could interfere with the subject's safety, obtaining informed consent, or compliance with study procedures.
11. A history of known Human Immunodeficiency Virus (HIV).
12. A history of retinal vein occlusion (RVO).
13. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to the study treatments, their excipients, and/or dimethyl sulfoxide (DMSO).
14. Pregnant or nursing females.
15. Previous RT to the same lesion or area due to receive the current course of palliative RT.

Note: patients who had previous RT to other areas are eligible to the study if the previous RT was completed more than 8 weeks prior.

16. A history of autoimmune diseases which are known to increase radiation toxicity, including systemic lupus erythematosus and scleroderma.
17. Genetic syndromes exhibiting increased radiosensitivity (e.g. ataxia telangiectasia).

6.2.3 Women of Childbearing Potential

6.2.3.1 Pregnancy Testing and Prevention

The need for a screening pregnancy test depends on whether a female subject is of childbearing potential or non-childbearing potential.

A female of non-childbearing potential (i.e. physiologically incapable of becoming pregnant) is defined as any female who has had a hysterectomy, bilateral oophorectomy (ovariectomy), bilateral tubal ligation or tubal occlusion, or is post-menopausal.

A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile, e.g. age appropriate, >45 years in the absence of hormone-replacement therapy (HRT). In questionable cases, the subject must have a follicle-stimulating hormone (FSH) value >40 mIU/mL and an estradiol value <40 pg/mL (<140 pmol/L).

A female of child-bearing potential is defined as any female who does not meet the criteria of non-childbearing potential as described in the previous paragraph.

If a female subject is of childbearing potential, she must have a serum β-human chorionic gonadotropin (HCG) pregnancy test performed within 7 days prior to enrolment. Subjects with a positive pregnancy test result must be excluded from the study. Subjects with a negative pregnancy test result must agree to use an effective contraception method as described below throughout study treatment and until 4 months after the last dose of study treatment.

Acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of the physician, are as follows:

- An intrauterine device with a documented failure rate of less than 1% per year.
- Male partner sterilization prior to the female subject's entry, and this male is the sole sexual partner for that female.
- Complete abstinence from sexual intercourse for 14 days prior to enrollment, throughout study treatment, and for at least 4 months after the last dose of study treatment. Abstinence is only acceptable when in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.
- Double-barrier contraception: condom and occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/cream/suppository).

Note: Hormonal-based methods (e.g. oral contraceptives) are not permitted as contraception due to potential drug-drug interactions with dabrafenib.

Female subjects who are lactating must discontinue nursing prior to the first dose of study treatment and must refrain from nursing throughout the treatment period and for 4 months following the last dose of study treatment.

Serum pregnancy tests will be repeated at 4 weeks post-RT and then every 12 weeks. If a subject becomes pregnant during the treatment period of the study, the study treatments should be stopped immediately.

6.2.3.2 Pregnancy Reporting

Any pregnancy that occurs during study participation must be reported to the Trial Coordinating Centre as an SAE within 24 hours of learning of its occurrence. The pregnancy must be followed-up to determine outcome (including premature termination) and status of mother and child.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to study treatment, must be promptly reported to the Trial Coordinating Centre.

In addition, the investigator must attempt to collect pregnancy information on any female partners of male study subjects who become pregnant while the subject is enrolled in the study. Pregnancy information must be reported to the Trial Coordinating Centre as described above.

6.3 Discontinuation of Subjects from Treatment and Study Completion

Subjects MUST discontinue study treatment for any of the reasons documented below. This should be recorded on the CRF and submitted along with any other CRF / medical report to the Trial Coordinating Centre:

- Withdrawal of informed consent (subject's decision to withdraw for any reason).
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject.
- Pregnancy.
- Termination of the study by the study sponsor.
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g. infectious disease) illness.
- Confirmed tumour progression according to RECIST 1.1 criteria, after which dabrafenib and trametinib should be discontinued.

All subjects who discontinue should comply with protocol specified follow-up procedures as outlined in Table 19. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (i.e. is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness). If a subject was withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate CRF.

Study follow-up will continue until the completion of the study, which occurs when the patient withdraws consent for the study, is lost to follow up, completes 12 months of post-RT follow up or dies (whichever occurs first).

7 TREATMENTS

7.1 Study Treatments

7.1.1 Dabrafenib and Trametinib

Patients may receive dabrafenib and trametinib via PBS authority approval for supply of medication.

Dabrafenib is available as 50 mg and 75 mg capsules. Each capsule will contain 50 mg or 75 mg of dabrafenib (present as the mesylate salt); the inactive ingredients will include microcrystalline cellulose, magnesium stearate, colloidal silicon dioxide, and HPMC (hydroxypropyl methyl cellulose) capsule shells. The 50 mg strength capsules are dark red opaque hypromellose capsules composed of red iron oxide (E172), titanium dioxide (E171), and hypromellose (E464). The 75 mg strength capsules are pink opaque hypromellose capsules composed of red iron oxide (E172), titanium dioxide (E171), and hypromellose (E464). All capsules are printed with four black bars using black ink. The black ink contains black iron oxide (E172), shellac, propylene glycol, and ammonium hydroxide.

Trametinib is available as 0.5 mg and 2.0 mg tablets. Each tablet will contain 0.5 mg or 2.0 mg of trametinib (present as the DMSO solvate); the inactive ingredients will include mannitol, sodium lauryl sulfate, colloidal silicon dioxide, microcrystalline cellulose, hypromellose, croscarmellose sodium, magnesium stearate, and film coating (Opadry a titanium dioxide-based formulation with yellow or red iron oxide as colourant). Both tablet strengths are biconvex film coated tablets with a different shape and size to facilitate the visual identification. The 0.5 mg strength is a 4.8x8.7 mm yellow, oval tablet, and the 2.0 mg strength is a 7.5 mm diameter, pink, round tablet.

7.1.2 Dosage and Administration

Both dabrafenib and trametinib should be administered in the morning at approximately the same time every day. The second dose of dabrafenib (150 mg) should be administered approximately 12 hours after the morning dose. Medication should be taken orally with approximately 200 mL of water under fasting conditions, either 1 hour before or 2 hours after a meal.

If a subject vomits after taking the medication, the subject should be instructed not to retake the dose and should take the next dose as originally scheduled.

If a subject misses a dose, the subject may take the dose immediately if the next dose is scheduled at least 6 hours later. If the next scheduled dose is due in less than 6 hours, the subject should skip the dose and resume dosing at the next scheduled dose. If a subject misses a dose of trametinib, the subject may take the dose immediately if the next dose is scheduled at least 12 hours later.

7.1.3 Handling and Storage of Dabrafenib and Trametinib

Dabrafenib and trametinib must be dispensed and administered in accordance with the protocol,. Dabrafenib and trametinib should be stored under the appropriate physical conditions for the product and at temperatures specified on the label.

7.1.4 Radiotherapy

The aim of palliative RT in advanced melanoma is to provide rapid symptomatic relief, defer or prevent complications from local disease, allowing preservation of quality of life. RT is an effective modality for symptom palliation [Seegenschmiedt, 1999; Corry, 1999; Rao, 2011]. A range of palliative RT dose has been used for the treatment of advanced melanoma, ranging from more conservative dose of 20-25Gy/5 daily fraction, to the higher dose of 40-8Gy/16-20 daily fraction which is typically used for treating unresectable stage III disease or large bulky metastases in the metastatic setting.

Single fraction palliative RT of 8 Gy can be used to achieve pain relief for non-complicated bony metastases, and has been shown to be equivalent in efficacy when comparing with fractionated RT [Lutz, 2011]. However, most of the randomised controlled trials comparing 8 Gy single fraction palliative RT with fractionated palliative RT contained few melanoma patients. Single fraction

palliative RT is not typically used to treat symptomatic or bulky soft tissue and nodal metastases, because of concern that the lower dose RT will not achieve durable disease control, especially in view of significant proportion of melanomas displaying various degrees of radio-resistance [Sambade, 2011]. Furthermore, fractionated RT may better exploit the synergistic effect from the dabrafenib / trametinib / RT combination. For the above reasons, 20-25Gy/ 5 daily fractions are used as the initial RT dose level for this prospective study.

RT technique employed and the dosage prescription will be at the discretion of the treating radiation oncologists. CT based planning allows better visualization of treatment target, and reduces the chance of geographical miss, and is therefore mandatory. For most clinical scenarios, palliative RT can be delivered with simple beam arrangement (e.g. ≤ 2 beams). However, three-dimensional technique with more complex beam arrangement may be needed in certain cases to improve dose coverage of the target and/or to reduce dose to the organs at risk, especially at higher RT dose level such as 40Gy in 16 fractions.

For palliative RT to bony metastases without tumour mass beyond the bone, simple RT techniques with parallel opposed fields dosing to the mid-point, or single field dosing to a specified depth are permitted. Electrons to skin lesions and ribs can also be used. Symptomatic area should be marked by wires and a PTV generated on CT planning for these. When skin is the target this should be captured in the CRF for correlation with the TLDs and skin reaction grading.

For palliative RT to soft tissue, nodal metastases, or bony metastases with soft tissue mass, gross tumour volume (GTV) should be outlined on the planning CT scan to encompass the visible tumour mass. The planning target volume (PTV) is generated by an expansion of the GTV with a suitable margin to account for microscopic disease beyond gross tumour, any delineation uncertainty and patient set up uncertainty. The extent of the GTV to PTV margin is at the treating radiation oncologist's discretion, but this margin should be greater or equal to 1cm. The aim is for at least 95% of the PTV to receive 95% of the prescribed dose, although it is acceptable if 95% of PTV receives more than 90% of the prescribed dose. For tumours involving the skin or situated close to the skin, tissue equivalent bolus may be used to deliver adequate dose to the skin.

The treating radiation oncologists should be aware that dose tolerance of potential organs at risk should not be exceeded. For patients receiving palliative RT to the vertebrae, single field palliative RT dosing to the depth of the spinal cord is allowed. However, the spinal cord should be delineated at least 2cm above and below the radiotherapy field, and the maximum point dose to the spinal cord, at equivalent 2 Gy fractions using an α/β ratio of 1, should not exceed 45Gy, i.e. EQD2 ≤ 45Gy. Therefore, **20 Gy in 5 fractions** (EQD2 = 33.3Gy, using α/β ratio of 1) and **30 Gy in 10 fractions** (EQD2 = 40Gy, using α/β ratio of 1) are acceptable dose fractionations for the treatment of vertebral metastases in this study.

Fractionated radiotherapy should be delivered on Monday to Friday, five daily fractions per week. However, delivery of nine daily fractions per fortnight is considered acceptable.

As radiation dermatitis is a potential RT related toxicity, and Grade 4 radiation dermatitis is a DLT, thermoluminescent dosimeter (TLD) measurement of skin dose is strongly encouraged during RT. TLD should be placed close to the center of the RT field. At the time of data analysis, the skin dose obtained from TLD measurement will be correlated with the grade of radiation dermatitis and reported accordingly.

7.1.4.1 Radiotherapy Quality Assurance (QA)

Sites are required to keep copies of the case history, treatment prescription, treatment administration sheet, portal verification films, dosimetry plans or clinical mark up tracings and

photographs. These will be available for future review if required by the Trial Coordinating Centre for the purposes of QA to ensure data integrity.

7.2 Method of Assigning Patient Enrolment Number

Once informed consent has been obtained, the sites will register the patient to the trial at the time of eligibility screening via the MASC Trials online enrolment system. Once the site receives a confirmation of enrolment email, RT can be commenced. RT can be delivered to the registered patient any time after 2 weeks of dabrafenib and trametinib alone.

Registration via the MASC Trials online enrolment system will ensure timely allocation of study numbers. Specific instructions for the enrolment procedure will be detailed in the Operations Manual.

7.3 Dose Modifications due to Toxicities that are Likely Attributable to Dabrafenib and Trametinib

The severity of AEs will be graded using the CTCAE, version 4.03. The section includes:

- general guidelines for clinically significant toxicities related to study treatments and
- specific guidelines for adverse events of special interest, which are events that have been observed with higher frequency or severity in subjects receiving dabrafenib, trametinib, or a combination of both therapies.

With the exceptions of pyrexia likely related to dabrafenib and LVEF (left ventricular ejection fraction) likely related to trametinib, the recommendations suggest that both therapies be reduced simultaneously in response to toxicities that are considered by the investigator to be treatment related.

Table 2 Categories of Dose Modification Recommendations

Adverse Event	Dabrafenib	Trametinib	Section
General Guidelines for Clinically Significant Toxicities	X	X	Section 7.3.2
Guidelines for Specific Adverse Events Cardiovascular Adverse Events			
LVEF		X	Section 7.3.3.1
Hypertension	X	X	Section 7.3.3.2.1 and Section 7.3.3.2.2
Prolonged QTc	X	X	Section 7.3.3.3
Skin –Related Adverse Events (Except cuSCC)[a]			
Rash	X	X	Section 7.3.4.1
Hand-Foot Skin Reaction	X	X	Section 7.3.4.2
Other Adverse Events			
Pyrexia	X		Section 7.3.5.1
Diarrhoea	X	X	Section 7.3.5.2
Renal Insufficiency	X	X	Section 7.3.5.3
Visual Changes	X	X	Section 7.3.5.4
Pneumonitis	X	X	Section 7.3.5.5
Liver Chemistry Stopping Criteria	X	X	Section 7.4

a. Refer to Section 7.3.4.3 for management of cuSCC

7.3.1 Dose Levels of dabrafenib and trametinib

The dose levels for this study are provided in **Table 3.**

Table 3 Dose Levels of Dabrafenib and Trametinib

Dose Level	Dabrafenib Dose/Schedule	Trametinib Dose/Schedule
Starting Dose	150 mg BID	2 mg once daily
-1 (1st Dose reduction)	100 mg BID	1.5 mg once daily
-2 (2nd Dose reduction)	75 mg BID	1 mg once daily

Abbreviation: BID = twice daily

If an AE resolves to grade 1 or baseline at the reduced dose level, and no additional toxicities are seen after 4 weeks of study treatment at the reduced dose, the dose may be increased to the previous dose level.

A dose reduction below 75 mg BID for dabrafenib and 1 mg once daily for trametinib is not allowed. If a dose reduction below 75 mg BID for dabrafenib is required, dabrafenib will be permanently discontinued, but the subjects will be allowed to continue trametinib. If a dose reduction below1.0 mg once daily for trametinib is required, then trametinib will be permanently discontinued, but these subjects will be allowed to continue dabrafenib.

7.3.2 General Recommendations for Clinically Significant Toxicities

General guidelines regarding management and dose reduction for adverse events that are considered by the investigator to be related to study treatment and which do not have specific guidelines (see **Table 2**) are provided in **Table 4**.

Table 4 Dose Modification Guidelines for Events Considered Related to Dabrafenib and Trametinib

CTCAE Grade	Action and Dose Modification
Grade 1	▪ Continue study treatment at current dose level ▪ Monitor closely ▪ Provide supportive care according to institutional standards
Grade 2	▪ Interrupt study treatment if clinically indicated ▪ Monitor closely ▪ Provide supportive care according to institutional standards ▪ When toxicity resolves to grade 1 or baseline, restart study treatment at current dose level
Grade 3	▪ Interrupt study treatment ▪ Monitor closely ▪ Provide supportive care according to institutional standards ▪ When toxicity resolves to grade 1 or baseline, restart study treatment **reduced by one dose level** ▪ If the grade 3 toxicity recurs, interrupt study treatment ▪ When toxicity resolves to grade 1 or baseline, restart study treatment **reduced by another dose level**
Grade 4	▪ Interrupt study treatment ▪ Monitor closely ▪ Provide supportive care according to institutional standards ▪ Restart with study treatment **reduced by one dose level** once toxicity resolves to grade 1 or baseline ▪ If the grade 4 toxicity recurs, **either permanently discontinue study treatment** or, if the subject is clinically benefiting, discuss continuation of study treatment with the Trial Coordinating Centre.

7.3.3 Recommendations for Cardiovascular Adverse Events

Cardiovascular adverse events have been seen in subjects receiving either dabrafenib, trametinib or both in combination.

7.3.3.1 Left Ventricular Ejection Fraction (LVEF)

Decreases of the left-ventricular-ejection-fraction (LVEF) have been observed in subjects receiving trametinib monotherapy and in combination with dabrafenib. Therefore, if the heart is directly within the radiation field, ECHOs must be performed to assess cardiac ejection fraction at baseline, at 4 weeks post-RT and every 16 weeks thereafter. Otherwise, an ECHO should be performed if and when clinically indicated as in the Schedule of Assessments (Table 19). Dose modification guidance and stopping criteria for LVEF decrease are provided in **Table 5**.

Table 5 Dose Modification Guidelines and Stopping Criteria for LVEF Decrease

Clinic	LVEF-drop (%) or CTCAE grade	Action and Dose Modification
Asymptomatic	Absolute decrease of >10% in LVEF compared to baseline and ejection fraction below the institution's LLN	• Interrupt trametinib and dabrafenib and repeat ECHO within 2 weeks[a] • If the LVEF recovers within 4 weeks (defined as LVEF ≥LLN and absolute decrease ≤10% compared to baseline) Consult with the Trial Coordinating Centre and Study Chairman and request approval for restart Restart treatment with trametinib or placebo reduced dose by one dose level Restart dabrafenib at previous dose level[b] Repeat ECHO 2 , 4 , 8 and 12 weeks after re-start; continue in intervals of 12 weeks thereafter • If LVEF does not recover within 4 weeks Consult with cardiologist Permanently discontinue trametinib Report as SAE to the Trial Coordinating Centre Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution Consult with Trial Coordinating Centre and Study Chairman[d]

Symptomatic[c]	Grade 3: resting LVEF 39-20% or >20% absolute reduction from baseline	• Permanently discontinue trametinib • Discontinue dabrafenib • Report as SAE to the Trial Coordinating Centre • Consult with cardiologist • Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution[e]
	Grade 4: resting LVEF <20%	

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; ECHO = echocardiogram; LLN = lower limit of normal; LVEF = left ventricular ejection fraction;

a. If ECHO does not show LVEF recovery after 2 weeks, repeat ECHO 2 weeks later.
b. If recurrent episodes of LVEF reduction occur dabrafenib monotherapy, consult Trial Coordinating Centre.
c. Symptoms may include: dyspnoea, orthopnoea, and other signs and symptoms of pulmonary congestion and oedema.
d. Once LVEF recovers, restarting dabrafenib monotherapy can be considered in consultation with Trial Coordinating Centre.
e. Once LVEF recovers, including resolution of symptoms, restart of dabrafenib monotherapy only can be considered in consultation with Trial Coordinating Centre.

7.3.3.2 Hypertension

Increases in blood pressure have been observed in subjects receiving trametinib. Recommendations for blood pressure monitoring and management are provided in Section 7.3.3.2.1 and Section 7.3.3.2.2.

7.3.3.2.1 Monitoring of Hypertension

All blood pressure assessments should be performed under the following optimal conditions:

- the subject has been seated with back support, ensuring that legs are uncrossed and flat on the floor
- the subject is relaxed comfortably for at least 5 minutes
- restrictive clothing has been removed from the cuff area and the right cuff size has been selected
- the subject's arm is supported so that the middle of the cuff is at heart level
- the subject remains quiet during the measurement.

In subjects with an initial blood pressure reading within the hypertensive range, a second reading should be taken at least 1 minute later, with the 2 readings averaged to obtain a final blood pressure measurement. The averaged value should be recorded in the CRF.

Persistent hypertension is defined as an increase of systolic blood pressure (SBP) > 140 mm Hg and/or diastolic blood pressure (DBP) > 90 mm Hg in three consecutive visits with blood pressure assessments from two readings collected as described above. Visits to monitor increased blood pressure can be scheduled independently from the protocol visits outlined in the Schedule of Events (Table 19). Ideally, subsequent blood pressure assessments should be performed within one week.

Asymptomatic hypertension is defined as an increase of SBP >140 mm Hg and/or DBP >90 mm Hg in the absence of headache, light-headedness, vertigo, tinnitus, episodes of fainting or other symptoms indicative of hypertension.

7.3.3.2.2 Management of Hypertension

For subjects experiencing an increase in systolic and/or diastolic blood pressure that is persistent and may be associated with the study treatment, recommendations for the clinical management of hypertension are described below:

Table 6 Management and Dose Modification Guidelines for Hypertension

Hypertension	Action and Dose Modification
(Scenario A) ▪ Asymptomatic and persistent SBP of ≥140 and <160 mmHg, or DBP ≥90 and <100 mmHg, or ▪ Clinically significant increase in DBP of 20 mmHg (but still below 100 mmHg).	▪ Continue study treatment at the current dose ▪ Adjust current or initiate new antihypertensive medication ▪ Titrate antihypertensive medication(s) during the next 2 weeks as indicated to achieve well-controlled[b] BP ▪ If BP is not well controlled within 2 weeks, consider referral to a specialist and go to scenario (B).
(Scenario B) ▪ Asymptomatic SBP ≥160 mmHg, or DBP ≥100 mmHg, or ▪ Failure to achieve well-controlled BP within 2 weeks in Scenario A	▪ Interrupt study treatment if clinically Indicated ▪ Adjust current or initiate new antihypertensive medication(s) ▪ Titrate antihypertensive medication(s) during the next 2 weeks as indicated to achieve well-controlled BP ▪ Once BP is well controlled[b], restart study treatment **reduced by one dose level**
(Scenario C) ▪ Symptomatic[c] hypertension, or ▪ Persistent SBP ≥160 mmHg, or DBP ≥100 mmHg, despite antihypertensive medication and dose reduction of study treatment	▪ Interrupt study treatment ▪ Adjust current or initiate new antihypertensive medication(s) ▪ Titrate antihypertensive medication(s) during the next 2 weeks as indicated to achieve well-controlled BP ▪ Once BP is well controlled[b], restart study treatment **reduced by one dose level**
(Scenario D) ▪ Refractory hypertension unresponsive to above interventions or hypertensive crisis.	▪ Permanently discontinue study treatment; ▪ Continue follow-up as per protocol.

Abbreviations: BP = blood pressure; DBP = diastolic blood pressure; mmHg = millimetres mercury; SBP = systolic blood pressure;
a. Hypertension detected in two separate readings during up to three consecutive visits
b. Well-controlled blood pressure defined as SBP ≤140 mm Hg and DBP ≤90 mm Hg in two separate readings during up to three consecutive visits.
c. Symptomatic hypertension defined as hypertension aggravated by symptoms (e.g., headache, light-headedness, vertigo, tinnitus, episodes of fainting) that resolve after the blood pressure is controlled within the normal range.

7.3.3.3. Guidelines for Prolonged QTc

Guidelines for dose modification and stopping criteria due to QTc-prolongation are provided in **Table 7.**

Table 7 Withholding and Stopping Criteria for QTc-Prolongation

QTc-Prolongation[a]	Action and Dose Modification
• QTcB ≥501 msec	• Interrupt all study treatments until QTcB prolongation resolves

	to grade 1 or baseline • Test serum potassium, calcium, phosphorus and magnesium. If abnormal correct per routine clinical practice to within normal limits. • Review concomitant medication usage for a prolonged QTc. • Restart at current dose level[b] • If event recurs, permanently discontinue study treatments • Continue follow-up as per protocol

Abbreviations: msec = milliseconds; QTcB = QT interval on electrocardiogram corrected using the Bazett's formula

a. Based on average QTc value of triplicate ECGs. For example, if an ECG demonstrates a prolonged QT interval, obtain two or more ECGs over a brief period, and then use the averaged QTc values of the three ECGs to determine if study treatments should be interrupted or discontinued.

b. If the QTc prolongation resolves to grade 1 or baseline, the subject may resume study treatment if the investigator, Trial Coordinating Centre and Study Chairman agree that the subject will benefit from further treatment.

7.3.4 Guidelines for Skin-related Adverse Events

Cutaneous adverse events have been observed in subjects receiving dabrafenib, trametinib or both therapies in combination (see the Investigator Brochures for more information). Recommendations for supportive care and guidelines for dose modifications are provided (Section 7.3.4.1, Section 7.3.4.2, and Section 7.3.4.3). The institutional standards for the management of skin-related AEs can differ from these guidelines. Biopsies of any new skin lesions especially those suspicious of cuSCC should be done as per standard practice.

7.3.4.1 Rash

Rash is a frequent AE observed in subjects receiving trametinib, dabrafenib, or the combination of both therapies. Guidelines for rash management are based on experience with other MEK inhibitors and EGFR inhibitors [Balagula, 2010; Lacouture, 2011] and are provided below (Table 8 and Table 9).

Table 8 Guidelines for Supportive Care of Rash

Type of Care	Action
Prevention/Prophylaxis: Start from Day 1	▪ Avoid unnecessary exposure to sunlight ▪ Apply broad-spectrum sunscreen (containing titanium dioxide or zinc oxide) with a skin protection factor (SPF) ≥15 at least twice daily. ▪ Use thick, alcohol-free emollient cream (e.g., glycerine and cetomacrogol cream) on dry areas of the body at least twice daily.
Prevention/Prophylaxis: Start from Day 29 and implement for a total of 6 weeks	▪ Topical steroids and antibiotics should be applied at least twice daily starting on Day 29 of study treatment, to body areas such as face, chest, and upper back. ▪ Use mild-strength topical steroid (hydrocortisone 1% cream) and ▪ topical antibiotic (e.g., clindamycin) or oral antibiotics (e.g., doxycycline100 mg BID, minocycline 100 mg BID)
Symptomatic Care[a]	▪ Pruritic lesions: cool compresses and oral

	antihistamine therapies ▪ Fissuring lesions: Monsel's solution, silver nitrate, or zinc oxide cream ▪ Desquamation: thick emollients and mild soap ▪ Paronychia: antiseptic bath, local potent corticosteroids in addition to oral antibiotics; if no improvement, consult dermatologist or surgeon ▪ Infected lesions: appropriate bacterial/fungal culture-driven systemic or topical antibiotics

Abbreviations: BID = twice daily; SPF = sun protection factor
a. Subjects who develop rash/skin toxicities should be seen by a qualified physician and should receive evaluation for symptomatic/supportive care management

Guidelines for management and dose reduction for rash considered to be related to study treatment are provided in Table 9.

Table 9 Management and Dose Modification Guidelines for Rash

CTCAE Grade	Adverse Event Management	Action and Dose Modification
Grade 1	▪ Initiate prophylactic and symptomatic treatment measures ▪ Use moderate strength topical steroid[a] ▪ Reassess after 2 weeks	▪ Continue study treatment ▪ If rash does not recover to baseline within 2 weeks despite best supportive care, reduced by one dose level
Grade 2	▪ Initiate prophylactic and symptomatic treatment measures ▪ Use moderate strength topical steroid[a] ▪ Reassess after 2 weeks	▪ Reduce study treatment by one dose level ▪ If rash recovers to ≤grade 1 within 2 weeks, increase dose to previous dose level ▪ If no recovery to ≤grade 1 within 2 weeks, interrupt study treatment until recovery to ≤grade 1 ▪ Restart study treatment at reduced dose level[b]
Grade ≥3	▪ Use moderate strength topical steroids[a] PLUS oral methylprednisolone dose pack ▪ Consult dermatologist	▪ Interrupt study treatment until rash recovers to grade ≤1 ▪ Restart[b] with study treatment reduced by one dose level[c] ▪ If no recovery to grade ≤2 within 4 weeks, permanently discontinue study treatment ▪ Continue follow-up as per protocol.

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events
a. Moderate-strength topical steroids: hydrocortisone 2.5% cream or fluticasone prioprionate 0.5% cream
b. Approval of Tral Coordinating Centre and Study Chairman is required to restart study treatment after ≥21 days of interruption.
c. Escalation of study treatment to previous dose level may be considered if no rash is evident 4 weeks after restarting study treatment

7.3.4.2 Guidelines for Hand-foot Skin Reactions (HFSR)

Episodes of Hand-foot Skin Reaction (HFSR) have been observed in subjects receiving dabrafenib. Guidelines for management of HFSR are based on experience with other kinase inhibitors [Lacouture, 2008; McLellan, 2011] and are listed Table 10.

Table 10 Management and Dose modification Guidelines for Hand-Foot Skin Reaction (HFSR)

CTCAE Grade	Adverse Event Management	Action and Dose Modification
Grade 1[a]	▪ Life style changes recommended[b] ▪ Initiate symptomatic treatment[c] if clinically appropriate	▪ Continue study treatment at current dose level
Grade 2	▪ Life style changes recommended[b] ▪ Initiate symptomatic treatment[c]	▪ Interrupt study treatment until recovery to ≤grade 1[d] ▪ Recovery to ≤grade 1 within 7 days: Restart study treatment at previous dose level ▪ No recovery to grade ≤1 within 7 days or ≥ 2nd occurrence: restart with study treatment reduced by one dose level[e]
Grade ≥3	▪ Life style changes recommended[b] ▪ Initiate symptomatic treatment[c] ▪ Consult dermatologist	▪ Interrupt study treatment until recovery to ≤grade 1[d] ▪ Restart with study treatment reduced by one dose level[e] ▪ If 3rd occurrence, discontinue study treatment permanently ▪ Continue follow-up as per protocol.

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events

a. A full-body skin examination and a removal of pre-existing calluses and keratotic skin is recommended prior to initiation of study treatment

b. Life-style changes: (1) reduce exposure of hands and feet to hot water, (2) avoid traumatic activity including vigorous exercise especially in the first 4 weeks after start of study treatment, (3) avoid constrictive footwear, (4) avoid excessive friction on the skin, when applying topical treatments, (5) wear thick cotton socks and gloves, and shoes with padded insoles

c. Symptomatic Treatments: (1) use moisturizing creams frequently and especially on hands and feet (2) consider topical keratolytics: urea 20-40 % cream, or salicylic acid 6%, or tazarotene 0.1% cream, or fluorouracil 5% cream; (3) erythrematous areas: clobetasol propionate 0.05% ointment; (4) Pain: topical lidocaine 2%, and / or systemic pain medication such as nonsteroidal anti-inflammatory drugs, codeine, and pregabalin

d. Approval of Trial Coordinating Centre and Study Chairman is required to restart study treatment after ≥21 days of interruption

e. Escalation of study treatment to the previous dose level is allowed if no HFSR is observed in the 4 weeks subsequent to dose reduction.

7.3.4.3 Guidelines for cuSCC

Cutaneous squamous cell carcinoma have been observed in subjects treated with dabrafenib and the combination of dabrafenib and trametinib (see dabrafenib and trametinib combination IB). These treatment-related cuSCC should be surgically removed according to institutional practice. Dose modifications or interruptions of the study treatment are not required for cuSCC. Occurrence of cuSCC must be reported as an SAE.

7.3.4.4 Recommendations for the management of radiation dermatitis

The following recommendations are taken from the consensus guidelines for the management of radiation dermatitis and coexisting acne-like rash in patients receiving radiotherapy plus EGFR inhibitors [Bernier, 2008].

Recommendations on general management include the following:

- A primary step in the management of radiation dermatitis of any grade is to establish that the skin reactions are not a result of any concomitant medication, other than the BRAF/

MEK inhibitor. In the case of more severe skin reactions, it should also be verified that radiation dose and distribution are correct.

- Patients should be encouraged to maintain good standards of hygiene. The irradiated area should be kept clean to minimise the risk of infection. Patients should wash the area with a gentle cleanser and dry it with a soft, clean towel. The use of a pH-neutral synthetic detergent is preferable to soap, which can irritate the skin.
- Topical treatment approaches may offer symptomatic relief and may help skin healing. Different areas of skin may require different treatment approaches.
    - Drying pastes may be appropriate for use within skin folds, where skin reactions remain moist.
    - Gels can be useful in seborrhoeic areas.
    - Creams can be used in areas outside skin folds and seborrhoeic areas.
    - Hydrophilic dressings may also be useful in moist areas. These are placed over the cleaned, dried wound and some can absorb wound exudate. They can be soothing for the patient and can help skin healing.
    - Greasy topical products should be avoided because they inhibit the absorption of wound exudate and promote superinfection.
- Topical moisturisers, gels, emulsions and dressings should not be applied shortly before radiation treatment as they can cause a bolus effect, thereby artificially increasing the radiation dose to the epidermis. It is important to instruct patients to gently clean and dry the skin in the radiation field before each irradiation session.
- While the use of corticosteroids, often applied in some centres during the course of radiotherapy in cancer patients, is not contra-indicated in the presence of radiation dermatitis, it is suggested that the overall treatment time of any corticosteroid-containing treatment be limited.
- Pain relief for skin reactions should be considered in the context of any pain relief medication the patient may already be receiving in the course of their treatment, for instance, for mucositis.
- Patients should be advised to avoid:
    - Sun exposure wherever possible. This can be achieved by using soft clothing to cover the area and/or the use of mineral sunblock.
    - The use of skin irritants, such as perfumes, deodorants or alcohol-based lotions.
    - Scratching of the skin in the affected area.

Recommendations on the management of **grade 1** radiation dermatitis:

- The NCI CTCAE (version 4.03) definition of grade 1 radiation dermatitis is faint erythema or dry desquamation. Grade 1 radiation dermatitis requires no specific treatment. Indeed, the most important step is to keep the area clean between treatments. The subsequent use of a non-perfumed moisturiser is optional. Moisturisers containing antibacterials (e.g. chlorhexidine or triclosan) can be used occasionally if anti-infective measures are considered appropriate. Overtreatment, including overuse of antiseptic creams, can irritate the skin. In general, skin reactions at this grade can be managed primarily by the nursing staff.

Recommendations on the management of **grade 2 and 3** radiation dermatitis:

- According to the NCI CTCAE (version 4.03) classification, grade 2 radiation dermatitis includes moderate to brisk erythema, patchy moist desquamation mostly confined to skin folds and creases and moderate oedema. Grade 3 radiation dermatitis consists of moist desquamation other than skin folds or creases and bleeding induced by minor trauma or abrasion.
- In grades 2 and 3 radiation dermatitis, as with grade 1, the irradiated area should be cleaned and dried, even when ulcerated. A number of topical applications can be considered. Examples are drying gels, with the addition of antiseptics if considered

appropriate (e.g. chlorhexidine-based creams, but not chlorhexidine in alcohol), hydrophilic dressings, an anti-inflammatory emulsion (e.g. trolamine, hyaluronic acid cream) and zinc oxide paste, if considered sufficiently easy to remove before radiotherapy. Silver sulfadiazine or beta glucan cream may also be useful (but should only be applied after radiotherapy, possibly in the evening, after cleaning the irradiated area).

- Where infection is suspected, the treating physician should use best clinical judgement for management, including considering swabbing the affected area for identification of the infectious agent. Topical antibiotics should be reserved for superinfection and should not be used prophylactically. Doxycycline is not recommended at this stage. In patients in whom skin infection is suspected or documented, the blood granulocyte count should also be checked. Indeed, severe desquamation is associated, in a number of cases, with a risk of septicaemia. Blood cultures should also be carried out if additional signs of sepsis and/or fever are present, particularly if the granulocyte count is low.
- Grades 2 and 3 radiation dermatitis can be managed by an integrated team comprising the radiation oncologist, medical oncologist, nurse and dermatologist, as required. Skin reactions should be assessed at least once a week.

Recommendations on the management of **grade 4** radiation dermatitis:

- Grade 4 radiation dermatitis is defined by the NCI CTCAE (version 4.03) as skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from the involved site. Grade 4 radiation dermatitis is relatively rare, generally occurring in <5% of patients receiving radiotherapy, but may be increased with concurrent use of BRAF and MEK inhibitors. This stage of radiation dermatitis requires specialised wound care and should be treated on a case-by-case basis. It is recommended that grade 4 radiation dermatitis should be managed primarily by a wound specialist, with the assistance of the radiation oncologist, medical oncologist, dermatologist and nurse, as required.
- Grade 4 radiation dermatitis is a DLT for the study.

7.3.5 Guidelines for Other Adverse Event of Special Interest

7.3.5.1 Guidelines for Pyrexia

Episodes of pyrexia have been observed in subjects receiving dabrafenib monotherapy or in combination with trametinib (see dabrafenib and dabrafenib and trametinib combination IBs). In a minority of cases the pyrexia was accompanied by symptoms such as severe chills, dehydration, hypotension, dizziness or weakness.

Pyrexia accompanied by ≥ Grade 3 hypotension, or hypotension that is clinically significant in the judgement of the investigator, or dehydration requiring IV fluids, or severe rigors/chills should be reported as an SAE per section 9.14.2

Subjects should be instructed on the importance of immediately reporting febrile episodes. In the event of a fever, the subject should be instructed to take non-steroidal anti-pyretics as appropriate to control fever. In subjects experiencing pyrexia associated with rigors, severe chills, dehydration, hypotension, etc., renal function should be monitored carefully (see Section 7.3.5.3).

Guidelines regarding management and dose reduction for pyrexia considered to be related to study treatment are provided in Table 11.

Table 11 Management and Dose Modification Guidelines for Pyrexia

Adverse Event	Adverse Event Management	Action and Dose Modification
Pyrexia[a]	1st Event[b]: ▪ Clinical evaluation for infection and hypersensitivity[c] ▪ Laboratory work-up[c] ▪ Hydration as required[d] ▪ Blood sample for cytokine analysis[e] ▪ Administer anti-pyretic treatment if clinically indicated and continue prophylactic treatment[f]	1st Event: ▪ Interrupt dabrafenib ▪ Continue trametinib ▪ Once pyrexia resolves to baseline, restart dabrafenib at the same dose level ▪ If fever was associated with dehydration or hypotension, reduce dabrafenib by one dose level
	2nd Event[g]: ▪ Clinical evaluation for infection and hypersensitivity[c] ▪ Laboratory work-up[c] ▪ Hydration as required[d] ▪ Blood sample for cytokine analysis[e] ▪ Within 3 days of onset of pyrexia ▪ Optimize anti-pyretic therapy ▪ Consider oral corticosteroids (i.e., prednisone 10 mg) for at least 5 days or as clinically indicated[f]	2nd Event: ▪ Interrupt dabrafenib ▪ Continue trametinib ▪ Once pyrexia resolves to baseline, restart dabrafenib at the same dose level ▪ If fever was associated with dehydration or hypotension, reduce dabrafenib by one dose level
	Subsequent Events: ▪ Clinical evaluation for infection and hypersensitivity[c] ▪ Laboratory work-up[c] ▪ Hydration as required[d] ▪ Blood sample for cytokine analysis[e] ▪ Within 3 days of onset of pyrexia ▪ Optimize oral corticosteroid dose as clinically indicated for recalcitrant pyrexia[g] ▪ If corticosteroids have been tapered and pyrexia recurs, restart steroids ▪ If corticosteroids cannot be tapered consult medical monitor	Subsequent Events: ▪ Interrupt dabrafenib ▪ Continue trametinib ▪ Hydration as required[d] ▪ Once pyrexia resolves to baseline, restart dabrafenib reduced by one dose level[h] ▪ If dabrafenib must be reduced to <75 mg BID, permanently discontinue dabrafenib ▪ Continue follow-up as per protocol.

a. Pyrexia is defined as a body temperature equal to or above 38.5 Celsius or 101.3° Fahrenheit.

b. For subjects experiencing pyrexia complicated by rigors, severe chills, etc., a clinical evaluation and laboratory work-up is mandatory for each event; anti-pyretic treatment should be started immediately at the first occurrence and prophylactic anti-pyretic treatment is recommended. For subjects experiencing rigors/chills without pyrexia, work-up and supportive care, including interruption of study treatment, are recommended.

c. Thorough clinical examination for signs and symptoms of infection or hypersensitivity is required; laboratory workup should include full-blood-count, electrolytes, creatinine, BUN, CRP, liver-function tests, blood culture, and urine culture.

d. Oral hydration should be encouraged in subjects without evidence of dehydration. Intravenous hydration is recommended in subjects experiencing pyrexia complicated by dehydration/hypotension.
e. Blood samples for cytokine analysis should be taken immediately at the start of fever (i.e., when the subject is being evaluated for fever), and after the fever has disappeared (i.e., during the next routine visit). Blood samples for cytokine analysis must be sent to your institution's laboratory for immediate anaylsis
f. Anti-pyretic treatment may include ibuprofen, or suitable anti-pyretic medication according to institutional standards. Acetaminophen should be used with caution, especially in subjects with elevated liver enzymes. Prophylactic anti-pyretic treatment may be discontinued after three days in the absence of pyrexia
g. In subject experiencing pyrexia complicated by rigors, severe chills, etc., which cannot be controlled with antipyretic medication, oral corticosteroids should be started at the 2nd event and doses should be gradually increased for subsequent events.
h. Dabrafenib should be reduced by one dose level after three episodes of pyrexia complicated by rigors, severe chills, etc., which cannot be managed by best supportive care and increasing doses of oral steroids. Escalation of dabrafenib is allowed if no episode of pyrexia is observed in the 4 weeks subsequent to dose reduction.

7.3.5.2 Guidelines for Diarrhoea

Episodes of diarrhoea have occurred in subjects receiving dabrafenib, trametinib, or both therapies in combination. Other frequent causes for diarrhoea including concomitant medications (e.g., stool softeners, laxatives, antacids, etc.), infections by C. difficile or other pathogens, partial bowel obstruction, etc. should be clinically excluded.

Guidelines regarding management and dose reduction for diarrhoea considered to be related to study treatment by the investigator are provided in **Table 12.**

Table 12 Management and Dose Modification Guidelines for Diarrhoea

CTCAE Grade	Adverse Event Management	Action and Dose Modification
Uncomplicated Diarrhoea[a] Grade 1 or 2	▪ Diet: stop all lactose containing products; eat small meals, BRAT-diet (banana, rice, apples, toast) recommended ▪ Hydration: 8-10 large glasses of clear liquids per day (e.g., Gatorade or broth) ▪ Diarrhoea > 24h: loperamide 2 mg every two hours; maximum 16 mg/day. Consider adding oral antibiotics ▪ Diarrhoea > 48h: loperamide 2 mg every two hours maximum 16 mg/day. Add budesonide or other second-line therapies (otreotide, or tincture of opium) and oral antibiotics	▪ Continue study treatment ▪ If diarrhoea is grade 2 for > 48h, interrupt study treatment until diarrhoea resolves to grade ≤1 ▪ Restart study treatment at the same dose level
Uncomplicated Diarrhoea[a] Grade 3 or 4 Any Complictaed Diarrhoea[b]	▪ Clinical evaluation mandatory ▪ Loperamide[c]: initially 4 mg, followed by 2 mg every four hours or after every unformed stool; maximum 16 mg/day. Continue until diarrhoea free for 12 hours ▪ Oral antibiotics and second-line therapies if clinically indicated ▪ Hydration: intravenous fluids if clinically indicated ▪ Antibiotics (oral or intravenous) if	▪ interrupt study treatment until diarrhoea resolves to grade ≤1 ▪ Restart study treatment reduced by one dose level[d] ▪ If 3 dose reductions of study treatment are clinically indicated, permanently discontinue study treatment ▪ Continue follow-up as per protocol.

	clinically indicated ▪ Intervention should be continued until the subject is diarrhoea free for ≥ 24 hours ▪ Intervention may require hospitalization for subjects at risk of life-threatening complications	

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events
a. Uncomplicated diarrhoea defined by the absence of symptoms such as, cramping, nausea/vomiting ≥grade 2, decreased performance status, pyrexia, sepsis, neutropenia grade ≥3, frank bleeding, and/or dehydration requiring intravenous fluid substitution
b. Complicated diarrhoea defined by the presence of symptoms such as, cramping, nausea/vomiting ≥grade 2, decreased performance status, pyrexia, sepsis, neutropenia grade ≥3, frank bleeding, and/or dehydration requiring intravenous fluid substitution
c. Loperamide should be made available prior to start of study treatment so loperamide administration can begin at the first signs of diarrhoea
d. Escalation of study treatment to previous dose level is allowed after consultation with the medical monitor and in the absence of another episode of complicated or severe diarrhoea in the 4 weeks subsequent to dose reduction.

7.3.5.3 Guidelines for Renal Insufficiency

Cases of renal insufficiency have occurred in subjects receiving dabrafenib and the combination of dabrafenib and trametinib. Prior to the start of study treatment, concomitant medications should be reviewed for the potential risk of inducing nephrotoxicity and concomitant medications should be modified if clinically possible.

Guidelines regarding management and dose reduction for renal insufficiency considered to be related to study treatment by the investigator are provided in Table 13.

Table 13 Management and Dose Modification Guidelines for Renal Insufficiency

Serum Creatinine Level	Adverse Event Management	Action and Dose Modification
Serum creatinine increase >0.2 mg/dL (18 umol/L) but ≤ 0.5 mg/dL (44 umol/L) above baseline	▪ Recheck serum creatinine within 1 week ▪ Serum creatinine increase > 1 week: contact Trial Coordinating Centre ▪ If pyrexia is present, treat pyrexia as per guidelines[a]	▪ Continue study treatment at the same dose level

Serum creatinine increase >0.5 mg/dL (44 umol/L) above baseline or serum creatinine >2 mg/dL (> 177 umol/L)	▪ Monitor serum creatinine ≥ 2-times per week
	▪ Hospitalization may be necessary if serum creatinine cannot be monitored frequently
	▪ If pyrexia is present, treat pyrexia as per guidelines[a]
	▪ Consult nephrologist if clinically indicated
	▪ Perform renal biopsy if clinically indicated, for example:
	  ▪ Renal insufficiency persists despite volume repletion
	  ▪ Subject has new rash or signs of hypersensitivity (such as elevated eosinophil count)
		▪ Interrupt study treatment until serum creatinine recovers to baseline
		▪ Restart with study treatment[b]

Abbreviation: NSAIDS = non-steroidal anti-inflammatory drugs

a. NSAIDs can induce renal insufficiency, especially in subjects with dehydration; encourage oral fluids or consider intravenous fluids as clinically indicated. See guidelines for pyrexia 7.3.5.1.
b. Investigator may restart at either the same or a reduced dose level. Escalation of study treatment to previous dose level is allowed if another episode of renal insufficiency does not occur after 4 weeks of dose reduction. Consultation with Trial Coordinating Centre and Study Chairman is required before restarting study treatment if there is evidence of thrombotic microangiopathy.

7.3.5.4 Guidelines for Visual Changes or Specific Ophthalmic Examination Findings

Episodes of visual changes have been observed in subjects receiving trametinib, and ocular adverse events are known to be related to trametinib. An ophthalmologist should be consulted if changes in vision develop. However, if the visual changes are clearly unrelated to study treatment (e.g. allergic conjunctivitis), then monitor closely as it may be reasonable to defer ophthalmic examination. Special attention should be given to retinal findings (e.g. retinal pigment epithelial detachment (RPED) or retinovascular abnormalities (i.e. branch or central retinal vein occlusions (RVO)). For events of visual changes (regardless of severity) for which an ophthalmic examination is conducted, a blood sample for PK analysis must be drawn as close as possible to the time of the event.

Guidelines regarding management and dose reduction for visual changes and/or ophthalmic examination finds considered to be related to study treatment are provided in **Table 14.**

Table 14 Management and Dose Modification Guidelines for Visual Changes and/or Ophthalmic Examination Findings

CTCAE Grade[a]	Adverse Event Management	Action and Dose Modification
Grade 1[b]	• Consult ophthalmologist within 7 days of onset	• If dilated fundus examination cannot be performed within 7 days of onset, interrupt trametinib until RPED and RVO can be excluded by retina specialist/ophthalmologist. • If RPED and RVO excluded, continue (or restart) trametinib at same dose level • If RPED suspected or diagnosed: see RPED dose modification table Y below; report as a SAE to the Trial Coordinating Centre • If RVO diagnosed: Permanently discontinue trametinib and report as a SAE to the Trial Coordinating Centre
Grade 2 and Grade 3	• Consult ophthalmologist immediately • Interrupt trametinib	• If RPED and RVO excluded, restart trametinib at same dose level • If RPED diagnosed, see RPED dose modification table below; report as a SAE to the Trial Coordinating Centre • If RVO diagnosed: Permanently discontinue trametinib and report as a SAE to the Trial Coordinating Centre
Grade 4	• Consult ophthalmologist immediately • Interrupt trametinib • Report as a SAE to the Trial Coordinating Centre	• If RPED and RVO excluded, may consider restarting trametinib at same or reduced dose after discussion with study medical monitor • If RVO or RPED diagnosed, permanently discontinue trametinib • Report as a SAE to the Trial Coordinating Centre

Abbreviations: RPED = retinal pigment epithelial detachment; CTCAE = Common Terminology Criteria for Adverse Events; RVO= retinal vein occlusion; SAE = serious adverse event

a. Refers to CTCAE Version 4.03 'Eye disorders – Other, specify'

b. If visual changes are clearly unrelated to study treatment (e.g., allergic conjunctivitis), monitor closely but ophthalmic examination is not required.

Guidelines regarding management and dose reduction for trametinib for retinal pigment epithelial detachments (RPED) are provided in **Table 15.**

Table 15 Recommended dose modifications for trametinib for retinal pigment epithelial detachments (RPED)[a]

CTCAE Grade	Action and Dose Modification
Grade 1 RPED (Asymptomatic; clinical or diagnostic observations only)	• Continue treatment with retinal evaluation monthly until resolution. If RPED worsens follow instructions below

Grade 2-3 RPED (Symptomatic with mild to moderate decrease in visual acuity; limiting instrumental ADL)	• Interrupt trametinib • Retinal evaluation monthly • If improved to ≤ Grade 1, restart trametinib at lower dose (reduced by 0.5 mg) or discontinue in patients taking trametinib 1 mg daily

a. Refers to CTCAE Version 4.03 'Retinopathy'

At certain time points in the trial and if visual changes develop, an eye exam is indicated. (Refer to Section 9.5). The exam will include best corrected visual acuity, tonometry, slit lamp biomicroscopic examination, visual field examination, and dilated indirect fundoscopy with special attention to retinal abnormalities. Optical coherence tomography is strongly recommended at scheduled visits, and if retinal abnormalities are suspected. Other types of ancillary testing including colour fundus photography and fluorescein angiography are also recommended if clinically indicated.

7.3.5.5 Guidelines for Pneumonitis

Pneumonitis has been observed in subjects receiving trametinib. To reduce the risk of pneumonitis, subjects will be monitored closely for symptoms, evaluated with imaging and functional tests. Dose modification and supportive care guidelines for pneumonitis are described in **Table 16.**

Table 16 Management and Dose Modification Guidelines for Pneumonitis

CTCAE Grade	Adverse Event Management	Action and Dose Modification
Grade 1	▪ CT scan (high-resolution with lung windows) recommended ▪ Clinical evaluation and laboratory work-up for infection ▪ Monitoring of oxygenation via pulse oximetry recommended ▪ Consultation of pulmonologist recommended	▪ Continue study treatment at current dose
Grade 2	▪ CT scan (high-resolution with lung windows) ▪ Clinical evaluation and laboratory work-up for infection ▪ Consult pulmonologist ▪ Pulmonary function tests -if < normal, repeat every 8 weeks until ≥ normal ▪ Bronchoscopy with biopsy and/or BAL recommended ▪ Symptomatic therapy including corticosteroids if clinically indicated	▪ Interrupt study treatment until recovery to grade ≤1 ▪ Restart with study treatment reduced by one dose level ▪ Escalation to previous dose level after 4 weeks and consultation with medical monitor possible ▪ If no recovery to grade ≤1 within 4 weeks, permanently discontinue study treatment ▪ Continue follow-up as per protocol.
Grade 3	▪ CT scan (high-resolution with lung windows) ▪ Clinical evaluation and laboratory work-up for infection ▪ Consult pulmonologist ▪ od to	▪ Interrupt study treatment until recovery to grade ≤1 ▪ After consultation with medical monitor, study treatment may be restarted reduced by one dose level ▪ If no recovery to grade ≤1 within 4

	▪ Bronchoscopy with biopsy and/or BAL if possible ▪ Symptomatic therapy including corticosteroids as clinically indicated	weeks, permanently discontinue study treatment ▪ Continue follow-up as per protocol.
Grade 4	▪ Same as grade 3	▪ Permanently discontinue study treatment ▪ Continue follow-up as per protocol.

Abbreviation: BAL= bronchoalveolar lavage; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events

7.4 Stopping, Follow-up, and Monitoring Criteria for Hepatobiliary Events

7.4.1 Liver Chemistry Stopping Criteria

These liver chemistry stopping and follow-up criteria have been designed to assure subject safety and evaluate liver event etiology in alignment with the FDA Guidance for Industry – Drug-Induced Liver Injury: Premarketing Clinical Evaluation (July 2009, www.fda.gov).

Liver chemistry stopping criteria 1-5 are defined as:

1. ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin) (or ALT ≥3xULN and INR>1.5, if INR measured)
   NOTE: If serum bilirubin fractionation is not immediately available, study treatment should be discontinued if ALT ≥3xULN and bilirubin ≥2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. ALT ≥8xULN
3. ALT ≥5xULN but <8xULN persists for ≥2 weeks
4. ALT ≥3xULN if associated with the appearance or worsening of symptoms of hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, pyrexia, rash or eosinophilia.
5. ALT ≥5xULN but <8xULN and cannot be monitored weekly for >2 weeks.

When any of the liver chemistry stopping criteria 1 - 5 is met, do the following:

- **Immediately discontinue subject from study treatment**
- Report the event to Trial Coordinating Centre **within 24 hours** of learning its occurrence
- Complete the Liver Event Adverse Event CRF and SAE CRF if the event also meets the criteria for an SAE:
  - All events of ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin) (or ALT≥3xULN and INR>1.5, if INR measured; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants), termed 'Hy's Law', **must be reported as an SAE.**
  - NOTE: if serum bilirubin fractionation is not immediately available, study treatment should be discontinued if ALT ≥3xULN and bilirubin ≥2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury
- Complete the liver imaging and/or liver biopsy CRFs if these tests are performed
- Perform liver event follow up assessments, and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below
- Follow up for overall survival is required following discontinuation from study treatment.
- Do not rechallenge with study treatment.

In addition, for subjects meeting liver stopping criterion 1:

- Make every reasonable attempt to have subjects return to clinic **within 24 hours** for repeat liver chemistries, liver event follow up assessments (refer to Section 7.4.1.1) and close monitoring
- A specialist or hepatology consultation is recommended
- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

For subjects meeting any of the liver stopping criteria 2 – 5:

- Make every reasonable attempt to have subjects return to clinic **within 24-72 hours** for repeat liver chemistries, liver event follow up assessments (refer to Section 7.4.1.1)
- Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values;
- Subjects meeting criterion 5 should be monitored as frequently as possible.

7.4.1.1 Liver Event Follow-up Assessments

For subjects meeting any of the liver chemistry stopping criteria 1 – 5, make every attempt to carry out the **liver event follow up assessments** described below:

- Viral hepatitis serology including:
  - Hepatitis A IgM antibody
  - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM)
  - Hepatitis C RNA
  - Cytomegalovirus IgM antibody
  - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing)
  - Hepatitis E IgM antibody
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin ≥2xULN.
- Obtain complete blood count with differential to assess eosinophilia.
- Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, pyrexia, rash or eosinophilia as relevant on the AE form. Please note that treatment with trametinib often associates with rash which is usually acneiform and affects the scalp, face, neck, chest, and upper back. Discuss with Trial Coordinating Centre and Study Chairman as needed.
- Record use of concomitant medications such as acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications form.
- Record alcohol use on the liver event alcohol intake form.

The following assessments are required for subjects with ALT ≥3xULN and bilirubin ≥2xULN (>35% direct) but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies and quantitative total immunoglobulin G (IgG or gamma globulins).
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.
- Serum acetaminophen adduct assay (quantifies potential acetaminophen contribution to liver injury, detectable by HPLC assay more than 1 week following acetaminophen use). Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen): quantitative hepatitis B DNA and hepatitis delta antibody. **NOTE:** if hepatitis delta

antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) – as outlined in: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1153793/.

7.4.1.2 Liver Chemistry Monitoring Criteria

For subjects with ALT ≥3xULN but <8xULN which exhibit a decrease to ALT ≥3xULN, but <5xULN and bilirubin <2xULN, without hepatitis symptoms or rash, and who can be monitored weekly for 4 weeks, the following actions should be taken:

- Notify the Trial Coordinating Centre and Study Chairman within 24 hours of learning of the abnormality to discuss subject safety
- Continue study treatment
- Return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline values
- If at any time the subject meets any of the liver chemistry stopping criteria 1 – 5, proceed as described above
- If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline values.

7.5 Blinding

Not applicable.

7.6 Product Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) may be required to document the amount of medication dispensed, administered and/or returned to subjects.

7.7 Treatment Compliance

Compliance with dabrafenib and trametinib will be assessed by querying the subject at each visit. The investigator will make every effort to bring non-compliant subjects into compliance.

8 Concomitant Medications and Non-Drug Therapies

8.1 Permitted Medications and Non-Drug Therapies

The investigator must be informed as soon as possible about any medication taken from the time of screening until 30 days after the last dose of dabrafenib and trametinib. Concomitant medication(s) taken during the study will be recorded in the CRF.
Subjects should receive full supportive care during the study, including transfusions of blood and blood products, treatment with antibiotics, anti-emetics, anti-diarrhoeals, analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines. Use of anticoagulants such as warfarin is permitted, however caution should be exercised and additional International Normalized Ratio (INR) monitoring is recommended when dabrafenib is used concomitantly with warfarin.

8.2 Prohibited Medications and Non-Drug Therapies

The use of certain medications and illicit drugs within 28 days or 5 half lives, whichever is shorter, prior to enrolment and for the duration of the study will not be allowed.

The following medications or non-drug therapies are also prohibited while on treatment in this study:

- Other anti-cancer therapies;
- Other investigational drugs;
- Antiretroviral drugs (Note: Subjects with known HIV are ineligible for study participation);
- Herbal remedies (e.g. St. John's wort);
- Dabrafenib is metabolized primarily by Cytochrome P450 (CYP) 2C8 and CYP3A4. Co-administration of dabrafenib with ketoconazole, a CYP3A4 inhibition, or with gemfibrozil, a CYP2C8 inhibitor, resulted in increases in dabrafenib AUC of 71% and 47%, respectively. Drugs that are strong inhibitors or inducers of CYP3A and CYP2C8 (see list in Table 17) may only be used under special circumstances (e.g. as a single use for a procedure) while treatment with study drug is interrupted as they may alter dabrafenib concentrations; consider therapeutic substitutions for these medications. Approval of the Trial Coordinating Centre and Study Chairman is required in these situations. The list may be modified based on emerging data.

Table 17 Prohibited Medications

PROHIBITED – strong inducers of CYP3A or CYP2C8, since concentrations of dabrafenib may be decreased	
Class/Therapeutic Area	**Drugs/Agents**
Antibiotics	Rifamycin class agents (e.g., rifampin, rifabutin, rifapentine),
Anticonvulsant	Carbamazepine, oxcarbazepine phenobarbital, phenytoin, s-mephenytoin
Miscellaneous	bosentan, St-John's wort
PROHIBITED – Strong inhibitors of CYP3A, or CYP2C8 since concentrations of dabrafenib may be increased	
Class/Therapeutic Area	**Drugs/Agents**
Antibiotics	Clarithromycin, telithromycin, troleandomycin
Antidepressant	Nefazodone
Antifungals	Itraconazole, ketoconazole, posaconazole, voriconazole
Hyperlipidaemia	Gemfibrozil
Antiretroviral	ritonavir, saquinavir, atazanavir
Miscellaneous	Conivaptan

8.3 Medications to be Used with Caution

The following medications should be used with caution as their concentrations may be altered by dabrafenib or they may alter dabrafenib concentrations:

- Drugs that are moderate inhibitors or inducers of CYP3A and CYP2C8 as they may alter concentrations of dabrafenib.
- Dabrafenib has been shown to induce CYP3A4 and CYP2C9 in vivo using midazolam (CYP3A4 substrate) and S-warfarin (CYP2C9 substrate). Dabrafenib is an in vitro inducer of CYP2B6 and other enzymes such as CYP2C8, CYP2C19, UDP-glucuronyl transferases, and transporters may also be affected. Co-administration of dabrafenib and medications which are affected by the induction of these enzymes (including warfarin) and transporters may result in loss of efficacy. If co-administration of these medications is

necessary, investigators should monitor subjects for loss of efficacy or consider substitutions of these medications. A partial list of these medications is provided in Table 18.

- Therapeutic level dosing of warfarin can be used with approval from the Trial Coordinating Centre and Study Chairman and close monitoring of PT/INR by the site. Warfarin exposure has been shown to decrease (37% decrease) due to dabrafenib-mediated enzyme induction. Conversely, if dabrafenib dosing is reduced, interrupted, or discontinued, warfarin exposure may be increased. Thus, warfarin dosing may need to be adjusted based on PT/INR during and after treatment with dabrafenib. Prophylactic low dose warfarin may be given to maintain central catheter patency.
- Dabrafenib solubility is pH-dependent with decreased solubility at higher pH. Drugs such as proton pump inhibitors that inhibit gastric acid secretion to elevate gastric pH may decrease the solubility of dabrafenib and reduce its bioavailability. No clinical study has been conducted to evaluate the effect of pH on dabrafenib pharmacokinetics. In an ad-hoc analysis, no differences in C_{max} and AUC were noted between subjects who reported taking pH-elevating products relative to other subjects. Due to the theoretical risk that pH-elevating agents may decrease oral bioavailability and exposure to dabrafenib, these medicinal products that increase gastric pH should be used with caution when administered with dabrafenib.
- Prophylactic tamoxifen may be used with the approval from the Trial Coordinating Centre and Study Chairman. Tamoxifen is a substrate for CYP2C9 and CYP3A4. Co-administration of dabrafenib with tamoxifen may result in loss of efficacy of tamoxifen.

Table 18 Medications to be used with Caution

USE WITH CAUTION: Moderate inhibitors of CYP3A, or CYP2C8 since concentrations of dabrafenib may be increased	
Class/Therapeutic Area	Moderate CYP3A and CYP2C8 Inhibitors
Antiarrhythmics	Diltiazem, verapamil
Antibiotic	Erythromycin
Antifungal	Fluconazole
Miscellaneous	Aprepitant
USE WITH CAUTION: Co-administration of these drugs with dabrafenib may result in loss of efficacy. Monitor subjects for loss of efficacy or substitute with another medication.	
Class/Therapeutic Area	CYP3A4, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or Transporter Substrates that May be Affected by Induction
Analgesics	Alfentanil, buprenorphine, celecoxib, codeine, fentanyl, methadone, oxycodone
Antiarrhythmics	Disopyramide, dronedarone, mexiletine, propafenone, quinidine
Antibiotics	Chloramphenicol, doxycycline, erythromycin, moxifloxacin
Anticoagulants/ Antiplatelets	Cilostazole, warfarin
Anticonvulsants	Divalproex, lamotrigine, valproate, zonisamide
Antidepressants and Antipsychotics	Aripiprazole, bupropion, buspirone, desipramine, haloperidol, mirtazapine, pimozide, quetiapine, trazodone, amitriptyline, clomipramine, imipramine
Antidiabetics	Glyburide, saxagliptin, tolbutamide, nateglinide, pioglitazone, repaglinide, rosiglitazone
Antifungals	Caspofungin, fluconazole, terbinafine
Antihistamines	Astemizole, chlorpheniramine, ebastine
Antihypertensives	Amlodipine, diltiazem, felodipine, nifedipine, nilvadipine, nisoldipine, verapamil
Antimigraine Agents	Diergotamine, eletriptan, ergotamine
Corticosteroids	Dexamethasone, methylprednisolone, oral budesonide
Erectile Dysfunction Agents	Sildenafil, tadalafil, vardenafil
HMG-CoA Reductase Inhibitors	Atorvastatin, lovastatin, simvastatin, rosuvastatin, pravastatin
Hypnotics and Sedatives	Alprazolam, brotizolam, diazepam, estazolam, midazolam, triazolam, zolpidem, zopiclone
Immunosuppressants	Everolimus, sirolimus, tacrolimus
Miscellaneous	Aprepitant, cisapride, darifenacin, digoxin, disopyramide, leflunomide, methohexital, oral contraceptives, quinine, ranitidine, solifenacin, sulfasalazine, tramadol, tolvaptan, chloroquine, zopiclone
Selective Aldosterone Blockers	Eplerenone
USE WITH CAUTION: Co-administration of drugs that increase gastric pH should be used with caution when administered with dabrafenib as exposure to dabrafenib may be decreased	
pH altering agents	dexlansoprazole. esomeprazole, famotidine, ilaprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, ranitidine

Abbreviations: CYP = cytochrome P450; HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A.

Questions regarding concomitant medications should be directed to the Trial Coordinating Centre and Study Chairman for clarification.

8.4 Treatment of Dabrafenib and Trametinib Overdose

In the event of a dabrafenib overdose, defined as administration of more than 300 mg as a single dose or 600 mg per day (the highest dose tested in clinical studies to date), and/or a trametinib overdose, defined as administration of more than 3.0 mg once daily (the maximum tolerated dose defined in the MEK111054 Study), the investigator should contact the Trial Coordinating Centre and Study Chairman immediately and closely monitor the subject for AEs/SAEs and laboratory abnormalities. The Trial Coordinating Centre will not recommend specific treatment and the investigator will be advised to use clinical judgment to treat any overdose. The Study Chairman and Trial Management Committee members may advise on a recommended treatment plan which will be communicated to the investigator and site staff in a timely manner.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Trial Coordinating Centre and Study Chairman based on the clinical evaluation of the subject.

9 STUDY ASSESSMENTS AND PROCEDURES

A signed, written informed consent form must be obtained from the subject prior to any study-specific procedures or assessments.

Procedures conducted as part of the subject's routine clinical management (e.g. imaging) and obtained prior to signing of informed consent may be used for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe specified in the protocol. Laboratory results for BRAF testing, coagulation, haematology, clinical chemistry, and serum pregnancy are required for eligibility.

Investigators may be requested to perform additional safety tests during the course of the study based on newly available data to ensure appropriate safety monitoring. Appropriate local regulatory and ethical approvals should be obtained before any additional testing is performed.

Clinical assessments performed as part of standard of care, e.g. routine CT scan prior to follow up visit, can be used as part of the study assessments as long as they are performed according to the schedule outlined in table 19.

Table 19 outlines study assessments and their timing.

Table 19 Schedule of Assessments: Time and Events Table

Study Treatment:	**Dabrafenib and Trametinib concurrent with palliative RT**		**Dabrafenib, Trametinib and palliative RT[a]**	**Dabrafenib and Trametinib[b]**		
Assessment:	**Screening and baseline assessments**		**During RT[c]**	**Week 1-3 post-RT[d]**	**Week 4 post-RT[e]**	**Until Study Completion[f,g]**
Visit Windows (days):	**≤ 28 days from day 1 except where noted**	**Day 1**	**(± 2 days)**	**(± 2 days)**	**(± 3 days)**	**(± 7 days)**
Informed consent to study participation	√	**Study Enrolment and Commence RT**				
Demographics	√					
Medical history	√					
Concurrent Medication	√				√	Every 8 weeks
Vital signs / Physical examination	√				√	Every 8 weeks
ECOG Performance Status	√				√	Every 8 weeks
Ophthalmic examination[h]	If clinically indicated		If clinically indicated			
Dermatological examination (include non-melanoma skin lesion photography)	If clinically indicated		If clinically indicated			
Echocardiogram[i]	If clinically indicated		If clinically indicated			
12-lead ECG[i]	If clinically indicated		If clinically indicated			
Haematology / Biochemistry	√ (≤ 14 days)				√	Every 8 weeks
INR / PT / PTT	√					
Serum pregnancy test	√ (≤ 7 days)				√	Every 16 weeks
MRI or CT of head[j]	√		If clinically indicated			
CT Chest, abdomen and pelvis	√				√	Every 8 weeks
FDG PET scan, bone scan, plain X-ray (optional)[k]	If clinically indicated		If clinically indicated			
RECIST 1.1 assessment and assessment of index lesion(s)	√				√	Every 8 weeks
Adverse event assessment	√ (≤ 7 days)		Weekly	Weekly	√	Every 8 weeks
Radiotherapy toxicities			Weekly	Weekly	√	Every 8 weeks
Photograph of irradiated area	√ (≤ 7 days)		Weekly	Weekly	√	Every 8 weeks
Patient's assessment of symptoms using VAS	√ (≤ 7 days)		Weekly	Weekly	√	Every 8 weeks
Optional tumour biopsy[l,m]	√			week 1[n]		
Optional - Blood stored for biomarker analyses	√ (≤ 14 days)			week 1[n]	√	Every 8 weeks[o]
Dispensation of medication		√	Dabrafenib and Trametinib dispensed/taken as per medical oncologist guidance			
Assessment of medication compliance			Final week of RT		√	Every 8 weeks
TLD measurement of skin dose[p]			√			

Abbreviation: RT = Radiotherapy; ECOG = Eastern Cooperative Oncology Group; ECG = Electrocardiogram; INR = International Normalised Ratio; PT = Prothrombin time; PTT = Partial thromboplastin time; MRI = Magnetic resonance imaging; CT = computed tomography; VAS = Visual Analog Scale; FDG PET = Fluorodeoxyglucose positron emission tomography

a. Palliative radiotherapy can be commenced concurrently with dabrafenib and trametinib at any time after 2 week of systemic therapy alone, i.e. dabrafenib and trametinib alone.

b. Dabrafenib and trametinib alone will be continued until there is evidence of overall disease progression according to RECIST criteria.

c. Weekly assessment during RT should start on the first Wednesday after the commencement of RT, and then every Wednesday after that until the completion of RT. A window of plus and minus 2 days applies to each visit.

d. Weekly assessment in the early post-RT phase, i.e. week 1-3 post-RT, should be carried out on the first, second and third Wednesday after the completion of RT. A window of plus and minus 2 days applies to each visit.

e. Week 4 post-RT assessments should be carried out on the fourth Wednesday after the completion of RT. A window of plus and minus 3 days apply to these assessments.

f. Clinical assessments in the follow up phase will be carried out at regular intervals from the fourth Wednesday after the completion of RT, as specified in table 19. A window of plus and minus 7 days apply to these assessments. These assessments will continue until study completion.

g. The study is completed when one of the following has occurred to each of the patients on the study: death, withdrawal from the study, lost to follow-up, or completion of 12 months of post-RT follow up.

h. If patients report new visual disturbances such as diminished central vision, blurry vision, or loss of vision at any time while on dabrafenib and trametinib therapy, a prompt ophthalmological assessment is recommended.

i. Echocardiogram and 12-lead ECG should be performed at baseline and whenever clinically indicated. For patients whose heart is directly within the radiation field, then an Echocardiogram and ECG should be performed at baseline, 4 weeks post-RT, and every 16 weeks thereafter.

j. MRI or CT of brain should be performed at baseline to exclude brain metastases and at any other time during the study period if clinically indicated.

k. FDG PET scan, bone scan, plain X-ray are optional baseline investigations, they can be performed if clinically indicated. These investigations can be repeated during the study period at the treating physician's discretion.

l. Biopsy of both irradiated index lesions are optional for patients. Biopsy should be performed at baseline and 1 week post RT. If biopsy is not carried out, archived tumour tissue can be used for analysis of biomarkers

m. An additional optional biopsy of the index lesion will be performed at the time of local disease progression.

n. Optional tumour biopsy and blood storage should be carried out on the first Wednesday after the completion of RT. A window of plus and minus 2 days applies this visit.

o. An additional blood storage will be performed at the time of disease progression.

p. As radiation dermatitis is a potential RT related toxicity, and Grade 4 radiation dermatitis is a DLT, TLD measurement of skin dose is strongly encouraged during RT. TLD should be placed close to the center of the RT field.

9.1 Baseline Confirmation of BRAF Mutation-positive Melanoma

Subjects with histologically confirmed cutaneous melanoma that is either Stage IIIC (unresectable) or Stage IV will be screened for eligibility after signing the informed consent form. Subjects will be screened prior to treatment to determine whether their tumour sample has a V600E or V600K mutation, indicating their eligibility for the study. Tumour BRAF mutation testing conducted on metastatic tumour tissues are preferred. If metastatic tumour tissue is not available then the most recently obtained tumour tissue (either archived material or fresh biopsy) is acceptable.

9.2 Medical history and Physical Examinations

Medical history will be obtained at the Screening Visit to capture relevant underlying conditions. Medical history must include date of diagnosis of melanoma, including histological or cytological documentation of malignancy.

Physical examination will include assessments of eyes, neurological and cardiovascular systems, lungs, abdomen, and any other areas with signs and symptoms of disease, and of the head, neck, ears, nose, mouth, throat, thyroid, lymph nodes and extremities. This will be performed at baseline, week 4 post-RT and every 8 weeks thereafter.

9.3 Vital Signs

Vital sign measurements will include systolic and diastolic blood pressure, body temperature, pulse rate, body weight, and height (only at Screening). Body temperature, weight and height measurements should be recorded in the metric scale.

All blood pressure assessments should be performed under optimal conditions i.e. after (i) subject has been seated with back support, ensuring that legs are uncrossed and flat on the floor, (ii) subject is relaxed comfortably for at least 5 minutes, (ii) preparatory steps including removal of any restrictive clothing over the cuff area and selection of the right cuff size have been ensured, (iii) the arm is supported so that the middle of the cuff is at the heart level, and (iv) the subject remains quiet during the measurement. In subjects with an initial blood pressure reading within the hypertensive range, a second reading should be taken at least 1 minute later, with the 2 readings averaged to obtain a final blood pressure measurement. Only the averaged value should be entered in the CRF.

9.4 ECOG Performance Status

Eastern Cooperative Oncology Group (ECOG) Performance Status will be evaluated and documented at Screening and at each follow up visit as outlined in Table 19. See Appendix 1 for description of ECOG status.

9.5 Ophthalmic Exam

At baseline, an ophthalmic exam may be required if clinically indicated from an ophthalmologist to assess patients if they have any visual disturbances such as diminished central vision, blurry vision, or loss of vision while on dabrafenib and trametinib. The exam will include best corrected visual acuity, tonometry, slit lamp biomicroscopic examination, visual field examination, and dilated indirect fundoscopy with special attention to retinal abnormalities. Optical coherence tomography is strongly recommended if retinal abnormalities are suspected. Other types of ancillary testing including colour fundus photography and fluorescein angiography are also recommended if clinically indicated.

At any time in the study duration, if visual disturbances develop, a full ophthalmic exam by an ophthalmologist may be indicated. (Refer to Section 7.3.5.4 for visual changes stopping criteria).

9.6 Dermatologic examination

If clinically indicated, dermatologic skin exams should be performed by a dermatologist. If possible, the same physician should perform each examination for the duration of the study to ensure consistency between evaluations (i.e. if the subject is referred to a dermatologist for the Screening examination, the same dermatologist should do all follow-up dermatologic skin assessments). At each visit, a full skin exam to assess cutaneous malignancies and proliferative skin diseases should be performed, this should include non-melanoma skin lesion photography. Dermatologic examinations should be performed at baseline, week 4 post-RT and every 16 weeks thereafter if clinically indicated. For the management of grade 3 or grade 4 radiation dermatitis, the treating clinicians are strongly recommended to seek advice from the dermatologist.

9.7 Electrocardiogram (ECG)

Twelve (12)-lead ECGs will be obtained using an ECG machine that automatically calculates heart rate and measures PR, QRS, QT, RR and QTcB intervals. An ECG should be performed at baseline if clinically indicated and whenever clinically indicated during the study period. For patients whose heart is directly within the radiation field, then ECG should be performed at baseline, 4 weeks post-RT, and every 16 weeks thereafter. A single 12-lead ECG will be performed by qualified site personnel after the subject has rested in a semi-recumbent or supine position for at least 5 minutes. Two copies of the ECG tracing should be obtained at the time of the ECG; the first copy will be kept in the subject's medical chart and the second copy will be kept in the study file for retrospective collection by the Trial Coordinating Centre if necessary. See Section 7.3.3.3 for instructions if QTc withholding criteria are met. An ECG should be performed at any time if clinical indication arises.

9.8 Echocardiograms (ECHO)

Echocardiograms (ECHO) may be performed at baseline if clinically indicated to assess cardiac ejection fraction and cardiac valve morphology, and then whenever clinically indicated. The echocardiographer's evaluation should include an evaluation for left ventricular ejection fraction and both right and left-sided valvular lesions. ECHO is only required for patients whose heart is directly within the radiation field, and is to be completed at baseline, 4 weeks post-RT, and every 16 weeks thereafter.

9.9 Pregnancy Testing

Women of child bearing potential are required to have pregnancy tests performed. A negative pregnancy test must be documented at the Screening visit. Serum pregnancy test will be repeated at 4 weeks post-RT and then every 16 weeks. For further details, see section 6.2.3.

9.10 Laboratory Assessments

All protocol-required laboratory assessments must be conducted in accordance with the Schedule of Assessments (Table 19). All laboratory assessments will be performed at the institution's local laboratory. If laboratory assessments are undertaken during the course of the trial and they result in a change in patient management (for example SAE or AE or dose modification) the assessment data must be recorded in the patient's CRF. Clinical chemistry and haematology parameters to be tested are listed in Table 20.

Table 20 Clinical Chemistry and Haematology Parameters

Clinical Chemistry Parameters
Albumin Alkaline Phosphatase Alanine Transaminase (ALT) or Serum Glutamic Pyruvic Transaminase (SGPT) Aspartate Aminotransferase (AST) or Serum Glutamic Oxaloacetic Transaminase (SGOT) Gamma glutamyl transferase (GGT) Blood Urea Nitrogen (BUN) or urea Calcium Creatinine[c] Glucose (random) Lactate Dehydrogenase (LDH) Phosphate Potassium Magnesium Sodium Total Bilirubin[b] Total Protein
Haematology Parameters
White Blood Cell (WBC) Count (absolute) Absolute neutrophil (ANC) count Hemoglobin Hematocrit International Normalized Ratio (INR; at Screening only)[a] Platelet Count Prothrombin Time (PT; at Screening only)[a] Partial Thromboplastin Time (PTT; at Screening only)[a] Automated WBC Differential (expressed as %): Basophils Eosinophils Lymphocytes Monocytes Neutrophils
Other tests
Amylase and lipase [monitor via local laboratory where appropriate to evaluate certain AEs (i.e., abdominal pain, pancreatitis, etc.)]
serum β-hCG (human chorionic gonadotrophin)
For subjects with a history of chronic HBV and/or HCV, the following tests will be performed at Screening: • Viral hepatitis serology; • Hepatitis B surface antigen and Hepatitis B core antibody (IgM); and/or • Hepatitis C RNA
A. Coagulation panel to be done at Screening only. c. Bilirubin fractionation is recommended if total bilirubin is > 2 x the upper limit of normal (ULN). d. If serum creatinine is > 1.5 mg/dL, creatinine clearance should be calculated using the standard Cockcroft-Gault formula

9.11 Baseline Documentation of Target and Non-target Lesions

All baseline lesion assessments, including brain MRI/CT to rule out brain metastases, must be performed within 4 weeks prior to enrolment.

- Lymph nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.
- Pathological lymph nodes with a short axis of < 15 mm but ≥ 10 mm are considered non-measurable.
- Pathological lymph nodes with a short axis of ≥ 15 mm are considered measurable and can be selected as target lesions. Lymph nodes should not be selected as target lesions when other suitable target lesions are available.
- Measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions, and recorded and measured at baseline.

These lesions should be selected on the basis of their size (i.e. lesions with the longest diameter) and their suitability for accurate repeated measurements (i.e. either by imaging techniques or clinically).

Note: Cystic lesions thought to represent cystic metastases should not be selected as target lesions when other suitable target lesions are available.

Note: Measurable lesions that have been previously irradiated and have not been shown to be progressing following irradiation should not be considered as target lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI can be considered measurable. Bone scans, fluorodeoxyglucose positron emission tomography (FDG-PET) scans or X-rays are not considered adequate imaging techniques to measure bone lesions.
- All other lesions (or sites of disease) should be identified as non-target and should also be recorded at baseline. Non-target lesions will be grouped by organ. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

9.12 Baseline Documentation of Index Lesions

An **index lesion** is the measurable lesion receiving palliative RT, for the definition of measurable lesion, see section 9.13.4.1. Measurement of index lesion(s) should be done at baseline, and then regularly throughout the study period as per the Schedule of Assessments table.

The index lesion(s) should be included in overall disease assessment according to RECIST 1.1 criteria (section 9.13.5), and can be used either as target or non-target lesion(s).

9.13 Efficacy

9.13.1 Efficacy Endpoints relating to overall disease control

Progression-free survival (PFS), defined as the time from enrolment until the earliest date of disease progression or death due to any cause.

Overall survival (OS), defined as the time from enrolment until death due to any cause.

9.13.2 Efficacy Endpoints relating to local disease control in the index lesions

Local tumour response in index lesion, defined as following:

- Complete Response (CR) locally: Disappearance of index lesion. Any pathological lymph nodes must have a short axis of <10 mm.

- Partial Response (PR) locally: At least a 30% decrease in the diameter of the index lesion, taking as a reference, the baseline diameter (i.e. percent change from baseline).

- Stable Disease (SD) locally: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD).

- Progressive Disease (PD) locally: At least a 20% increase in the diameter of the index lesion, taking as a reference, the smallest diameter recorded since the treatment started (i.e. percent change from nadir, where nadir is defined as the smallest diameter recorded since treatment start). In addition, the diameter must have an absolute increase from nadir of ≥ 5 mm.

Time to local progression in index lesions, is defined as the time from commencement of palliative RT to the index lesions, until documented evidence of PD in the index lesions.

Following local disease progression of the index lesions, further surgical excision or palliative RT to index lesions are permitted at the discretion of the treating physician, but the Trial Coordinating Centre should be notified of any further RT.

RT can be delivered concurrently with dabrafenib or trametinib, and clinical assessment prior to the commencement of RT, during RT and following RT should be performed as per Table 19. The prescribed dose of the re-irradiation is at the discretion of the treating radiation oncologists and the accumulative RT dose to the normal tissue should be within safe limit.

9.13.3 Efficacy assessment of overall disease control

Disease progression and response evaluations will be determined according to the definitions established in RECIST, version 1.1 [Eisenhauer, 2009].

The following scans/assessments are required at baseline: contrast CT (preferred method) of chest/abdomen/pelvis or MRI of abdomen/pelvis and any area of known disease, skin lesion photography, and clinical disease assessment for palpable lesions.

Exception: If a chest CT cannot be performed, chest X-ray can be used only to document the absence of disease (no tumour lesions) or the presence of new lesions. If lesions are detected at baseline by chest X-ray, chest CT must be done to properly document these lesions at baseline and in follow-up tumour assessments. At each post-baseline assessment, evaluations of the sites of disease identified by these scans are required.

A brain MRI (preferred) or CT scan is required for all subjects at baseline to assess brain metastases. If clinically indicated, a CT or MRI scan of affected bone areas will be required at baseline. Bone lesions, if present, will continue to be followed consistently throughout the study until disease progression, death, or withdrawal of consent.

Scans will be assessed by investigators as per RECIST 1.1 criteria.

9.13.3.1 Assessment Guidelines

Please note the following:

- The same diagnostic method, including use of contrast when applicable, must be used throughout the study to evaluate lesions.
- A patient should be scanned using the same machine throughout the study where possible.
- The same lesions as those reported at baseline should be measured throughout the study. All measurements should be taken and recorded in millimetres (mm), using a ruler or calipers.
- Ultrasound is not a suitable modality of disease assessment. If new lesions are identified by ultrasound, confirmation by CT or MRI is required.
- Fluorodeoxyglucose-positron emission tomography (FDG-PET) is generally not suitable for ongoing assessments of disease. It can, however, be useful in confirming new sites of disease when a positive FDG-PET scan correlates with the new site of disease present on CT/MRI or when a baseline FDG-PET was previously negative for the site of the new lesion. Fluorodeoxyglucose (FDG)-PET may also be used in lieu of a standard bone scan providing coverage allows interrogation of all likely sites of bone disease and FDG-PET is performed at all assessments.

- If PET/CT is performed then the CT component can only be used for standard response assessments if performed to diagnostic quality, which includes the required anatomical coverage and prescribed use of contrast. The method of assessment should be noted as CT in the CRF.

Clinical Examination: Clinically detected lesions will only be considered measurable when they are superficial (e.g. skin nodules). In the case of skin lesions, documentation by colour photography, including a ruler/calipers to measure the size of the lesion, is required [Eisenhauer, 2009].

CT and MRI: Contrast enhanced CT with 5 mm contiguous slices is recommended. Minimum size of a measurable baseline lesion should be twice the slice thickness, with a minimum lesion size of 10 mm when the slice thickness is 5 mm. Magnetic resonance imaging (MRI) is acceptable, but when used, the technical specification of the scanning sequences should be optimized for the evaluation of the type and site of disease and lesions must be measured in the same anatomic plane by use of the same imaging examinations. Whenever possible, the same scanner should be used [Eisenhauer, 2009].

X-ray: In general, X-ray should not be used for target lesion measurements owing to poor lesion definition. If a chest CT cannot be performed, chest X-ray can be used only to document **the absence of disease** (no tumour lesions) or the **presence of new lesions.** If lesions are detected at baseline by chest X-ray, chest CT must be done to properly document these lesions at baseline and in follow-up tumour assessments.

Brain Scan: Contrast enhanced MRI is preferable to contrast enhanced CT for assessment of brain lesion(s).

Bone Scan (typically bone scintigraphy): If a bone scan is performed and a new lesion(s) is equivocal, then correlative imaging (i.e., X-ray, CT, or MRI) is required to demonstrate malignant characteristics of the lesion(s).

Note: Positron emission tomography (PET; FDG or fluoride) may be used in lieu of a standard bone scan providing coverage allows interrogation of all likely sites of bone disease and PET is performed at all assessments.

9.13.3.2 Follow-up Assessments for Subjects Permanently Discontinued from both Dabrafenib and Trametinib

All subjects who permanently discontinue both dabrafenib and trametinib without disease progression will have radiographic disease assessments performed on the same assessment schedule noted in the Schedule of Assessments (Table 19) until the last patient has completed at least 12 months of follow up.

In addition, all subjects who permanently discontinue both dabrafenib and trametinib will be followed for survival and new anti-cancer therapy. Follow-up contact to assess survival and new anti-cancer therapy may be made via clinic visit, phone, or email; follow-up will continue until study completion.

9.13.3.3 Assessment at Subject Completion

If the last radiographic assessment was more than 8 weeks prior to study withdrawal and progressive disease had not been documented, a disease assessment should be obtained at the time of withdrawal if possible.

9.13.4 Guidelines for Evaluation of Disease

9.13.4.1 Measurable and Non-measurable Definitions

Measurable lesion(s):

A non-nodal lesion that can be accurately measured in at least one dimension (the longest dimension) of:

- ≥10 mm with MRI or CT when the scan slice thickness is ≤ 5 mm. If the slice thickness is >5 mm, the minimum size of a measurable lesion must be at least double the slice thickness (e.g. if the slice thickness is 10 mm, a measurable lesion must be ≥20 mm).

- ≥10 mm caliper/ruler measurement by clinical exam or medical photography.

Additionally, lymph nodes can be considered pathologically enlarged and measurable if:

- The short axis measures ≥15 mm when assessed by CT or MRI (the slice thickness is recommended to be ≤5 mm). At baseline and follow-up, only the short axis will be measured [Eisenhauer, 2009].

Non-measurable lesion(s):

All lesions other than those considered measurable, including lesions too small to be considered measurable (i.e. longest diameter < 10 mm or pathological lymph nodes with a short axis of ≥10 mm but < 15 mm) as well as truly non-measurable lesions, which include: leptomeningeal disease, ascites, pleural or pericardial effusions, inflammatory breast disease, lymphangitic involvement of the skin or lung, and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques [Eisenhauer, 2009].

Measurable disease:

The presence of at least one measurable lesion. Palpable lesions that are not measurable by radiologic or photographic evaluations may not be used as the only measurable lesion.

Non-measurable only disease:

The presence of only non-measurable lesions. Note: Non-measurable only disease is not allowed per protocol.

9.13.5 Response Criteria

9.13.5.1 Evaluation of Target Lesions

Definitions for assessment of response for target lesion(s) are as follows:

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes must have a short axis of <10 mm.

- Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the baseline sum of the diameters (i.e., percent change from baseline).

- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD).

- Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions,

taking as a reference, the smallest sum of diameters recorded since the treatment started (i.e., percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of ≥5 mm.

- Not Evaluable (NE): Cannot be classified by one of the 4 preceding definitions.

Note:

- If lymph nodes are documented as target lesions the short axis is added into the sum of the diameters (i.e. sum of diameters is the sum of the longest diameters for non-nodal lesions and the short axis for nodal lesions). When lymph nodes decrease to non-pathological size (short axis < 10 mm), they should still have a measurement reported in order not to overstate progression.

- If at a given assessment timepoint all target lesions identified at baseline are not assessed, the sum of the diameters cannot be calculated for purposes of assessing CR, PR, or SD, or for use as the nadir for future assessments. The sum of the diameters of the assessed lesions and the percent change from nadir should, nevertheless, be calculated to ensure that PD has not been documented. If an assessment of PD cannot be made, the response assessment should be NE.

- All lesions (nodal and non-nodal) should have their measurements recorded even when very small (e.g. 2 mm). If lesions are present but too small to measure, 5 mm should be recorded and should contribute to the sum of the diameters, unless it is likely that the lesion has disappeared in which case 0 mm should be reported.

- If a lesion disappears and reappears at a subsequent time point it should continue to be measured. The response at the time when the lesion reappears will depend upon the status of the other lesions. For example, if the disease had reached a CR status then PD would be documented at the time of reappearance; if the response status was PR or SD, the diameter of the reappearing lesion should be added to the remaining diameters and response determined based on percent change from baseline and percent change from nadir.

9.13.5.2 Evaluation of Non-target Lesions

Definitions for assessment of response for non-target lesion(s) are as follows:

- Complete Response (CR): The disappearance of all non-target lesions. All lymph nodes identified as a site of disease at baseline must be non-pathological (i.e. a short axis of <10 mm).

- Non-CR/Non-PD: The persistence of 1 or more non-target lesion(s) or lymph nodes identified as a site of disease at baseline with a short axis of ≥10 mm.

- Progressive Disease (PD): Unequivocal progression of existing non-target lesions.

- Not Applicable (NA): No non-target lesions at baseline.

- Not Evaluable (NE): Cannot be classified by one of the 4 preceding definitions.

Note:

- In the presence of measurable disease, progression on the basis of solely non-target disease requires substantial worsening such that even in the presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy.

9.13.5.3 New Lesions

New malignancies denoting disease progression must be unequivocal. Lesions identified in follow-up in

an anatomical location not scanned at baseline are considered new lesions.

Any equivocal new lesions should continue to be followed. Treatment can continue at the discretion of the investigator until the next scheduled assessment. If at the next assessment the new lesion is considered to be unequivocal, progression should be documented.

9.13.5.4 Evaluation of Overall Response

Table 20 presents the overall response at an individual time point for all possible combinations of tumour responses in target and non-target lesions with or without the appearance of new lesions for subjects with measurable disease at baseline.

Table 20 Evaluation of Overall Response for Subjects with Measurable Disease at Baseline

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR or NA	No	CR
CR	Non-CR/Non-PD or NE	No	PR
PR	Non-PD or NA or NE	No	PR
SD	Non-PD or NA or NE	No	SD
NE	Non-PD or NA or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR = complete response; NA = not applicable; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Note:

- Subjects with a global deterioration of health status requiring treatment discontinuation without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Objective response status is determined by evaluations of disease burden. Every effort should be made to document the objective progression even after treatment discontinuation.

- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (e.g. fine needle aspirate/biopsy) to confirm the CR.

9.14 Safety

9.14.1 Safety Endpoints

The primary objective of the study is to characterize the safety of dabrafenib, trametinib and palliative RT combination therapy. As a consequence, clinical assessments including vital signs and physical examinations, 12-lead ECG (if clinically indicated), ECHO (if clinically indicated), chemistry and haematology laboratory values, and AEs will be monitored and evaluated.

9.14.2 Adverse Events

The investigator or site staff will be responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as outlined in Section 9.14.2.1 and Section 9.14.2.2, respectively.

9.14.2.1 Definition of an AE

For the purposes of this trial, an adverse event is defined as any untoward medical occurrence in a participant administered a treatment which may have causal relationship to the patient's melanoma diagnosis and/or with the treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the patient's melanoma and/or treatment. For marketed medicinal products, this also includes failure to produce expected benefits, abuse, or misuse. Examples of events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or grade of the condition;
- New conditions detected or diagnosed after treatment administration even though it may have been present prior to the start of the study;
- Signs, symptoms, or the clinical sequelae of a suspected interaction; and
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either dabrafenib or trametinib or a concomitant medication (overdose per se will not be reported as an AE/SAE) unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae.
- 'Lack of efficacy' or 'failure of expected pharmacological action' per se is not to be reported as an AE or SAE. Any signs, symptoms, and/or clinical sequelae resulting from 'lack of efficacy' will, however, be reported as an AE or SAE, if they fulfill the definition of an AE or SAE.

Events that do not meet the definition of an AE include:

- Medical or surgical procedure (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an AE;
- Situations where an untoward medical occurrence did not occur (e.g. social and/or convenience admission to a hospital);
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen; and/or
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

9.14.2.2 Definition of an SAE

A serious adverse event (SAE) is any untoward medical occurrence that is related to the patient's melanoma and/or to dabrafenib, trametinib or RT treatment:

a. Results in death;

b. Is life-threatening;
Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization;
Note: In general, hospitalization signifies that the subject has been detained (i.e. usually involving at least one overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.
Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity; and/or
Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical

significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and/or accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect.
Medical or scientific judgment should be exercised in deciding whether reporting 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 subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, 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.

f. Protocol-specific SAEs:

- Dose limiting toxicity for RT includes CTC grade 4 radiation dermatitis or any other CTC Grade 3 or above RT related toxicity.

- All events of possible drug-induced liver injury with hyperbilirubinaemia defined as ALT ≥3xULN and bilirubin ≥2xULN (>35% direct) (or ALT ≥3xULN and INR>1.5, if INR measured) or termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants).

NOTE: bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥ 2xULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

- Any new primary cancers and treatment emergent malignancies (including squamous cell carcinoma and second primary melanoma) with the exception of basal cell carcinoma (BCC). BCC should be reported as an AE or SAE based on the discretion of the investigator.

- Laboratory abnormalities as referenced in Section 9.14.2.3.

- LVEF that meets stopping criteria Section 7.3.3.1.

- Central serous retinopathy (CSR) or retinal vein occlusion (RVO).

- Pyrexia accompanied by hypotension or dehydration requiring IV fluids or renal insufficiency or severe rigors/chills in the absence of an obvious infectious cause.

9.14.2.3 Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis), or other safety assessments (e.g. ECGs, radiological scans, vital sign measurements, etc.) including those that worsen from baseline, and events felt to be clinically significant in the medical and scientific judgment of the investigator, are to be recorded as AEs or SAEs, in accordance with the definitions provided.

In addition, an associated AE or SAE is to be recorded for any laboratory test result or other safety assessment that led to an intervention, including permanent discontinuation of study treatment and/or dose modification/interruption.

Any new primary cancer must be reported as an SAE.

Any clinically significant safety assessments that are associated with melanoma, unless judged by the investigator to be more severe than expected for the subject's condition, are not to be reported as AEs or SAEs.

9.14.2.4 Disease-related Events and/or Disease-related Outcomes Not Qualifying as SAEs

An event which is part of the natural course of melanoma (i.e. disease progression or hospitalization due to disease progression) does not need to be reported as an SAE, however should be reported in the CRF. If however, death due to melanoma (i.e. progression) is greater than that which would normally be expected for the subject, or if the investigator considers that there was a causal relationship between study treatment or protocol design/procedures and disease progression, then this must be reported as an SAE.

9.14.2.5 Time Period and Frequency for Detecting AEs and SAEs

The investigator or site staff is responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE.

Adverse events (AEs) will be collected from enrolment until 30 days after discontinuation of study treatment (RT) regardless of initiation of a new anti-cancer therapy or transfer to hospice.

Serious adverse events (SAEs) will be collected over the same time period as stated above for AEs. In addition, any **new malignancy** (defined in Section 9.14.2.2) or any SAE assessed as **related** to study participation (e.g. protocol-mandated procedures, invasive tests, or change in existing therapy) or study treatment must be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.

All SAEs will be reported to Trial Coordinating Centre within 24 hours of knowledge of the event, as indicated in Section 9.14.2.6. For any new malignancy, every effort should be made to identify the RAS mutation status; the mutation test should be performed locally and reported within 12 weeks of diagnosis. Additional genetic analysis may be performed depending on the tumour types, and the results reported at the discretion of the investigator.

After study treatment discontinuation, the investigator will monitor all AEs/SAEs that are ongoing until resolution or stabilization of the event or until the subject is lost to follow up. At any time after 30 days from the last study visit, the investigator may report any AE that he/she believes is **possibly related** to study treatment.

9.14.2.6 Prompt Reporting of SAEs to the Trial Coordinating Centre

All serious adverse events (SAEs) that occur whilst the trial participant is receiving trial treatment (from enrolment to 30 days after the last dose of RT) are required to be reported if considered related to the treatment under investigation. An SAE must be reported for all events occurring from the time a participant is registered on the trial to within 30 days of the final treatment.

The Investigator at the trial site must sign off all final reports. The initial report may be completed by any member of the hospital staff. This form should be signed off by the investigator. Should the Investigator not be available to sign off the SAE form within the 24 hour period, a comment to this effect must be included on the form and the form returned without signature or electronic sign-off. The investigator must sign off the form as soon as possible and the SAE form must be re-sent. The investigator may also be asked to provide follow-up information.

Follow up information for all SAEs must also be reported within 24 hours of becoming aware of any change in the event. A new SAE Report Form must be completed stating that the report is a follow up to a previously reported serious adverse event and should describe whether the event has resolved or continues, if and how it was treated and whether the patient continued or discontinued study participation.

All SAEs must be reported using the SAE form by ensuring the Trial Coordinating Centre receives notification of this within 24 hours. The Trial Coordinating Centre will escalate all events to the Study Chairman.
Trial Coordinating Centre requires that SAE reporting occurs as per the following:

INITIAL REPORT	WITHIN ONE WORKING DAY/24 HOURS OF DISCOVERY OR NOTIFICATION OF THE EVENT. IF THE REPORTING OF AN SAE IS DELAYED BY MORE THAN 24 HOURS, AN EXPLANATION MUST BE PROVIDED IN THE COMMENTS SECTION OF THE SAE FORM. PLEASE PROVIDE COPIES OF RELEVANT SOURCE DOCUMENTS, IF AVAILABLE.
INCOMPLETE INITIAL REPORTS	IF ALL DETAILS ARE NOT AVAILABLE AT THE TIME OF THE INITIAL REPORT, A COMPLETED REPORT MUST BE SENT WITHIN THE NEXT 5 WORKING DAYS. PLEASE PROVIDE COPIES OF RELEVANT SOURCE DOCUMENTS, IF AVAILABLE.
UPDATED REPORT	IF THE EVENT IS NOT RESOLVED (OR 'ON-GOING') AT THE TIME OF THE INITIAL REPORT, A NEW SAE FORM MUST BE SUBMITTED EVERY 30 DAYS UNTIL THE EVENT IS RESOLVED, DEATH HAS OCCURRED OR THE CONDITION HAS STABILISED. IF A CHANGE OCCURS IN A STABLE CONDITION (I.E. EITHER WORSENS OR IMPROVES), THEN A NEW SAE FORM SHOULD BE FAXED. PLEASE PROVIDE COPIES OF RELEVANT SOURCE DOCUMENTS, IF AVAILABLE.

SAE reports will collect the following information:

- event description
- start date
- action taken
- relationship to treatment (related / not related)
- expectedness (expected / unexpected)
- status (resolved, ongoing)
- end date
- any other relevant details

The investigator should also notify the HREC of SAE occurring at the site in accordance with the local procedures.

In addition, events deemed to be both serious and unexpected and related to the study intervention (i.e. Suspected Unexpected Serious Adverse Reaction / SUSAR) will be reported by the Trial Coordinating Centre on behalf of the Sponsor to the Regulatory Agency (TGA). For fatal or life-threatening events, the initial report should be sent within 7 calendar days of first knowledge and follow up with complete report within 8 additional calendar days. For all other serious AND unexpected events, the full report should be sent no later than 15 calendar days of first knowledge.

A participant may also voluntarily withdraw from treatment due to what he/she perceives as an intolerable adverse event. If this occurs, the participant should undergo an end-of study assessment and be given appropriated care under medical supervision until symptoms cease or the condition becomes stable.

Pregnancy during the study period should be reported as an SAE, see section 6.2.3.2 for details.

9.14.2.7 Criteria for assessing causality

The SAE form requires the site investigator to define the attribution to protocol treatment (dabrafenib, trametinib and RT) and the nature of the event (expected or unexpected). In general, AEs possibly related to RT should occur within the RT field and/or in the vicinity of the RT field.

9.14.2.8 SAEs responsibilities

The trial site is responsible for:

1. Complying with the Serious Adverse Events reporting guidelines stated by the Protocol.

2. Ensuring that any Serious Adverse Events are reported to the Trial Coordinating Centre within 24 hours of notification.

3. Inform the responsible HREC of all serious or unexpected adverse events (including serious adverse drug reactions) that occur during the trial in accordance with local requirements.

4. In the event of an adverse drug reaction, each site is to comply with institutional guidelines for ADRAC notification in Australia. Investigator safety reports will be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and will be forwarded to investigators as necessary.

The Trial Coordinating Centre is responsible for:

1. Implementing and maintaining a record of all SAEs received from trial sites.

2. Considering information provided by (non-serious) adverse event data.

3. Informing each trial site of new information arising from serious and non-serious adverse events and adverse drug reactions that may affect the conduct of the trial or the rights, interests, safety or wellbeing of trial participants.

9.15 Health Outcomes

9.15.1 Health Outcomes Endpoints

As part of the objectives of this study, changes in pain from baseline will be assessed by a visual analog scale as shown in Appendix 2.

9.16 Translational Research - Optional

Comparative examination of biomarker profiles of participants at regular intervals of the study may uncover known or novel candidate biomarkers/profiles which could be used to predict response to study treatments or provide new insights into melanoma and medically related conditions.

In this study, blood/plasma samples are stored at baseline, week 1 post-RT, week 4 post-RT and then every 8 weeks thereafter until study completion. At documented time of disease progression, an additional sample of blood/plasma will be collected.

Optional core biopsy of the index lesion(s) will be carried out at baseline, week 1 post-RT, and time of local disease progression in each lesion. It is highly recommended that a biopsy is undertaken for lesions which are accessible to core biopsy. If a biopsy is not carried out, archived tumour tissue can be used for analysis of biomarkers

All samples may be retained at the Trial Coordinating Centre site for a maximum of 15 years after the last subject completes the trial.

Novel candidate biomarkers and subsequently discovered biomarkers of the biological response associated with melanoma or medically related conditions and/or the action of the study treatments may be identified by application of:

- DNA/gene and protein analysis of tumour tissue
- BRAF mutation assay
- Circulating cell-free DNA analysis of tumour tissue and blood/plasma

9.16.1 Tumour Biomarker Analysis

The exploratory research objectives of this study include characterizing further the subject population through analysis of tumour DNA, RNA, and protein, or other aberrations from tumour tissue, and to determine whether these are associated with clinical outcome in response to therapy. Mutations in BRAF, MEK1, MEK2, RAS, PTEN, P53 and other cancer-related genes may be assessed. Other biomarkers (e.g. expression of genes and proteins) related to the activity of dabrafenib and/or trametinib may also be measured. These analyses may be performed on the mandatory tumour and/or optional tumour tissue samples depending on availability and consent. Targeted mutation screening will be conducted using capillary sequencing of RT-PCR products as recently described [Rizos, 2014]. Exome sequencing will also be performed on selected biopsy samples using the Illumina TrueSeq technology.

9.16.2 Circulating cell-free DNA (cfDNA)

Tumour-specific cfDNA levels detected in plasma or serum have been found to correlate with increasing tumour burden and decline following therapy. Furthermore, cfDNA in cancer patients can harbor many genetic alterations (e.g. mutations, microsatellite alterations, aberrant methylation), which are generally consistent with the tumour. Thus, tumour-specific cfDNA has the potential to be a useful biomarker of therapeutic response and to offer a less invasive blood-based technique for identifying and selecting subjects for certain treatments.

Given the promise of a cfDNA blood-based test for subject selection, this test will be explored to determine whether BRAF mutations in cfDNA correlate with that in the tumour tissue from which it is derived. This test will also be explored to correlate cfDNA levels with tumour burden. Additionally, cfDNA may be evaluated for other gene mutations associated with response to dabrafenib and/or trametinib at baseline and at disease progression. Proportion of tumour-specific mutant BRAF alleles in patient-derived plasma will be measured using digital droplet PCR prior to treatment initiation, during the course of therapy at regular intervals and on RECIST-determined tumour progression.

10 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

An independent Data Safety Monitoring Committee (DSMC) will be formed prior to trial start to review the information from the safety analyses performed for each of the cohorts. The DSMC will provide recommendations to the Study Chairman and TMC members, who will have responsibility for any final decisions about protocol stopping or modification. Any decision will be communicated by the Trial Coordinating Centre to the participating investigators and sites.

11 STATISTICAL CONSIDERATIONS

11.1 Sample Size Determination

As this is an early phase study to assess safety and efficacy which would then be evaluated in larger (appropriated powered) future studies, a phase I study design is selected. The goal of this research is to confirm that systemic dabrafenib, trametinib and palliative RT is safe to give concurrently. In our study design, a minimum RT dose is mandated for the treatment of soft tissue and nodal metastases, and for the treatment of bony metastases, the maximum sample size is 30 patients.

11.2 Populations for Analyses

- Enrolled subject population includes all subjects who provided informed consent.
- Treated subject population is defined as the subjects who received at least one dose of the combination of dabrafenib, trametinib and RT. This is the primary population for safety and efficacy.

11.3 Analyses

Analysis safety and efficacy will be performed at study completion

11.3.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics.

11.3.2 Efficacy Analyses

Pre- and post-treatment tumour measurements and radiological responses will be compared graphically and using descriptive statistics.

Overall survival and progression-free survival will be summarized using the Kaplan-Meier estimates, and medians with corresponding two-sided 95% confidence intervals. The 1-year OS rate and corresponding exact two-sided 95% confidence interval will be calculated.

Time to local progression on index lesion(s) will be summarized using accumulative incidence curve to account for competing risks, e.g. death.

11.3.3 Safety Analyses

Adverse events (AEs) will be coded using the standard format and grouped by system organ class. Adverse events (AEs) will be graded by the investigator according to the NCI CTCAE, version 4.03.

Events will be summarized by frequency and proportion of total subjects, by system organ class and preferred term. Separate summaries will be given for all AEs, RT-related AEs, drug-related AEs, SAEs and AEs leading to treatment discontinuation.

If the AE is listed in the NCI CTCAE (version 4.03) table, the maximum grade will be summarized. RT-related AE which is assessed to be grade 3 or 4 according to NCI CTCAE (version 4.03), except for grade 3 radiation dermatitis, will be classified as a DLT.

Any AEs of special interest (including SCC and other proliferative diseases) will be summarized as detailed in the reporting and analysis plan (RAP).

The incidence of deaths and the primary cause of death will be summarized.

Haematology and clinical chemistry data will be summarized at each scheduled assessment according to NCI CTCAE (version 4.03) Grade. The proportion of values lying outside the reference range will also be presented for laboratory tests that are not graded because there are no associated NCI CTCAE criteria. Summaries by visit will include data from scheduled assessments only, and all data will be reported according to the nominal visit date for which it was recorded (i.e. no visit windows will be applied). Unscheduled data will be included in 'worse case post baseline' summaries which will capture a worst case across all scheduled and unscheduled visits after the first dose of study treatment. Further details will be provided in the Reporting and analysis plan.

The results of scheduled assessments of vital signs, ECOG performance status, 12-lead ECG, and ECHO will be summarized. Summaries by visit will include data from scheduled assessments only. All data will be reported according to the nominal visit date for which it was recorded (i.e. no visit windows will be applied). Unscheduled data will be included in 'worse case' summaries which will capture a worst case across all scheduled and unscheduled visits after the first dose of study treatment. All data will be listed. Further details will be provided in the reporting and analysis plan.

11.3.4 Health Outcomes Analyses

As part of the objectives of this study, changes in pain from baseline will be assessed by a visual analog scale as shown in Appendix 2.

11.3.5 Translational Analyses- Optional

The results of translational research investigations will be reported separately from the main clinical study report.

As data warrant, analyses will be performed to further characterize the subject population through analysis of tumour DNA (mutation profiling for established resistance mechanisms and alterations that may diminish therapy response), tumour RNA (gene set enrichment analyses of gene expression based on Nanostring and/or Illumina whole genome arrays), and protein (including immuohistochemical analyses of proliferation, apoptotic and resistance markers). Analyses will determine whether or not tumour markers are associated with clinical outcome in response to therapy.

All endpoints of interest will be descriptively and/or graphically summarized as appropriate to the data. Further details of the translational research analyses will be described in the reporting and analysis plan.

12 STUDY MANAGEMENT

12.1 Compliance

12.1.1 Compliance with the Protocol and Protocol Revisions

Changes and amendments to the protocol can only be made by the TMC. Approval of amendments by the HREC is required prior to their implementation. In some instances, an amendment may require a change to the participant information sheet and/or consent form. The Investigator must receive approval/advice of the revised consent form prior to implementation of the change. In addition, changes to the CRFs, if required, will be incorporated in the amendment.

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the HREC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining HREC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- HREC for review and approval/favorable opinion
- TMC
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the HREC must be sent to the TMC.

12.1.2 Monitoring

Monitoring will include centralised review of CRFs and other study documents for protocol compliance, data accuracy and completeness by the Trial Coordinating Centre.

Representatives of the Trial Coordinating Centre may visit all study site locations to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable. Certain CRF pages and/or electronic files may serve as the source documents (e.g. CT scan reports).

In addition, the study may be evaluated by the Trial Coordinating Centre and government inspectors who must be allowed access to CRFs, source documents, other study files and study facilities.

The investigator must notify the Trial Coordinating Centre promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to Trial Coordinating Centre.

12.1.3 Investigational Site Training

The Trial Coordinating Centre (MASC Trials) will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: ICH GCP, AE reporting, study details and procedure, CRFs, study documentation, and informed consent procedures.

12.2 Records

12.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the Trial Coordinating Centre, whichever is longer. The investigator must contact the Trial Coordinating Centre prior to destroying any records associated with the study.

The Trial Coordinating Centre will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (e.g. relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g. another investigator, HREC). Notice of such transfer will be given in writing to Trial Coordinating Centre.

12.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of investigational product is maintained at each study site where study drug is inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label ID number or batch number
- amount dispensed and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- non-study disposition (e.g. lost, wasted)
- amount destroyed at study site, if applicable
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Site Delegation of Authority Form.

12.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

Source documents pertaining to the trial must be maintained by investigational sites. Source documents may include a subject's medical records, hospital charts, clinic charts, the investigator's subject study files, radiation treatment prescriptions, radiation treatment administration sheets, isodose plans (colour copies), simulator film or DRR image as well as the results of diagnostic tests such as CT scans, laboratory tests, MRI scan, echocardiogram and electrocardiograms. Sites may be asked to submit copies of source documents to the Trial Coordinating Centre, however, all reports must be de-identified prior to sending or uploading, with only participant trial number and initials detailed.

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any SAE/pregnancy CRFs, must be reviewed by a qualified physician who is an investigator or co-investigator.

The study will be conducted in accordance with applicable Privacy Acts and Regulations. All data generated in this study will remain confidential. All information will be stored securely at the Trial Coordinating Centre (MASC Trials) and will only be available to staff directly involved with the study.

Personal data identifying trial subjects will be held securely at the sites according to local institutional requirements for the purpose of follow up after the conclusion of the protocol-specified period.

12.3 Clinical Study Report and Publications

Acknowledgement of the collaboration between MASC Trials is required in all publications, abstracts and presentations. Publications and abstracts must be presented to the Study Chair and TMC for review and approved prior to submission. Draft publications will be presented to the Publications/Writing Committee of each collaborating group for comment prior to submission.

In line with the MASC Trials "Authorship and Publications Policy" standard operating procedure, publications must be reviewed by MASC Trials prior to submission.

The data collected during this study are confidential and proprietary to the investigators.

The Study Chair and TMC will be responsible for decisions regarding presentations and publications arising from this study.

Authorship credit should be based on the Vancouver statement by the International Committee of Medical Journal Editors, i.e. substantial contribution to all three of the following criteria:

- Conception and design OR analysis and interpretation
- Drafting article OR critically revising it for intellectual content
- Final approval of version to be published

Or, a fourth criterion is:

- Contributors who register 5% or more (accrual by institution) of the evaluable cases on a study will be listed as authors. The designated author is the choice of the institution's PI and in most cases would be the investigator with the highest accrual. If an institution places a large number of cases on the study, that institution will get an additional author for every 10% of the participants accrued, not to exceed a total of three authors (i.e. two authors for $\geq$ 15% accrual and three authors for $\geq$ 25% accrual)

13 FINANCIAL DISCLOSURE

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Appendix 1 ECOG performance status

Grade	ECOG performance status*
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 slight or sedentary nature, e.g. light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disable. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

* Oken, M.M., et al., Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol, 1982. 5(6): p. 649-55.

Appendix 2 Assessment of patients' pain using visual analog

We ask you to rate how severe the pain has been in the last 24 hours. Please circle the number below from 0 (pain has not been present) to 10 (pain was as bad as you can imagine it could be).

Your pain at its WORST:

0	1	2	3	4	5	6	7	8	9	10
Not Present										**Worst Imaginable**

Huskisson EC. Measurement of pain. Lancet. 1974; 2(7889): 1127-31.

Appendix 3 NCI Common Terminology Criteria for Adverse Events version 4.03

The National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (NCI CTCAE v4.03) can be found at: http://evs.nci.nih.gov/ftp1/CTCAE/About.html

REFERENCES

Anker CJ, Ribas A, Grossmann AH, et al. Severe liver and skin toxicity after radiation and vemurafenib in metastatic melanoma. J Clin Oncol 2013; 31: e283-7.

Balagula Y, Huston KB, Busam KJ, et al. Dermatologic side effects associated with the MEK 1/2 inhibitor selumetinib (AZD6244, ARRY-142886). Invest New Drugs 2010; 29: 1114-1121

Bernier J, Bonner J, Vermorken JB, et al. Consensus guidelines for the management of radiation dermatitis and coexisting acne-like rash in patients receiving radiotherapy plus EGFR inhibitors for the treatment of squamous cell carcinoma of the head and neck. Annals of Oncology 2008; 19: 142–149

Burmeister BH, Henderson MA, Ainslie J, et al. Adjuvant radiotherapy versus observation alone for patients at risk of lymph-node field relapse after therapeutic lymphadenectomy for melanoma: a randomised trial. Lancet Oncol. 2012; 13: 589-97.

Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011; 364: 2507-2516.

Corry J, Smith JG, Bishop M, et al. Nodal radiation therapy for metastatic melanoma. Int J Radiat Oncol Biol Phys 1999; 44: 1065-9.

Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. Nature 2002; 417(6982): 949-954.

Eisenhauer EA, Therasse P, Bogaert J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45(2): 228-247.

Flaherty KT, Infante JR, Daud A, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. N Engl J Med. 2012; 367: 1694-1703.

Gordon MS, Osman I, Gai W, et al. Analysis of BRAF and N-RAS mutations in metastatic melanoma tissues. Cancer Res. 2003; 63: 3955-3957.

Hatzivassiliou G, Song K, Yen I, et al. RAF inhibitors prime wild-type RAF to activate the MAPK pathway and enhance growth. Nature 2010; 464: 431-436.

Hauschild A, Grob JJ, Demidov LV et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2012; 380: 358-365.

Houben R, Becker JC, Kappel A, et al. Constitutive activation of the Ras-Raf signalling pathway in metastatic melanoma is associated with poor prognosis. J Carcinog. 2004; 3:6.

Huncharek M, Caubet JF, McGarry R. Single-agent DTIC versus combination chemotherapy with or without immunotherapy in metastatic melanoma: a meta-analysis of 3272 patients from 20 randomized trial. Melanoma Res 2001; 11(1):75-81.

Huskisson EC. Measurement of pain. Lancet. 1974; 2(7889):1127-31.

Kirschner M, Helmke B, Starz H, et al. Preponderance of the oncogenic V599E and V599K mutations in the B-raf kinase domain is enhanced in melanoma lymph node metastases. Melanoma Res. 2005; 15: 427-434.

Konefal JB, Emami B, Pilepick MV. Analysis of dose fractionation in the palliation of metastases from malignant melanoma. Cancer 1988; 61: 243-246.

Korn EL, Liu PY, Lee SJ, et al. Meta-analysis of phase II cooperative group trials in metastatic stage IV melanoma to determine progression-free and overall survival benchmark for future phase II trials. J Clin Oncol 2008; 26(4): 527-534.

Kumar R, Angelini S, Czene K, et al. BRAF mutations in metastatic melanoma: a possible association with clinical outcome. Clin Cancer Res. 2003; 9: 3362-3368.

Lacouture ME, Anadkat MJ, Bensadoun RJ, et al, Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. Support Care Cancer 2011; 19:1079-1095.

Lacouture ME, Shenhong W, Robert C, et al. Evolving strategies for the management of hand-foot skin reaction associated with the multitargeted kinase inhibitors sorafenib and sunitinib. The Oncologist 2008; 13: 1001-1011.

Libra M, Malaponte G, Navolanic PM, et al. Analysis of BRAF mutation in primary and metastatic melanoma. Cell Cycle 2005; 4: 1382-1384.

Lutz S, Berk L, Chang E, et al. Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. Int J Radiat Oncol Biol Phys 2011; 79: 965-76.

McLellan B, Kerr H. Cutaneous toxicities of the multikinase inhibitors sorafenib and sunitinib. Dermatologic Therapy 2011; 24: 396-400.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649-655.

Olivier KR, Schild SE, Morris CG, et al. A higher radiotherapy dose is associated with more durable palliation and longer survival in patients with metastatic melanoma. Cancer 2007; 110: 1791-1795.

Omholt K, Platz A, Kanter L, et al. NRAS and BRAF mutations arise early during melanoma pathogenesis and are preserved throughout tumor progression. Clin Cancer Res. 2003; 9: 6483-6488.

Peters S, Michielin O, Zimmermann S. Dramatic response induced by vemurafenib in a BRAF V600E-mutated lung adenocarcinoma. J Clin Oncol 2013; 31: e341-4.

Pulvirenti T, Hong A, Clements A, et al. BRAF inhibitors enhanced acute radiation skin toxicity. J Clin Oncol (accepted for publication in 2014)

Rao NG, Yu HH, Trotti A 3rd, et al. The role of radiation therapy in the management of cutaneous melanoma. Surg Oncol Clin N Am 2011; 20: 115-31.

Rizos H, Menzies AM, Pupo GM, et al. BRAF inhibitor resistance mechanisms in metastatic melanoma: spectrum and clinical impact. Clin Cancer Res 2014; 20:1965-77.

Rompoti N, Schilling B, Livingstone E, et al. Combination of BRAF Inhibitors and Brain Radiotherapy in Patients With Metastatic Melanoma Shows Minimal Acute Toxicity. J Clin Oncol 2013; 31: 3844-3845.

Sambade MJ, Peters EC, Thomas NE, et al. Melanoma cells show a heterogeneous range of sensitivity to ionizing radiation and are radiosensitized by inhibition of B-RAF with PLX-4032. Radiotherapy and Oncology 2011; 98: 394-399.

Seegenschmiedt MH, Keilholz L, Altendorf-Hofmann A, et al. Palliative radiotherapy for recurrent and metastatic malignant melanoma: prognostic factors for tumor response and long-term outcome: a 20-year experience. Int J Radiat Oncol Biol Phys 1999; 44: 607-18.

Stazger I, Degen A, Asper H, et al. Serious skin toxicity with the combination of BRAF inhibitors and radiotherapy. J Clin Oncol 2013; 31: e220-2.

Wellbrock C, Karasaides M, Marais R. The RAF proteins take center stage. Nature Reviews Mol Cell Biol. 2004; 5: 875-885.