Clinical Trial Protocol

Trial Title:	INTERIM: a randomised phase II feasibility study of INTERmittent versus continuous dosing of oral targeted combination therapy In patients with BRAFV600 mutant stage 3 unresectable or metastatic Melanoma
Protocol Number:	INTERIM17
EudraCT Number:	2016-005228-27
ISRCTN Number:	18183156
NIHR Portfolio CPMS:	33584
Investigational Product:	Dabrafenib & Trametinib
Protocol Version:	V1.1
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An NCRI Skin Cancer Clinical Studies Group Trial

1 Protocol Signatures:

I give my approval for the attached protocol entitled INTERIM: a randomised phase II feasibility study of INTERmittent versus continuous dosing of oral targeted in patients with BRAF mutant unresectable or metastatic Melanoma dated 21st September 2017

Chief Investigator

Name:

Signature: _____

Date: _____

Site Signatures

I have read the attached protocol entitled INTERIM: a randomised phase II feasibility study of INTERmittent versus continuous dosing of oral targeted in patients with BRAF mutant unresectable or metastatic Melanoma dated 21st September 2017 and agree to abide by all provisions set forth therein.

I agree to comply with the conditions and principles of Good Clinical Practice as outlined in the European Clinical Trials Directives 2001/20/EC and the GCP Directive 2005/28/EC, the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) and any subsequent amendments of the clinical trial regulations, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

Principal Investigator

Name:

Signature: _____

Date: _____

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3 Abbreviations

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AR	Adverse reaction to an investigational medicinal product
AST	Aspartate aminotransferase
CA	Competent authority
CCF	Congestive cardiac failure
CCTU-CT	Cambridge Clinical Trials Unit – Cancer Theme
CI	Chief Investigator
CR	Complete response
CRF	Case report form
CT	Computerised tomography
CTA	Clinical Trial Authorisation
CTCAE	Common terminology criteria for adverse events
ctDNA	Circulating tumor deoxyribonucleic acids
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DSUR	Development Safety Update Report
EAS	Expanded Access Study
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC	European Organisation for Research and Treatment of Cancer
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FBC	Full blood count
FDA	Food and drug administration
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GMP	Good Manufacturing Practice
GP	General Practitioner
Hb	Haemoglobin
HR	Hazard ratio
HRA	Health Research Authority
ICF	Informed consent form
IMP	Investigational Medicinal Product
ISF	Investigator Site File
IQR	Interquartile range
ISDMC	Independent Safety Data Monitoring Committe
ITT	Intention-to-treat Population
IUD	Intrauterine device
K	Potassium
LDH	Lactate dehydrogenase
LLN	Lower Limit of Normal
LVEF	Left ventricular ejection fraction
MAP	Mitogen activated protein
MHRA	Medicines and healthcare products regulatory agency

MI	Myocardial infarction
MRI	Magnetic resonance imaging
Na	Sodium
NCI	National Cancer institute
NCI CTCAE	National Cancer institute Common terminology Criteria for Adverse Events
NHS	National Health Service
NICE	National institute for Health and Care Excellence
NIMP	Non Investigational Medicinal Product
NYHA	New York Heart Association
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PI	Principal Investigator
PIS	Patient Information Sheet
PR	Partial response
PRO	Patient reported outcome
PRO-CTCAE	Patient reported outcomes version of the Common Terminology Criteria for Adverse Events
PROMS	Patient reported outcome measures
PSA	Participating site agreement
QALY	Quality-adjusted life years
QoL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
R&D	Research and Development
RA	Regulatory Agency
REC	Research Ethics Committee
RfPB	Research for Patient Benefit
RPED	Retinal pigment epithelial detachment
RSI	Reference safety information
RVO	Retinal vein occlusion
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Stable disease
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TIA	Transient ischaemic attack
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom
ULN	Upper limit of normal range
WBC	White blood cell
WCBP	Women of child-bearing potential

4 Trial Synopsis

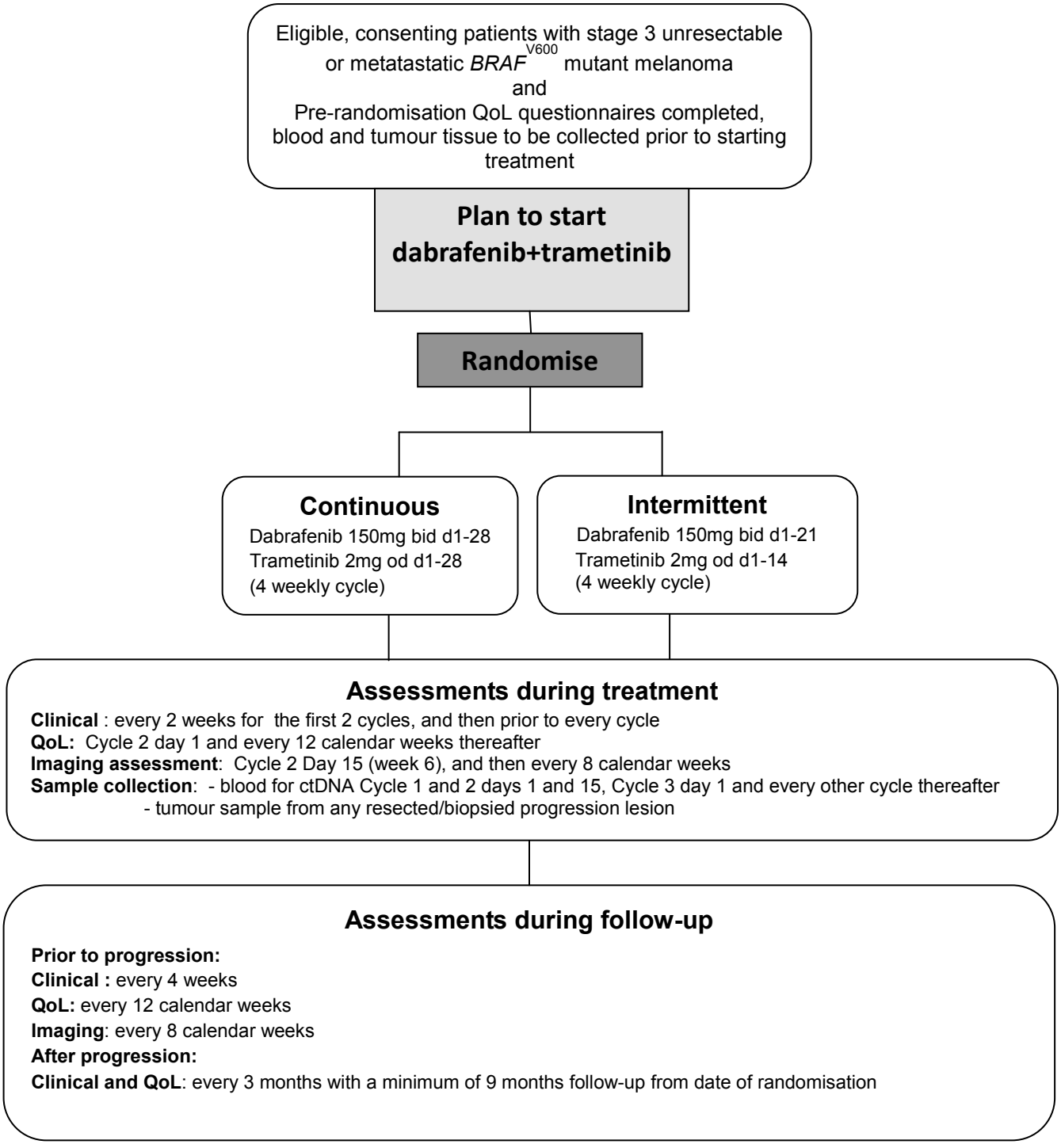
Title of clinical trial	INTERIM: a randomised phase II feasibility study of INTERmittent versus continuous dosing of oral targeted combination therapy In patients with *BRAF*V600 mutant stage 3 unresectable or Metastatic melanoma
Sponsor name	Cambridge University Hospitals NHS Foundation Trust
EudraCT number	2016-005228-27
Medical condition or disease under investigation	*BRAF*V600 mutant stage 3 unresectable or metastatic melanoma
Purpose of clinical trial	To investigate continuous versus intermittent dosing of dabrafenib plus trametinib in patients with *BRAF*V600 mutant stage 3 unresectable or metastatic melanoma
Primary objectives	• To assess recruitment rate and treatment compliance of the intermittent dosing schedule as a measure of acceptance of intermittent dosing to patients and physicians; • To evaluate the impact on Overall quality of life (QoL) with intermittent dosing using European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30; • To estimate the size of clinical efficacy of intermittent dosing compared to continuous dosing, measured by progression-free survival (PFS).
Secondary objectives	• To evaluate safety, objective response rate, time to treatment failure and overall survival • To evaluate skin toxicity as assessed by clinicans and patients using patient reported outcome measures (PROMS) (Skindex-16 and patient-reported outcomes version of the CTCAE (PRO-CTCAE)) • To assess factors which influence patients' decision to enter/decline entering the trial • To evaluate patient experience of participation in this trial (using mixed methods) • To determine the QoL and cost-effectiveness of intermittent dosing compared with standard continuous dosing
Exploratory objectives	• To explore emergence of resistance by means of circulating tumour DNA (ctDNA) collected from patients during the course of their treatment

	• To determine the role of ctDNA as a useful biomarker for therapeutic monitoring • In a subset of patients (up to 20), explore pharmacokinetics of standard versus intermittent dosing schedules
Trial Design	INTERIM is a multi-centre, open label, two-arm, randomised phase II feasibility trial.
Trial Outcome Endpoints	Primary endpoints: • Recruitment rate • Treatment compliance • Overall QoL (global health status) • PFS Secondary endpoints: • Safety • Objective response rate • Time to treatment failure • Overall survival (OS) • Patient reported outcomes focussing on skin toxicity • Patient experience consent and treatment • QoL and Health Economic Evaluation Exploratory endpoints: • Predictive biomarkers • Pharmacokinetics
Sample Size	150 patients
Summary of inclusion criteria	Main inclusion criteria: • Signed informed consent • Age ≥18 years old • Histologically or cytologically confirmed *BRAF*V600 mutant stage 3 unresectable or metastatic melanoma • Measurable disease by Response Evaluation Criteria In Solid Tumors (RECIST V1.1) • Eastern Cooperative Oncology Group (ECOG) performance status 0-2 • Minimum life expectancy 12 weeks • Adequate bone marrow, renal and liver function • Received no prior BRAF or MEK inhibitor therapy for metastatic disease • Willing and able to comply with the scheduled visits, treatment plans, laboratory tests, completion of QoL questionnaires and other trial procedures • Archival tumour tissue sample available
Summary of exclusion criteria	Main exclusion criteria: • Concomitant immunotherapy

	• Other invasive malignancies diagnosed within last year • Significant acute or chronic medical or psychiatric condition, disease or laboratory abnormality • Women who are pregnant, plan to become pregnant or are lactating • Other investigational anti-cancer drugs • Use of strong inducers and inhibitors of CYP3A or CYP2C8
Investigational medicinal product and dosage (Standard, Continuous arm)	Dabrafenib 150mg twice daily 12 hours apart, on days 1 – 28 of a 28 day cycle. Trametinib 2mg once daily, on days 1 – 28 of a 28 day cycle
Investigational medicinal product and dosage (Experimental, Intermittent arm)	Dabrafenib 150mg twice daily 12 hours apart, on days 1 – 21 of a 28 day cycle. Trametinib 2mg once daily, on days 1 – 14 of a 28 day cycle
Route(s) of administration	Both drugs are administered orally
Maximum duration of treatment of a patient	Treatment will continue until disease progression or beyond, at the investigator's discretion
Procedures: Screening & enrolment	Assessments for all inclusion and exclusion criteria will be performed within 28 days prior to randomisation. The key assessments are: • Written informed consent • Computerised tomography (CT) scan head/chest/abdomen/pelvis • Medical review • ECOG & Karnofsky performance status • Physical Examination & Blood Pressure • Haematology/biochemistry • Electrocardiogram (ECG) • Echocardiogram (ECHO) • Baseline skin record • QoL Questionnaires • Women of Child Bearing Potential (WCBP): Pregnancy Test as per local practise • Confirmation of archival tumour sample availability
Procedures prior to randomisation	• Confirmation that the patient satisfies all the eligibility criteria
Treatment period procedures	The key assessments are: • Clinical assessment and physical examination at 2,4,6 and 8 weeks, then every cycle until disease progression • CT scan chest/abdomen/pelvis +/- head at 6 weeks, then every 8 calendar weeks until disease progression • ECOG & Karnofsky performance status

	• Haematology/biochemistry • Adverse event documentation • QoL questionnaires at 4 weeks, then every calendar 12 weeks until end of the trial
End of Trial	End of trial for regulatory purposes is defined as 9 months from the date of randomisation of the last patient. Follow-up for survival will be a minimum of 9 months, maximum of 5 years from date of randomisation of last patient, as survival beyond this point is unlikely.
Procedures for safety monitoring during trial	The Trial Management Group (TMG) and Independent Safety Data Monitoring Committee (ISDMC) will regularly review the patient safety data. Pharmacovigilance will be performed by the co-ordinating centre.
Criteria for withdrawal of protocol treatment	A patient may withdraw, or be withdrawn, from trial treatment for the following reasons: • Progression whilst on therapy • Unacceptable toxicity • Intercurrent illness which prevents further treatment • Patient choice • Any alterations in the patient's condition which justifies the discontinuation of treatment in the investigator's opinion. • No further clinical benefit expected • Patient misses more than 28 consecutive days of planned treatment Following withdrawal of protocol treatment, patients will be followed up according to the protocol visit schedules.

4.1 Trial Flow Chart



5 Introduction

5.1 Background

Melanoma is the most lethal form of skin cancer: over 13,000 patients are diagnosed in the United Kingdom (UK) annually. Although the majority of patients are diagnosed with primary tumours that can be removed by surgery, around 20% will relapse. Recent developments in non-surgical treatments for metastatic melanoma have extended median survival from around 8 months to 2 years. Even so, for the majority of patients with advanced melanoma, this remains a terminal diagnosis: 5 year survival in 2011 was 16%. (http://www.cancerresearchuk.org/aboutcancer/type/melanoma/treatment/melanoma-statistics-and-outlook).

There are two classes of drugs now established to treat metastatic melanoma: immune checkpoint inhibitors and, for the 45% of patients whose tumours harbour a *BRAF*V600 gene mutation, mitogen activated protein (MAP) kinase pathway targeted small molecule inhibitors. In 2011, vemurafenib became the first BRAF kinase inhibitor approved for treatment of *BRAF* mutant metastatic melanoma, offering significant improvement in progression-free survival (PFS) and overall survival (OS) compared with standard chemotherapy (BRIM-3 trial[1]: median PFS 5.8 months, median OS 13.2 months). Although remarkably high response rates are achieved with vemurafenib and another BRAF inhibitor, dabrafenib[2], longer term experience suggested that most patients will suffer disease progression within 6-8 months of treatment due to emerging secondary resistance.

Several resistance mechanisms have now been described, most of which result in re-activation of intracellular signalling activity through MEK, downstream of BRAF[3]. Combined BRAF and MEK inhibition has been shown to be an effective strategy in the clinic, extending PFS and OS of treated metastatic melanoma patients compared with BRAF inhibitor alone[4–6]. Two BRAF and MEK combination regimens have been licensed for use to date: dabrafenib plus trametinib (dab+tram) and vemurafenib plus cobimetinib. Dab+tram received positive National Institute for Health and Care Excellence (NICE) guidance in June 2016 and is routinely available to treat patients with *BRAF* mutant advanced melanoma across the UK. Preliminary results of a trial comparing a third combination regimen, encorafenib plus binimetinib, with vemurafenib monotherapy reported improved OS in September 2016. Licensing of this regimen is predicted for 2018. BRAF+MEK inhibitor combination therapy has now largely replaced BRAF inhibitor monotherapy as standard of care worldwide.

Despite these combination regimens improving patient outcomes, key challenges remain. Firstly, secondary resistance to therapy limits duration of benefit in most patients: median PFS with BRAF+MEK inhibitor combinations is around 12 months[4–6]. The need for effective strategies to overcome or delay the emergence of resistance has been highlighted in several international fora as a major research priority.

Secondly, chronic toxicity associated with continuous daily dosing of oral molecular targeted agents is a recognised problem affecting patient compliance with treatment and requires active management[7]. The main toxicities of concern affect the skin, with rash and/or hyperkeratosis occurring in up to 40% of treated patients. Photosensitivity appears to be drug-specific and while almost universal in patients receiving vemurafenib, occurs in around 10% of patients receiving dab+tram. Interestingly, premalignant lesions and squamous cell skin cancers can occur in around 30% patients receiving BRAF inhibitor monotherapy, but the incidence reported with dab+tram is less than 5%, suggesting that addition of the MEK inhibitor attenuates BRAF-driven

hyperproliferation of normal skin. Although not usually life-threatening, these chronic skin adverse events mean that close patient monitoring is required and suspicious lesions need to be removed promptly.

Other common side effects affecting patient quality of life (QoL) include fatigue and diarrhoea. Less common events include choreoretinopathy, hypertension and left ventricular failure. Unique to dab+tram is a syndrome of intermittent fevers and chills affecting over half of treated patients, often most prevalent at the onset on treatment. These symptoms occur most often in the absence of infection, although myelosuppression has been reported rarely. Even so, in a cancer population, hospitalisation and treatment for non-neutropenic sepsis is not uncommon. Toxicity is particularly concerning in older patients, who make up an increasing proportion of cancer sufferers in keeping with an ageing population. A large scale, multi-centre Expanded Access Study (EAS) of vemurafenib demonstrated a higher frequency of grade 3 and 4 adverse events in patients aged 75 years and over (59% had grade 3 events vs 43% of under 75 years)[8].

The final key challenge is that BRAF+MEK inhibitors are high cost drugs and their prescription and toxicity management contribute to the rising overall health service expenditure.

Clinical experience shows that intermittent dosing can successfully manage drug-induced toxicity and sustain patients on BRAF targeted treatment. In the BRIM-3 trial[1], 38% of patients required modification and/or interruption of vemurafenib treatment. In the EAS, the proportion was even higher at 58%, but even so, outcomes in terms of PFS and OS were consistent with BRIM-3, suggesting that these changes in dosing do not compromise efficacy[1,9]. Therefore, pre-planned intermittent dosing of oral BRAF targeted agents may be an important way of sustaining patients on treatment for longer. Furthermore, intermittent drug dosing may delay the onset of disease progression, since continuous dosing promotes clonal expansion of drug resistant cells[3]. In a mouse model, vemurafenib resistant tumour cells were shown to become drug-dependent[10]. Resistant cells suffered a fitness deficit in the absence of drug suggesting that intermittent dosing can delay or prevent the emergence of resistant tumour clones. Mice survived twice as long (200 days compared with 100 days) on an intermittent dosing schedule of vemurafenib (4 weeks on 2 weeks off) compared with continuous daily dosing. Clinical case reports also suggest that interrupted dosing of BRAF inhibitors can reverse resistance to the drugs[11] and improve tolerability[9]. Intermittent dosing can attenuate relief of upstream feedback within the MAPkinase pathway, a mechanism known to contribute to drug resistance[12].

In summary, both preclinical and clinical data suggest that intermittent dosing could serve to eliminate the fitness advantage of resistant cells exposed to MAPkinase inhibitors, delay onset of disease progression and improve tolerability. These outcome benefits might be achieved with a reduction in health care costs. The intermittent dosing concept has never been formally tested in humans, but is the rationale for the INTERIM randomised trial.

5.2 Choice of regimen and intermittent dosing schedule

The INTERIM trial is designed to test intermittent scheduling of optimal MAPkinase therapy in a BRAF mutant advanced melanoma population. Dab+tram is a routinely available BRAF+MEK inhibitor combination therapy accepted as the international

standard of care for these patients. Therefore, standard continuous administration of dab+tram will be compared with an intermittent dosing schedule of these two drugs.

The choice of the intermittent dosing schedule has taken into account both pharmacokinetic and pharmacodynamic considerations as well as acceptability to patients and physicians. Dabrafenib has a 5.2 hour half life, but generates several active metabolites which persist, while trametinib has a mean terminal half life of 5.3 days (Trametinib Summary of Product Characteristics [SmPC]). Taken together, the preclinical data suggest that a minimum of 1 week break from BRAF inhibitor and 2 weeks break from MEK inhibitor is required to relieve inhibition of the MAPkinase pathway. The only published preclinical model of intermittent dosing is with vemurafenib: 4 weeks on 2 weeks off. Based on extensive experience using these targeted agents in the clinic as well as direct patient feedback, a 4 weekly intermittent dosing cycle has been designed for testing against standard of care:

Continuous vs Intermittend Dosing cycles of Dabrafenib and Trametinib

	Standard Arm (continuous)	Experimental Arm (intermittent)
Dabrafenib	150mg bid, d1-28	150mg bid, d1-21
Trametinib	2mg od, d1-28	2mg od, d1-14

The intermittent dosing regimen aims to (1) be acceptable to patients and clinicians, (2) improve treatment tolerance, and (3) potentially overcome drug resistance thereby enhancing efficacy.

6 Rationale for the INTERIM Trial

A strong scientific rationale argues for intermittent dosing of MAPkinase inhibitors. However, the concept of administering less rather than more treatment may be challenging in practice. A survey of metastatic melanoma patients receiving BRAF targeted agents identified that despite experiencing toxicity, most patients were either undecided or reluctant to consider interrupting their treatment either for 1 or 2 weeks (P Corrie, unpublished data). This feasibility trial aims to determine if intermittent dosing is deliverable, based on patient and professional willingness to take part in a randomised trial evaluating less than standard durations of treatment.

The trial will evaluate treatment compliance, PFS and QoL, to inform whether a subsequent definitive trial is justified and how it should be designed. The trial will incorporate detailed clinician and patient (using patient reported outcome measures) evaluation of frequently occurring and problematic skin toxicities and will address the cost-effectiveness of an intermittent dosing regimen. In addition, tissue and blood samples will be collected to demonstrate proof of principle as well as to explore the role of circulating tumour DNA (ctDNA) as a non-invasive predictive biomarker in *BRAF* mutant melanoma.

7 Trial Design

7.1 Statement of design

INTERIM is a multi-centre, open label, two-arm, randomised phase II feasibility trial aimed at investigating the role of intermittent dosing of the combination BRAF and MEK inhibitor regimen, dab+tram.

7.2 Number of Centres

Approximately 20 UK sites will participate. INTERIM is centrally co-ordinated at the Cambridge Clinical Trials Unit – Cancer Theme (CCTU-CT).

7.3 Number of Patients

150 patients will be randomised 1:1.

7.4 Patients Trial duration

The time from consent to randomisation is up to 28 days. The duration of treatment is until disease progression or beyond, at the investigator's discretion. A minimum of 9 months follow-up from the date of randomisation is required for all surviving patients.

7.5 Trial objectives

7.5.1 Primary Objectives

- To assess recruitment rate and treatment compliance of the intermittent dosing schedule as a measure of acceptance of intermittent dosing to patients and physicians
- To evaluate the impact on overall QoL with intermittent dosing using European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30
- To estimate the size of clinical efficacy of intermittent dosing compared to continuous dosing, measured by PFS

7.5.2 Secondary Objectives

- To evaluate safety, objective response rate, time to treatment failure and overall survival
- To evaluate skin toxicity as assessed by clinicians and patients using patient reported outcome measures (PROMS) (Skindex-16 and patient-reported outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE))
- To assess factors which influence patients' decision to enter/decline entering the trial
- To evaluate patient experience of participation in this trial (using mixed methods)
- To determine the QoL and cost-effectiveness of intermittent dosing compared with standard continuous dosing

7.5.3 Exploratory Objectives

- To explore emergence of resistance by means of ctDNA collected from patients during the course of their treatment
- To determine the role of ctDNA as a useful biomarker for therapeutic monitoring
- In a subset of patients (up to 20), explore pharmacokinetics of standard versus intermittent dosing schedules

7.6 Trial Endpoints

7.6.1 Primary Endpoints

- **Recruitment rate** for endpoint analysis will be assessed once the trial has been recruiting for 15 months, or when 15 sites have been open for 6 months, whichever is sooner. It will be measured as the average number of patients recruited per site per 2 months

- **Treatment compliance** is defined as the percentage of patients completing the allocated treatment at 6 months from the date of randomisation. Although the primary aim is to assess the compliance of the intermittent dosing schedule, compliance of the standard continuous dosing schedule will also be assessed and compared with the experimental arm in an exploratory manner

- **Overall QoL** is defined as the global health status score derived from the standard EORTC QLQ-C30 questionnaire at 6 months from date of randomisation

- **PFS** is calculated as the duration from date of randomisation to the date of first progression or death from any cause, whichever occurs first. Progression is assessed according to standard Response Evaluation Criteria In Solid Tumours (RECIST v1.1 – appendix 1)

7.6.2 Secondary Endpoints

- **Safety** is assessed using the standard cancer National Cancer institute (NCI) CTCAE v4.03 criteria

- **Objective Response Rate** is assessed according to RECIST v1.1 (Appendix 1)

Time to treatment failure is the time from starting drug treatment with dabrafenib+trametinib on day 1 of cycle 1 until the date of day 1 of the last cycle +28 days;

- **Overall survival** is calculated as the duration from the date of randomisation to the date of death from any cause

- **Patient reported outcomes** focussing on skin toxicity evaluation is assessed using skin-specific patient reported outcome measures (PROM) – the Skindex-16 and NCI PRO-CTCAE

- **Patient experience** is assessed by a) patient experience survey of patients in each arm of the trial and b) semi-structured interviews in a subset of patients who have volunteered

- **QoL & Health Economic Evaluation:** the EORTC QLQ-C30 and EQ5D generic measure of health status will be used for the cost-effectiveness analysis.

7.6.3 Exploratory Endoints

Using blood and tumour tissue collected from recruited patients, we will explore:

- the kinetics of *BRAF* mutation load in each arm of the trial

- emerging genetic changes associated with acquired resistance and whether these differ with intermittent therapy
- the pharmacokinetics of intermittent drug scheduling

8 Selection and withdrawal of patients

8.1 Inclusion Criteria

- Signed informed consent for the INTERIM trial
- Aged ≥ 18 years old
- Histologically or cytologically confirmed *BRAF*V600 mutant stage 3 unresectable or metastatic melanoma
- Radiologically and/or clinically measurable disease, by RECIST version 1.1; baseline tumour assessments and measurements must be done within 28 days prior to randomisation
- Eastern Cooperative Oncology Group (ECOG) performance status 0-2
- Predicted life expectancy >12 weeks
- Adequate bone marrow function
    - Absolute neutrophil count (ANC) ≥1.2 x 10^9 /L
    - Haemoglobin (Hb) ≥ 90 g/L
    - Platelets ≥75 x 10^9 /L
    - White blood cell count (WBC) ≥ 2 x 10^9 /L
- Adequate liver function
    - Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≤3 x upper limit of normal range (ULN)
    - Total bilirubin <1.5 x ULN (except if the patient has Gilbert Syndrome or liver metastases, in which case the bilirubin must be <3 x ULN)
- Adequate renal function defined as a serum creatinine ≤1.5 x ULN or calculated creatinine clearance by Cockcroft-Gault of ≥40 mL/min
- Received no prior BRAF or MEK inhibitors for metastatic disease (Prior adjuvant therapy is allowed)
- Plan to start dabrafenib + trametinib treatment
- If radiotherapy has previously been given; there is measurable disease which has not been irradiated
- Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, completion of QoL questionnaires and other procedures described in the protocol
- Confirmation of archival tumour tissue sample available
- Women of child-bearing potential (WCBP) and all sexually active male patients must agree to use effective contraception methods throughout treatment as per section 10.8 of this protocol

8.2 Exclusion Criteria

The presence of any of the following will exclude patients:

- Concomitant immunotherapy being administered to treat advanced melanoma
- Other invasive malignancies diagnosed within the last year which are not in complete remission, or for which additional therapy is required
- Significant acute or chronic medical or psychiatric condition, disease or laboratory abnormality which in the judgment of the investigator would place the patient at undue risk or interfere with the trial. Examples include, but are not limited to:
    - Patients with uncontrolled ischaemic heart or other cardiovascular event (myocardial infarction (MI), new angina, stroke transient ischaemic attack (TIA), or new congestive cardiac failure (CCF)) within the last 6 months
    - Patients with stable but significant cardiovascular disease defined by heart failure (New York Heart Association Functional Classification (NYHF) III or IV, see Appendix 3) or frequent angina. Patients with baseline QTC interval $\geq$ 480 msec.
    - Presence of active infection
    - Cirrhotic liver disease, known chronic active or acute hepatitis B, or hepatitis C
    - Known allergy or hypersensitivity to dabrafenib or trametinib, or their excipients
- Women who are pregnant, plan to become pregnant or are lactating during the trial period
- Other investigational anti-cancer drugs
- Use of strong inducers and inhibitors of CYP3A or CYP2C8

8.3 Patient consent

Patients will be approached to consent to participate in this trial. Individuals who consent to the trial will be requested to complete a Consent Process Patient Experience Survey. Individuals who decline to participate will be invited to complete a separate Patient Experience Survey for individuals who declined, to explore their reasons for declining.

Trial-specific screening activities will only be performed after patients have consented to trial participation and signed the informed consent form.

8.4 Screening Procedures and Pre-randomisation investigations

The assessments below must be performed within 28 days prior to randomisation.

- Patient must give written informed consent prior to any other trial-specific screening activities
- QoL questionnaires
- Medical history (including previous and current clinically important diseases and medications) and demographic data

- Physical examination, including assessment of weight and blood pressure
- Concomitant medication assessment
- Assessment of ECOG and Karnofsky performance status
- Confirmation of disease diagnosis, stage and *BRAF* mutation status
- Assessment of disease by Computerised tomography (CT) scan of head/chest/abdomen/pelvis, or Magnetic resonance imaging(MRI) if allergic to intravenous contrast and/or clinical measurements of visible/palpable disease; confirmation of measurable disease by RECIST version 1.1,
- Biochemistry: urea, sodium (Na) , potassium (K), gamma glutamyl transferase (GGT), serum ALT or serum AST, total bilirubin, albumin, total protein, serum creatinine and creatinine clearance, serum calcium, alkaline phosphatase (ALP), lactate dehydrogenase (LDH)
- Haematology: haemoglobin (Hb), WBC, differential ANC, platelets
- Electrocardigoram (ECG)
- Echocardiogram (ECHO) are standard safety monitoring of patients receiving dab+tram, not a research requirement – please refer to SmPC.
    - ECHO must be done as part of screening and left ventricular function confirmed to be ≥LLN prior to randomisation in patients with any significant cardiac history including:
        - current hypertension defined as systolic BP > 140mm Hg or diastolic BP > 90mm Hg, or
        - requirement for regular cardiac medication (other than aspirin or statin), or
        - abnormal ECG
    - ECHO is not required at screening prior to randomisation, but must be performed before the Cycle 1 day 15 clinic visit in patients who fulfil all of the criteria below:
        - no cardiac history
        - normotensive
        - normal ECG at screening
- Women of child bearing potential: Pregnancy test (as per local hospital procedures)
- Confirmation of the availability of archival tumour tissue
- Verify that patient satisfies all protocol eligibility criteria
- Baseline skin record completed (includes clinician record of skin assessment and baseline patient-reported PRO-CTCAE record)
- Adverse Event (AE) assessment (recorded from the point of consent
- Consent process Patient Experience Survey

The above screening procedures are summarised, together with the other procedures and assessments required throughout the trial, in Section 10.2 and the Schedule of Assessments in Section 10.7.

8.5 Treatment Assignment and Randomisation Number

8.5.1 Method of randomisation

Eligible patients will be randomly assigned to either the standard continuous arm (dabrafenib 150mg bid d1-28, trametinib 2mg od d1-28) or the experimental intermittent arm (dabrafenib 150mg bid d1-21, trametinib 2mg od d1-14) in a 1:1 ratio using the minimisation with random element method. Stratification factors are:

- ECOG performance status
- Disease stage (IIIc/IVM1a/IVM1b/IVM1c)
- Presence or absence of brain metastases
- LDH ($\leq$ULN; >ULN and $\leq$2 X ULN; >2 X ULN)

8.5.2 Procedure of randomisation

A web-based central randomisation system supplied by Sealed Envelope will allocate patient randomisation numbers sequentially in the order in which the patients are enrolled. At the site initiation, the trial coordinator will arrange for the members of the trial team to be provided with a unique system username and password, which will allow them to access the central randomisation system.

Following confirmation of eligibility and completion of pre-randomisation QoL questioinnaires, patient eligibility details will be sent to the INTERIM trial office. Patient data will be entered on the central randomisation system by the INTERIM trial office. The following data will be required in order to randomise a patient:

- Confirmation that the patient satisfies all the eligibility criteria
- Patient's date of birth
- Patient's initials
- Disease stage
- ECOG PS
- Baseline LDH
- Presence of brain metastases (yes, no)
- Date of archival tumour sample

The treatment arm will be allocated and a unique trial number will be assigned by the randomisation system. Sites will receive email notification of randomisation details.

8.6 Patient withdrawal criteria

8.6.1 Withdrawal from Protocol Treatment

A patient may withdraw from trial treatment for the following reasons:

- Progression whilst on therapy
- Unacceptable toxicity
- Intercurrent illness which prevents further treatment
- Patient choice

- Any alterations in the patient's condition which justifies the discontinuation of treatment in the investigator's opinion
- No further clinical benefit expected
- Patient misses more than 28 consecutive days of planned treatment (see section 9.6.3)

With ongoing consent, patients should remain in the trial and be followed up according to the protocol visit schedules.

8.6.2 Withdrawal of consent

Patients may withdraw their consent to participate in the trial at any time. If the patient explicitly states their wish not to contribute further data to the trial, the investigator should inform the co-ordinating centre in writing and the withdrawal of consent should be documented by the investigator in the patient's case report form (CRF). However, data and samples collected up to the time of consent withdrawal will be included in the data reported for the trial.

9 Trial Treatments

9.1 General Principles

- Patients in both arms of the trial should begin their allocated treatments within 7 days from the date of randomisation.

- Safety assessments including haematology and biochemistry assessments are required prior to Day 1 treatment of each cycle for the first year and every other cycle thereafter. Safety assessments should also be performed, at the end of protocol treatment (30 days from the date of last protocol treatment dose administered); Details are provided in Section 10.2 and summarised in the Schedule of Assessments in Section 10.7.

- Dosage modifications are summarised in Section 9.6.

Specific details for the dabrafenib + trametinib regimen are given below. It is the responsibility of the investigator to ensure that recommendations in the UK SmPCs for administration of the dabrafenib and trametinib are followed. The SmPC is updated from time to time, up-to-date UK SmPCs are posted on the Medicine Guides Website http://www.medicines.org.uk.

9.2 Investigational Medicinal products

For the purpose of this trial, dabrafenib and trametinib are both considered as Investigational Medicinal Products (IMPs) conducted within a Clinical Trial Authorisation (CTA) under the Notification Scheme for Type A trials.

9.2.1 Legal status of the drugs and Risk Categorisation.

The current regulatory framework in the UK/EU allows for a range of risk-adapted approaches.

In this instance Dabrafenib and trametinib are both licensed for use in the UK for the treatment of BRAFV600 mutant stage 3 unresectable and metastatic melanoma.

Dabrafenib and trametinib are commercially available within the UK and are fully commissioned standard treatments for advanced melanoma.

The INTERIM trial is designed to test intermittent scheduling of optimal MAPkinase therapy in a BRAF mutant advanced melanoma population.

Clinical experience shows that intermittent dosing can successfully manage drug-induced toxicity and sustain patients on BRAF targeted treatment. Intermittent dosing can attenuate relief of upstream feedback within the MAPkinase pathway, a mechanism known to contribute to drug resistance.

Using the risk-categorisation method, this trial has been categorised as Type A.

For further details of composition of either IMP, refer to the current version of the manufacturer's Summary of Product Characteristics (SmPC) for the brand used, which can be accessed via the Electronic Medicines Compendium (eMC) website: http://www.medicines.org.uk/emc. A reference copy of both SmPCs can be found in the Investigator Site Files; please note however that these may not necessarily be the most up-to-date versions.

9.3 Treatment Summary

Patients will be randomised equally between the following arms and self administer both dabrafenib and trametinib.

9.3.1 Standard Arm: dabrafenib + trametinib standard arm (continuous schedule)

Dabrafenib taken orally 150mg twice daily 12 hours apart, on days 1 – 28 of a 28 day cycle
Trametinib taken orally 2mg once daily, on days 1 – 28 of a 28 day cycle

9.3.2 Experimental Arm: dabrafenib + trametinib experimental arm (intermittent schedule)

Dabrafenib taken orally 150mg twice daily 12 hours apart, on days 1 – 21 of a 28 day cycle
Trametinib taken orally 2mg once daily, on days 1 – 14 of a 28 day cycle

9.3.3 Duration of treatment

Patients will continue on allocated treatment as long as they benefit from the treatment and it is tolerable (see section 8.6.1 for full protocol treatment withdrawal criteria)

9.3.4 Drug administration

Dabrafenib
Dabrafenib capsules are to be swallowed whole with water. The capsules should not be chewed or opened and should not be mixed with food or liquids due to chemical instability of dabrafenib. Dabrafenib should be taken at least one hour before, or at least 2 hours after a meal.

It is recommended that the doses of dabrafenib are taken at **similar times every day**,

leaving an interval of approximately 12 hours between doses. When dabrafenib and trametinib are taken in combination, the once-daily dose of trametinib should be taken at the same time each day with either the morning dose or the evening dose of dabrafenib.

Trametinib
Trametinib should be taken orally with a full glass of water. Trametinib tablets should not be chewed or crushed. Trametinib should be taken without food, at least 1 hour before or 2 hours after a meal.

It is recommended that the dose of trametinib is taken at a **similar time every day**. When dabrafenib and trametinib are taken in combination, the once-daily dose of trametinib should be taken at the same time each day with either the morning dose or the evening dose of dabrafenib.

If a patient vomits after taking dabrafenib or trametinib, the patient should not retake the dose. The next scheduled dose should be taken at the normal time.

For further details of administration of either IMP, refer to the current version of the manufacturer's Summary of Product Characteristics (SmPC) for the brand used, which can be accessed via the Electronic Medicines Compendium (eMC) website: http://www.medicines.org.uk/emc.

9.4 Drug storage, supply and accountability

9.4.1 Supply

Both Dabrafenib and Trametinib are used within their licensed indication and general 'off the shelf' supplies will be used. There is no requirement to ring-fence 'off the shelf' supplies of dabrafenib and Trametinib for the INTERIM trial. Both IMPs will be handled in line with manufacturer's recommendations. For further details, refer to the current version of the manufacturer's SmPC for the brand used.

9.4.2 Labelling (Type A)

Under the Article 14 of Directive 2001/20/EC allows for adaptable provisions relating to labelling when the product does not require particular manufacturing or packaging processes and has a marketing authorisation.

Dabrafenib and Trametinib will be used in accordance with the conditions set out in Regulation 46 (2) of the Medicines for Human Use (Clinical Trials) Regulations 2004 (and amended in 2006). As both IMPs will be used within their licensed indication and under Type A categorisation, no special trial labelling requirements apply and both dabrafenib and trametinib may be labelled in accordance with the requirements of Schedule 5 to the Medicines for Human Use (Marketing Authorisation etc.) Regulations 1994.

9.4.3 Storage, Formulation and Preparation

Dabrafenib and Trametinib formulation, storage, and preparation are in line with the manufacturers' recommendations. For further details, refer to the current version of the relevant manufacturer's SmPC (via http://www.medicines.org.uk/emc) for the brand used.

9.4.1 Use of 3rd Party Supply and Delivery of IMP

IMP supply and/or delivery to a participant or their home by 3rd party home community pharmacy or healthcare companies is permitted if this is in accordance with routine NHS practice at the participating trial site. The trial does not require any additional actions beyond existing standard care practices. CCTU should be informed during the site set-up process, or if this is adopted during the life of the study.

9.4.2 Accountability and Patient compliance (patient diaries)

In this trial patient diaries and case report forms (CRF) will be used to capture information of IMPs dispensed/used.

The sites will not require to keep detailed accountability records of batch numbers and expiry dates of the IMPs dispensed.IMPs dispensed will be commercially available and may also be dispensed by a third party other then the trial site.

Participating patients will be provided with a patient diary to keep detailed record of all dabrafenib capsules and trametinib tablets taken by the patient during the trial.
Study-site personnel will review dosing information with the patient (or legally authorised representative) on scheduled clinic visit days, providing instructions regarding dose, dose frequency and the number of tablets/capsules to be taken for each dose. Patients (or legally authorised representative) will be instructed to return all unused tablets/capsules and containers (empty, partially used, and/or unopened) for compliance check at the next scheduled clinic visits.
A compliance check and tablet/capsule count will be performed by study personnel during clinic visits. Study site personnel will record compliance information on the case report form (CRF).

9.5 Known drug reactions & interaction with other therapies

For known drug reactions please refer to the current UK SmPCs for dabrafenib and trametinib. The SmPC is updated from time to time. Up to date UK SmPCs are posted on the Medicines Guide Website: http://www.medicines.org.uk.

9.6 Dosage modifications

9.6.1 Dose level reduction guidelines

Dose level	Dabrafenib	Trametinib
Starting dose	150mg bid	2mg od
1st dose reduction	100mg bid	1.5mg od
2nd dose reduction	75 mg bid	1mg od
3rd dose reduction	50mg bid	1mg od

9.6.2 Missed doses

If a dose of dabrafenib is missed at the normal time, it should not be taken if it is less than 6 hours until the next dose.

If a dose of trametinib is missed at the normal time, only take the dose of trametinib if it is more than 12 hours until the next scheduled dose.

If treatment is interrupted within a cycle for whatever reason, please keep to the planned 28 day cycle visit (see section 10 for further details).

9.6.3 Maximum permitted dose delay

The maximum permitted dose delay for omitting both dabrafenib and trametinib when scheduled for administration in order to allow recovery from severe toxicity or unscheduled procedures (eg. appendectomy) is 28 days from day 29 of the cycle in which the dose is interrupted. If longer delays are required then the patient will be discontinued from the trial treatment.

It is permitted for the patient to remain on trial if only one of the two drugs is either stopped temporarily for any amount of time or permanently due to toxicity.

9.6.4 Specific dose modifications

Dose modifications or interruptions are not required for adverse reactions of actinic keratoses, keratoacanthoma, cutenous squamous cell carcinoma, or new primary cutaneous melanoma.

In general, dose modifications (dose interruption, reduction, discontinuation) should be made to both drugs simultaneously, unless otherwise specified in Section 9.6.5 below.

Grade CTCAE	Dose Modification
1-2 (tolerable)	Continue treatment and monitor as clinically indicated
2 (intolerable) or 3	Interrupt treatment until toxicity is $\leq$ grade 1, then resume treatment at a reduced dose level
4	Interrupt treatment until toxicity is $\leq$ grade 1, then resume treatment at a reduced dose level, or discontinue permanently

When an adverse event has been actively managed, dose re-escalation following the same dosing steps as for de-escalation is allowed.

9.6.5 Dose modifications specific to one of the two drugs

9.6.5.1 Pyrexia

Dabrafenib therapy should be interrupted if the patient's temperature is $\geq$ 38.5^{o}C. Trametinib should be continued at the same dose. Patients should be evaluated for signs and symptoms of infection, including performing a Full blood count (FBC).

Treatment for pyrexia should include use of antipyretics such as ibuprofen or acetaminophen/paracetamol. Use of oral corticosteroids should be considered when anti-pyretics are insufficient.

If FBC is normal and there is no evidence of infection, restart dabrafenib treatment either at the same dose or reduced by one dose level if pyrexia is recurrent and/or is accompanied by other severe symptoms such as dehydration, hypotension or renal failure.

9.6.5.2 Uveitis

Dose modifications are not required for uveitis as long as effective local therapies can control ocular inflammation. If uveitis is not controlled by local therapy, withhold dabrafenib until resolution, then restart dabrafenib reduced by one dose level. No dose modification of trametinib is required.

9.6.5.3 Left ventricular ejection fraction (LVEF) reduction

In the event of an absolute decrease of >10% in LVEF, withhold trametinib. No dose modification of dabrafenib is required. If the LVEF recovers, treatment with trametinib may be restarted at a dose reduced by one dose level with careful monitoring. Grade 3 or 4 left ventricular cardiac dysfunction or if LVEF does not recover, trametinib should be permanently discontinued.

9.6.5.4 Retinal vein occlusion (RVO) or retinal pigment epithelial detachment (RPED)

New visual disturbance such as diminished central vision, blurred vision or loss of vision at any time requires interruption of trametinib and prompt ophthalmological assessment. No modification of dabrafenib is required. Retinal vein occlusion warrants permanent discontinuation of trametinib. For RPED, the following trametinib dose modification table must be used:

Grade 1 RPED	Continue treatment with retinal evaluation monthly until resolution. If RPED worsens follow instructions below and withhold trametinib for up to 3 weeks.
Grade 2-3 RPED	Withhold trametinib for up to 3 weeks
Grade 2-3 RPED improving to grade 0-1 within 3 weeks	Resume trametinib at a lower dose (reduced by 0.5 mg) or discontinue trametinib in patients taking trametinib 1 mg daily
Grade 2-3 RPED that does not improve to at least grade 1 within 3 weeks	Permanently discontinue trametinib

9.6.5.5 Interstitial lung disease/pneumonitis

Patients developing new or progressive pulmonary symptoms and findings such as cough, dyspnoea, hypoxia, pleural effusion, pulmonary infiltrates which cannot be explained by malignancy should have their trametinib stopped. No dose modification of dabrafenib is required. Diagnosis of pneumonitis requires permanent discontinuation of trametinib.

9.7 Additional treatment

Patients should receive full supportive care during and after the administration of dab+tram. Over the course of this trial, additional medications may be required to manage aspects of the disease state of the patients, including side effects from anticancer drugs or disease progression. Please refer to toxicity management guidelines supplied by Welsh & Corrie[7]. A copy of this reference publication will be supplied to all trial sites for ease of reference. Details of the concomitant medication given, including blood and blood products, must be recorded in the patient's medical records and the CRF.

Supportive care, including but not limited to anti-pyretics, corticosteroids, anti-emetic and anti-diarrhhoeal medications, may be administered at the discretion of the investigator, as medically indicated. Choice of agents should be according to local

practice. All non-cancer treatments that the responsible physician feels are appropriate are allowed.

Palliative radiotherapy, surgery, transfusion with blood products and bisphosphonates are all allowed.

9.8 Treatment for Disease Progression

Treatment for disease progression is based on the investigator's discretion and local practice. Patients deriving clinical benefit may continue on their allocated regimen at the investigator's discretion.

Patients with RECIST disease progression and disease amenable to surgical resection can undergo surgical resection of progressing disease and may continue to receive dabrafenib + trametinib as per their allocated arm after surgical resection for as long as they continue to derive benefit, based on patient and physician assessment. The first RECIST progression date will be used for measuring PFS in this trial.

All anti-cancer interventions will be recorded on trial CRFs during the on-treatment and follow-up periods.

9.9 Co-enrolment guidelines

Patients who have not reached inoperable disease progression may not enrol in any other clinical protocol or investigational treatment trial while enrolled in this study unless observational in nature.

10 Procedures and assessments

Clinical Assessments

Patients will be clinically assessed every 2 weeks during the initial 2 cycles, then prior to the beginning of every cycle until inoperable disease progression, then 3-monthly for a minimum of 9 months follow-up from their randomisation date. Patients remaining on treatment beyond 52 weeks may have their treatment visits and drug prescriptions extended to 8 weekly.

Drug should be prescribed and dispensed on the day of the clinic visit, as per schedule of assessments (Section 10.7). A treatment cycle starts with the morning dose, therefore a clinic visit associated with the start of a new cycle may occur up to 2 days prior to day 1 of a treatment cycle.

If a clinic visit is missed for medical reasons (for example, due to a hospital admission), drugs can be restarted between visits as appropriate according to where the patient is on their defined schedule and they should return to clinic at the next preplanned visit.

If the beginning of a cycle is delayed the date when a patient is ready to restart treatment becomes the first day of the cycle and therefore clinical visits should be amended in line with the new cycle pattern ie up to 2 days prior to the start of the new cycle. Please note that imaging for disease measurement must remain on the 8-weekly calendar dates set on cycle 1 day 1.

Scheduled safety assessments described in section 10.7 will be undertaken at scheduled clinic visits.

Imaging Assessments
Tumour imaging assessments at baseline should be performed no more than 28 days prior to the date of randomisation. After starting treatment the first scan will be at 6 weeks and then every 8 calendar weeks (±7 days), until inoperable disease progression. Patients continuing their treatment/follow-up prior to disease progression beyond 52 calendar weeks can have their scanning frequency reduced to every 12 calendar weeks. The same imaging modality as the baseline scans for a patient should be used throughout the trial.

At baseline, imaging must include the brain by either CT or MRI modality. Cutaneous lesions can be included for measurable disease if photographed with a ruler depicting clearly the size of target lesion(s). The same method will be used to assess response of the cutaneous lesions identified at baseline throughout the trial, that is, two tumour assessments (one for each method) will be performed at each planned assessment time if the ruler method is used.

For patients with brain metastases at baseline, reassessment of measurable disease must include brain imaging with the same modality as at baseline. For patients with no evidence of brain metastases at baseline, regular imaging of the brain is recommended, but investigators should follow local guidance. It is recommended that the brain be imaged at least every 16 calendar weeks.

Summary information on timing of interventions, procedures and assessments are given in the Schedule of Assessment in Section 10.7. Details are listed below.

10.1 Screening evaluation, pre-randomisation and randomisation procedures

See section 8.4 and 8.5.

10.2 Trial assessments

10.2.1 Timing of assessments

For safety reasons, patients will attend clinic every 2 weeks in the first 8 weeks. A window of +/- 2 days is allowed for clinic visits and associated assessments to ensure a treatment cycle starts with the morning dose, to account for bank holidays and other unforeseen circumstances.

For safety reasons, the first reassessment for measurable disease will be done at cycle 2 d8 – d15 (week 6) (the scan(s) can be planned for any time within an 8 day window). In order to ensure all scans are undertaken for when patients on either arm of the trial are taking tablets, subsequent scans will be every 8 calendar weeks (±7 days) thereafter ie. weeks 14, 22, 30 etc.

The 'Treatment Patient experience survey' should be completed 9 months after randomisation within the trial. A subset of patients who volunteered, will be invited to take part in a semi structured interview at a later date.

10.2.2 Cycles 1 and 2, Day 1 and Day 15

The following assessments are to be performed during cycles 1 and 2 on days 1 (prior to drug treatment) and 15:

- Concomitant medication assessment
- Drug compliance assessment
- Adverse event (AE) assessment
- For those patients experiencing skin AEs, additional skin toxicity questionnaires to be completed by the patient and clinician
- ECOG and Karnofsky performance status
- Physical examination, Weight & Blood Pressure
- Haematology (WBC, differential ANC, Platelets, Hb)- Cycle 1, day 1 may be omitted if screening haematology is done within 2 weeks.
- Biochemistry (Urea, Na, K, GGT, ALT or AST, Total Bilirubin, Albumin, Total Protein, Serum Creatinine, Creatinine Clearance, Serum Calcium, ALP, LDH) Cycle 1, day 1 may be omitted if screening biochemistry is done within 2 weeks.
- CT/MRI scans for reassessment of measureable disease using RECIST version 1.1 **(Cycle 2 Between days 8-15 only)**
- QoL questionnaires **(Cycle 2 day 1 only)**
- ECHO (any time during **Cycle 2 only**)
- Prescription and dispensing of treatment (Day 1 only)
- Research blood sample (baseline sample must be taken before starting drug treatment)
- Pharmacokinetic research blood sampling (subset of patients only) on cycle 1 day 1, cycle 2 day 15– see Section 13 for details

10.2.3 Cycles 3 and all subsequent cycles

The following assessments are to be performed on day 1 of all cycles after cycle 2*: (prior to drug treatment).

- Concomitant medication assessment
- Drug compliance assessment
- AE assessment
- For patients experiencing skin AEs, additional skin toxicity questionnaires to be completed by the patient and clinician
- ECOG and Karnofsky performance status
- Physical Examination, Weight & Blood Pressure
- Haematology (WBC, differential ANC, Platelets, Hb)
- Biochemistry (Urea, Na, K, GGT, ALT or AST, Total Bilirubin, Albumin, Total Protein, Serum Creatinine, Creatinine Clearance, Serum Calcium, ALP, LDH)
- QoL questionnaires (every 12 calendar weeks)
- CT/MRI for reassessment of measureable disease using RECIST version 1.1 (every 8 calendar weeks ie. week 14, 22, 30 etc). Patients continuing treatment beyond 52 weeks can have their scanning frequency reduced to 12 weekly.
- ECHO (during cycle 5 and subsequently every 3 cycles ie. cycle 5, cycle 8, cycle 11 etc. while on treatment)
- Prescription and dispensing of treatment
- Research blood sample, cycle 3, cycle 4 and every other cycle ie. cycles 6, 8, 10 etc while on treatment
- Pharmacokinetic research blood sampling (subset of patients only) – see Section 13 for timepoints.

*If patients have been on treatment for more than 52 weeks, clinic visits can be every other cycle, with telephone follow-up to ensure patient review is at least every 4 weeks until progression.

10.2.4 End of Treatment visit

This visit can take place up to 30 days after treatment discontinuation.

- Concomitant medication assessment
- Compliance assessment
- AE assessment
- For patients experiencing skin AEs, additional skin toxicity questionnaires to be completed by the patient and clinician
- ECOG and Karnofsky performance status
- Physical Examination, Weight & Blood Pressure
- Haematology (WBC, differential ANC, Platelets, Hb)
- Biochemistry (Urea, Na, K, GGT, ALT or AST, Total Bilirubin, Albumin, Total Protein, Serum Creatinine, Creatinine Clearance, Serum Calcium, ALP, LDH)

10.3 Disease Progression

At the time of the protocol-defined disease progression (no more than 7 days after) and before further protocol treatment or any new treatment is initiated, the following assessments are required:

- Concomitant medication assessment
- Compliance assessment
- AE assessment
- ECOG and Karnofsky performance status
- Physical Examination, weight & Blood Pressure
- Haematology (WBC, differential ANC, Platelets, Hb)
- Biochemistry (Urea, Na, K, GGT, ALT or AST, Total Bilirubin, Albumin, Total Protein, Creatinine Clearance, Serum Creatinine, Serum Calcium, ALP, LDH)
- QoL questionnaires
- CT/MRI for reassessment of measureable disease using RECIST version 1.1
- Research blood sample
- Pharmacokinetic research blood sampling (subset of patients only) – see Section 13
- In patients undergoing surgical resection or biopsy of a progressing lesion, a tumour sample will be requested.

10.4 Follow-up if stopping treatment prior to disease progression

Patients will be followed-up every 4 weeks (±7 days) after stopping treatment* until disease progression, as follows:

- Physical examination, Weight & Blood Pressure
- Concomitant medication assessment
- ECOG and Karfnofsky performance status
- QoL questionnaires (every 12 calendar weeks only)
- CT/MRI for reassessment of measureable disease (every 8 calendar weeks)

*If patients have been on treatment/follow-up for more than 52 weeks prior to disease progression, follow-up visits can be every 8 weeks, with telephone follow-up to ensure patient review is at least every 4 weeks until progression, and repeat imaging can be reduced to 12 weekly.

10.5 Follow-up if stopping treatment at or beyond disease progression

Patients will be followed-up every three months (±7 days) after disease progression for a minimum of 9 months from randomisation. At every three month follow-up, the following assessments should be completed:

- Concomitant medication assessment
- ECOG and Karnofsky performance status
- Physical Examination, Weight & Blood Pressure
- QoL questionnaires

10.6 End of Trial Participation

A patient's participation in the trial will finish at the end of trial declaration (a minimum of 9 months from randomisation of the last patient). Following the end of the trial patients may remain on dabrafenib and trametinib if the treating physician believes it is in the patients' best interest to do so. Once the trial has closed, the choice of schedule and doses will be at the discretion of the treating physician.

10.7 Schedule of Assessments

	Screening Pre-randomisation	Cycle 1		Cycle 2		Cycle 3 onwards[1]	End of Treatment	4-weekly Follow-up (prior to progression)[1]	Disease Progression	3-Monthly Follow-up after progression
		Day 1	Day 15	Day 1	Day 15	Day 1				
	-28 days	±2 days					+ 30 days	±7 days	+7 days	±7 days
Inclusion/Exclusion Assessment	X									
Informed Consent	X									
Medical History[2]	X									
Pregnancy Test	X									
Physical Examination, weight & Blood pressure	X	X	X	X	X	X	X	X	X	X
Baseline Skin Record	X									
ECG[3]	X									
ECHO	X[4]			X		X[5]				
Concomitant medication assessment	X	X	X	X	X	X	X	X	X	X
Compliance Assessment		X	X	X	X	X	X		X	
AE assessment	X	X	X	X	X	X	X		X	
Skin Toxicity Questionnaire[6] (Patient and Clinician)		X	X	X	X	X	X			
ECOG and Karnofsky Performance Status	X	X	X	X	X	X	X	X	X	X
Haematology[7] & Biochemistry[8]	X	X	X	X	X	X	X		X	
RECISTv1.1 Disease measurement[9]	X[10]				X[11]	Every 8 weeks (±7 days) until protocol defined disease progression[11]			X	
Prescription & Dispensing[12]		X		X		X				
Treatment w/ dab+tram – Std arm		dab + tram D1-28								
Treatment w/ dab+tram – Exp arm		dab D1-21 + tram D1-14								
QoL Questionnaires	X			X		Every 12 weeks[13]			X	X
Research blood sample		X	X	X	X	X Cycle 4, day 1 and then every other cycle			X	
PK sampling[14]		X			X	X Cycle 4, day 1 and then every other cycle			X	
Tumour tissue[15]	X								X	
Patient Experience Survey	X[16]					9 months after randomisation[17]				
Patient Experience Interview						X				

1) If patients have been on treatment, or progression-free follow-up, for more than 52 weeks, clinic visits can be every other cycle, with telephone follow-up to ensure patient review is at least every cycle until progression
2) To include confirmation of disease diagnosis, stage and BRAF mutation status
3) Then as clinically indicated
4) Screening ECHO to be done prior to randomisation in patients with a cardiac history including current hypertension defined as systolic BP > 140mm Hg or diastolic BP > 90mm Hg, or requirement for regular cardiac medication (other than aspirin or statin), or an abnormal ECG. In patients without a cardiac history who are normotensive with a normal ECG, the baseline ECHO should be done prior to Cycle 1 day 15 and is not mandated prior to randomisation.
5) ECHOs are recommended to be repeated during cycle 5 and every 12 weeks thereafter whilst on treatment (ie. during cycles 8, 11, 14 etc.) as per SmPC guidance. The LVEF should be within normal limits to commence/continue treatment.
6) If Skin AEs are reported, skin specific questionnaires to be completed
7) Haematology: WBC, differential ANC, Platelets, Hb (Not required Cycle 1, day 1 if within 2 weeks of screening)
8) Biochemistry: Urea, Na, K, GGT, ALT or AST,total bilirubin, albumin, total protein, Serum creatinine, Creatinine Clearance, serum calcium, ALP, LDH (Not required Cycle 1, day 1 if within 2 weeks of screening)
9) Disease measurement will use CT/MRI scans (and ruler) and RECIST version 1.1
10) Baseline imaging to include head aswell as chest/abdo/pelvis. If head scan is clear, imaging of head to follow local practice but recommended to be repeated at least every 16 calendar weeks
11) Imaging to be performed at or during week 6, then every 8 calendar weeks until disease progression. If follow-up continues prior to disease progression beyond 52 calendar weeks since start of treatment than imaging can be reduced to every 12 calendar weeks.
12) Prescription & dispensing should be within 2 days prior to the first dose of each cycle, which should start with the morning dose
13) Quality of Life Questionnaires to be completed every 12 calendar weeks at the closest clinical visit
14) In a subset of consenting patients only, PK samples to be collected, see section 13 for further details
15) Archival tumour block to be requested prior to randomisation; tumour sample to be collected from any resected/biopsied progression lesion
16) Consent Process Patient Experience Survey
17) Treatment Patient Experience Survey

10.8 Trial restrictions

Women of child-bearing potential are required to use adequate contraception for the duration of treatment and for 4 months after the last dose. This includes:

- Barrier contraception (condom and occlusive cap e.g. diaphragm or cervical cap with spermicide)
- True abstinence (where this is in accordance with the patients preferred and usual lifestyle)

Please note: **If a Hormonal based contraception** (pill, contraceptive injection or implant etc) or Intrauterine Device (IUD) **is used another method of contraception must also be used** as dabrafenib may render hormonal contraceptives less effective

Men are required to use adequate contraception for the entire duration of treatment and for 4 months after the last dose. This includes:

- Barrier contraception (condom and spermicide) even if female partner(s) are using another method of contraception or are already pregnant
- True abstinence (where this is in accordance with the patients preferred and usual lifestyle)

The potential for sperm banking/egg collection should be discussed, where appropriate, according to local practice.

11 Assessment of Safety

11.1 Definitions

11.1.1 Adverse event (AE)

Any untoward medical occurrence in a patient or clinical trial patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product.

Please note: Recording of all adverse events must start from the point of Informed Consent regardless of whether a patient has yet received a medicinal product.

11.1.2 Adverse reaction to an investigational medicinal product (AR)

All untoward and unintended responses to an investigational medicinal product related to any dose administered. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

11.1.3 Unexpected adverse reaction

An adverse reaction, the nature, or severity of which is not consistent with the current approved reference safety information (RSI)

When the outcome of the adverse reaction is not consistent with the current approved RSI this adverse reaction should be considered as unexpected.

The term "severe" is often used to describe the intensity (severity) of a specific event. This is not the same as "serious," which is based on patient/event outcome or action criteria.

11.1.4 Serious adverse event or serious adverse reaction (SAE / SAR)

Any untoward medical occurrence that at any dose:
- results in death,
- is life-threatening
- requires hospitalisation or prolongation of existing inpatients´ hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly or birth defect.
- is an important medical event - Some medical events may jeopardise the patient or may require an intervention to prevent one of the above characteristics/ consequences. Such events (hereinafter referred to as 'important medical events') should also be considered as 'serious'.

Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the patient was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

11.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature and severity of which is not consistent with the information set out in the Reference Safety Information

11.1.6 Reference Safety Information (RSI)

The information used for assessing whether an adverse reaction is expected.

For the INTERIM trial the Reference Safety Information is contained in the trial-specific RSI document approved by the MHRA for use in this trial and attached as appendix 8 – Reference safety information.

11.2 Expected Adverse Reactions/Serious Adverse Reactions (AR /SARs)

All expected Adverse Reactions are listed in the reference safety information contained in Appendix 8 as specified in section 11.1.6. This must be used when making a determination as to the expectedness of the adverse reaction.
Use the following tables to determine expectedness:

- **Table 1:** To determine expectedness in relation to dabrafenib in patients taking dabrafenib monotherapy
- **Table 2:** To determine expectedness in relation to trametinib in patients taking trametinib monotherapy
- **Table 3:** To determine expectedness in relation to dabrafenib in patients taking dabrafenib in combination with trametinib
- **Table 4:** To determine expectedness in relation to trametinib in patients taking trametinib in combination with dabrafenib

If the adverse reaction meets the criteria for seriousness, this must be reported as per section 11.5.

11.3 Expected Adverse Events/Serious Adverse Events (AE/SAE)

For this trial the following events must not be reported as SAEs, but must be recorded on the patient CRF:

- Disease progression or death as a result of disease progression
- Elective hospitalisation and surgery for treatment of melanoma
- Elective hospitalisation for pre-existing conditions that have not been exacerbated by trial treatment
- Elective hospitalisation for trial treatment or disease related procedures unless associated with another serious event

11.4 Evaluation of adverse events

Adverse events will be recorded from the point of starting treatment until 30 days after the last dose of protocol treatment and resolution of all ≥grade 2 AEs . Individual adverse events should be evaluated by the investigator. This includes the evaluation of its seriousness, causality and any relationship between the investigational medicinal product(s) and/or concomitant therapy and the adverse event.

11.4.1 Assessment of seriousness

Seriousness is assessed against the criteria in section 11.1.4.This defines whether the event is an adverse event, serious adverse event or a serious adverse reaction

11.4.2 Assessment of causality

Definitely: A causal relationship is clinically/biologically certain. **This is therefore an Adverse Reaction**

Probable: A causal relationship is clinically / biologically highly plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product and there is a reasonable response on withdrawal. **This is therefore an Adverse Reaction.**

Possible: A causal relationship is clinically / biologically plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product. **This is therefore an Adverse Reaction.**

Unlikely: A causal relation is improbable and another documented cause of the AE is most plausible. **This is therefore an Adverse Event.**

Unrelated: A causal relationship can be definitely excluded and another documented cause of the AE is most plausible. **This is therefore an Adverse Event.**

Unlikely and Unrelated causalities are considered NOT to be trial drug related
Definitely, Probable and Possible causalities are considered to be trial drug related

A pre-existing condition must not be recorded as an AE or reported as an SAE unless

the condition worsens during the trial and meets the criteria for reporting or recording in the appropriate section of the CRF.

11.4.3 Clinical assessment of severity

All events should be graded for severity according to the NCI-CTCAE Toxicity Criteria (Version4. 03). CTCAE v4. 03 can be downloaded from the following URL: http://ctep.cancer.gov/reporting/ctc.html

11.4.4 Recording of adverse events

All Serious Adverse Events and Serious Adverse Reactions should be reported to the sponsor as detailed in section 11.5.

Adverse events not meeting SAE criteria should be reported if they meet one of the following criteria:

- Any grade $\geq$ 2 CTCAE
- Skin related AE of any grade (Adverse event of special interest)
- Any other adverse event that the clinician considers to be clinically significant

In the event of any skin AE being reported, the patient and clinician will complete the skin toxicity questionnaires.

11.5 Reporting serious adverse events

Each Principal Investigator needs to record all adverse events and report serious adverse events to the Chief Investigator using the trial specific SAE form within 24 hours of their awareness of the event. The Chief Investigator is responsible for ensuring the assessment of all SAEs for expectedness and relatedness is completed and the onward notification of all SAEs to the Sponsor immediately but not more than 24 hours of first notification. The sponsor has to keep detailed records of all SAEs reported to them by the trial team.

The Chief Investigator is also responsible for prompt reporting of all serious adverse event findings to the competent authority (e.g. MHRA) of each concerned Member State if they could:

- adversely affect the health of patients
- impact on the conduct of the trial
- alter the risk to benefit ratio of the trial
- alter the competent authority's authorisation to continue the trial in accordance with Directive 2001/20/EC.

An adverse event or reaction that meets serious criteria, irrespective of consistency (expected or unexpected) with the current approved Reference Safety Information contained in Appendix 8, must be reported to the Sponsor, with the exception of events listed within Section 11.3 Expected Serious Adverse Events.

In the case of an SAE, the Investigator or designee must immediately:
Complete a 'Serious Adverse Event Form' and Fax it to the CCTU-CT at Fax number: 01223 586839

The SAE form should be completed and signed by an appropriate member of the site trial team and faxed within 24 hours of becoming aware of the event to the CCTU-CT. The Principal Investigator must counter sign as soon as possible.

Even if only limited information is initially available, this should be provided and faxed on an SAE form. Further details should be submitted as soon as they become available.

Relevant AEs related to the SAE, in the opinion of the Principal Investigator, should be reported at the same time as the SAE.

In the case of death or life-threatening events, in addition to faxing an SAE form to the CCTU-CT, please TELEPHONE the CCTU-CT (on day of awareness), on

Tel number: 01223 216083

Where available, autopsy data for deaths occurring from registration until 30 days after last drug administration should be provided to the CCTU-CT. In addition, available autopsy data should be provided for any death occurring after this time, if there is a possibility that the death could be related to protocol treatment with the trial drug.

Where a reported serious adverse event is judged to be both related to the IMP and unexpected (i.e. is a SUSAR), the investigator must assist the CCTU-CT by supplying all requested information to the Sponsor to allow the appropriate regulatory timeline to be met. The CCTU-CT will inform the Research Ethics Committee (REC), the MHRA (Medicines and healthcare products regulatory agency) and the sponsor within the legally required time frame.

11.6 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

All suspected adverse reactions related to an investigational medicinal product (the tested IMP and comparators) which occur in the concerned trial, and that are both unexpected and serious (SUSARs) are subject to expedited reporting. Please see Appendix 8 – Reference Safety Information (RSI) for the Reference Safety Information to be used in this trial.

11.6.1 Who should report and whom to report to?

The Sponsor delegates the responsibility of notification of SUSARs to the Chief Investigator. The Chief Investigator must report all the relevant safety information previously described, to the:

- Sponsor,
- Competent authorities in the concerned member states (eg MHRA)
- Ethics Committee in the concerned member states

The Chief Investigator shall inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of patients.

11.6.2 When to report?

11.6.2.1 Fatal or life-threatening SUSARs

All parties listed in 11.6.1 must be notified as soon as possible but no later than **7 calendar days** after the trial team and Sponsor has first knowledge of the minimum criteria for expedited reporting.
In each case relevant follow-up information should be sought and a report completed as soon as possible. It should be communicated to all parties within an additional **8 calendar days**.

11.6.2.2 Non fatal and non life-threatening SUSARs

All other SUSARs and safety issues must be reported to all parties listed in section 11.6.1 as soon as possible but no later than **15 calendar days** after first knowledge of

the minimum criteria for expedited reporting. Further relevant follow-up information should be given as soon as possible.

11.6.3 How to report?

11.6.3.1 Minimum criteria for initial expedited reporting of SUSARs

Information on the final description and evaluation of an adverse reaction report may not be available within the required time frames for reporting. For regulatory purposes, initial expedited reports should be submitted within the time limits as soon as the minimum following criteria are met:
a) a suspected investigational medicinal product,
b) an identifiable patient (e.g. trial patient code number),
c) an adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship,
d) an identifiable reporting source,

and, when available and applicable:
- an unique clinical trial identification (EudraCT number or in case of non-European Community trials the sponsor's trial protocol code number)
- an unique case identification (i.e. sponsor's case identification number).

11.6.3.2 Follow-up reports of SUSARs

In case of incomplete information at the time of initial reporting, all the appropriate information for an adequate analysis of causality should be actively sought from the reporter or other available sources. Further available relevant information should be reported as follow-up reports.

In certain cases, it may be appropriate to conduct follow-up of the long-term outcome of a particular reaction.

11.6.3.3 Format of the SUSARs reports

Electronic reporting is the expected method for expedited reporting of SUSARs to the competent authority. The format and content as defined by the competent authority should be adhered to.

11.7 Pregnancy Reporting

All pregnancies occurring during the trial period (either the trial participant or the participant's partner) should be reported to the Chief Investigator and the Sponsor using the relevant Pregnancy Reporting Form within 24 hours of notification. Completed Pregnancy Reporting Forms must be reported using the contacts as detailed in section 11.5.

Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets the serious criteria, this would be considered an SAE.

12 Evaluation of Patient Reported Outcome, Health Economics & Patient Experience Assessments

In this study the generic instrument EQ-5D will be used to evaluate global health-related quality of life and the cancer-specific instrument – EORTC-QLQ-C30 will be used to measure impact of the treatment arms on quality of life (41-43).

12.1 Patient Reported Outcome (PRO)

A variety of cutaneous adverse effects have been reported with BRAFi monotherapy, MEK inhibitor monotherapy and combination therapy[7,13–18]. These range from common morbilliform drug eruptions to unique toxicities (such as cutaneous squamous cell carcinoma development and severe photosensitivity) to life-threatening drug reactions including Stevens Johnson syndrome and toxic epidermal necrolysis[18]. Adverse effects affecting the skin as a result of targeted therapies have significant impact on QoL, which includes emotional, psychological, social and physical well-being[19]. The severity of skin toxicity is often underestimated by clinicians[20,21] and the visible degree of involvement may not correlate with impact on QoL. PRO instruments have the potential to better capture these data. While standardised assessment tools have been developed for physicians to assess severity of adverse events (e.g. NCI CTCAE), it is well recognised that there is discord between objective and subjective measures. A systematic review reported moderate agreement at best between NCI CTCAE and PRO reporting of adverse effects in cancer clinical trials, highlighting the importance of integrating PROs with clinician reporting[22].

Several PRO instruments have been used to evaluate skin toxicity in cancer clinical trials of targeted therapies[20] and a systematic review recently evaluated PRO instruments of dermatologic adverse events associated with targeted therapies in particular[19]. The two PRO questionnaires used in the INTERIM trial (Skindex-16 and NCI PRO-CTCAE) were chosen based on these data.

12.1.1 Skindex-16

The Skindex-16 is a 16-question survey developed from the longer Skindex-29 that has been validated to accurately and sensitively measure how much a patient is bothered by a skin condition. It uses questions to assess how bothered a patient is by his/her skin condition on a seven-point scale (0-6) from 'never bothered' (0) to 'always bothered' (6) and assesses health-related QoL as it pertains to three domains of life – symptoms, emotions and functioning. The Skindex-16 has been shown to have good reproducibility (r=0.88-0.90)[23]. The survey has also been tested with several targeted therapies, including epidermal growth factor receptor inhibitors and tyrosine kinase inhibitors and these have shown significant correlation between survey QoL scores and other outcome measures including severity grading and NCI CTCAE scores[24–27]. The Skindex-16 has been shown to add supplemental information regarding skin toxicity which are not captured by CTCAE and also allows patient rating of emotional and functional burden which the CTCAE does not take into account[28].

The single-page length of the PRO instrument reduces patient burden[29]. The disadvantage is that the Skindex-16 does not specifically address toxicities of hair, nails or mucous membranes.

12.1.2 NCI PRO-CTCAE

A PRO version of the NCI CTCAE was developed by multidisciplinary collaborators with NCI and Food and Drug Administration(FDA) input in 2008[30] and is called the PRO-CTCAE. It consists of a library of 78 toxicities mapped to the CTCAE with up to three patient questions per toxicity. Patient questions were developed with extensive qualitative patient input including cognitive interviewing[31] and quantitative evaluation of measurement properties[32,33]. The purpose of the PRO-CTCAE is to improve the precision and patient-centredness of symptomatic adverse event assessment[30] and for the purpose of the INTERIM trial will be limited to skin specific items. NCI PRO-CTCAE skin

specific items relating to symptoms previously identified in trials of BRAF-inhibitors, MEK-inhibitors and combination treatment[7,13–18] were chosen for inclusion.

To evaluate skin toxicity in the INTERIM trial, two sources of data will be concurrently collected using a) the Clinician Skin Toxicity Q and b) the Patient Skin Toxicity Q. The statistical plan for data analysis is detailed in section 14.2.2.1.

12.2 Health Economics assessments

The economic evaluation will be a cost-effectiveness analysis which will compare the costs and effects of intermittent dosing compared with standard continuous dosing of oral targeted combination therapy in patients with *BRAF*V600 mutant stage 3 unresectable or metastatic melanoma and will follow established guidelines as set out by NICE[34]. The main outcome measure for the economic evaluation will be quality adjusted life years (QALYs)[35], estimated using the EuroQol EQ-5D 5L,which will be administered pre-randomisation (screening visit) , day 1 of cycle 2, and then every 12 weeks until the end of the trial, plus at Progression. Resource use data will be collected on the two alternative treatment regimens, treatment complications (including non serious and serious adverse events), and length of stay by adding questions to the trial CRFs. Unit costs will be derived from nationally published sources such as eMIT[36], the British National Formularly[37] and Department of Health reference cost database[38] and attached to the resource use data.

We will report the cost and QoL data for each trial arm and the difference between the trial arms. Then we will calculate the average cost and outcome on a per patient basis to produce incremental cost-effectiveness ratios for the two arms, producing an incremental cost per QALY[39] This incremental analysis will be able to provide evidence on which treatment option is most likely to provide value for money for the National Health Service (NHS) and the greatest value for patients. Finally, we will undertake a budget impact analysis to estimate what the likely financial impact of moving to intermittent dosing is likely to be for the NHS.

12.3 Patient Experience evaluation

12.3.1 Patients who decline to enter the trial

12.3.1.1 Patient experience survey

Patients who are approached to enter the trial but decline to participate will be invited to complete a Patient Experience Survey to explore their reasons for not participating. The questionnaire will be self-completed.

12.3.2 Trial Participants

12.3.2.1 Patient Experience Survey

Patients who agree to participate in the trial will be requested to complete a Consent Process-Patient Experience survey at the first screening visit. In addition, after 9 months participation within the trial a short Trial Treatment Patient Experience Survey will be administered to all participants. Questions in the latter survey will include exploration of:

A) experience of participating in the trial
B) experience of toxicity – single global scale

C) relevance of the PROMS tools used to measure toxicity

The questionnaire will be self-completed.

12.3.2.2 Semi-Structured interviews

Patients will be invited to volunteer their contact details in section 3 of the Patient Trial Treatment Experience Survey, if they are willing to be contacted to participate in semi-structured interviews at a later date.

Patients who have volunteered their contact details in section 3 of the Patient Experience Survey, will be contacted by the qualitative researcher, who will confirm they are still willing to participate in an interview before sending them further information about the interviews and answering any questions they may have. Patients who agree to participate in the interviews will be consented by the qualitative researcher and invited to attend face-to-face / skype / telephone interviews.

A convenience sample of patients will be recruited from up to four sites. Fifteen patients will be interviewed from each arm of the trial (total 30 interviews). Patients will be informed that it is possible that they will not be interviewed if too many people volunteer. Patients will be selected as they volunteer consecutively and opportunistically.

A dedicated qualitative researcher will lead and undertake patient interviews evaluating three main areas detailing topics covered in the Patient Experience Survey. The responses from the Consent and Trial Treatment Patient Experience Surveys will inform the interview but the interview schedule will broadly expand on the following issues:

A) Trial participation and the consent process (Consent Patient Experience Survey)
    a. How did you decide to consent to be a participant in the trial?
    b. What was your experience of being a research participant?
    c. Were you given enough information prior to entering the trial?
    d. What are your feelings about being randomized in a trial i.e. acceptability of the two arms of the trial in principle and in practice?
    e. Overall experience of the trial
B) Experience of toxicity of treatment
    a. What was your experience of the treatment?
    b. What toxicity did you experience and what was the severity?
    c. What was the impact of the toxicity on your quality of life? e.g. social impact, psychological and emotional well-being.
C) Experience of Patient Skin Toxicty Q and PROMS tools
    a. How easy was it to complete?
    b. What was the burden of completion?
    c. Did the tools capture the aspects of quality of life it affected which are relevant to the patient?
    d. How useful was the Patient Skin Toxicity Q?

13 Research Blood and Tissue Samples

13.1 Translational Research

Tissue and blood samples will be collected from all patients for analysis of ctDNA.

Research blood samples (20mls, 40mls baseline) will be taken from all 150 patients at the following time points: Baseline (pre-treatment), 2 weeks, 4 weeks, 6 weeks, 8 weeks, 12 weeks and then every 8 weeks until progression, plus at progression.

Research blood samples will be taken at the same time, where possible, as routine haematology and biochemistry blood samples to minimise the impact on the patient.

A block of the most recent archived melanoma tumour sample (from a metastasis or primary site) will be requested at screening. Additional blocks will be collected from any patients undergoing routine surgery to remove metastatic melanoma at progression.

Blood and tissue samples will be sent to Oxford University for analysis. Please refer to the INTERIM Laboratory Manual for details of sample collection and processing procedures.

13.2 Pharmacokinetics

In a subset of patients (up to 20) the pharmacokinetics of standard versus intermittent dosing schedules will be explored. Patients who have consented to take part in the additional pharmacokinetic study will have samples collected during the following visits; Cycle1, day 1 and cycle 2, day 15 (6 weeks into treatment).
Blood (2mls) will be taken at the following time points:

Pre-dose	
30mins	+/- 5mins
1hr	+/- 5mins
1hr 30mins	+/- 5mins
2hrs	+/- 5mins
3hrs	+/- 30mins
4hrs	+/- 30mins
6hrs	+/- 30mins
8hrs	+/- 60mins

In addition a blood sample (2mls) will be taken pre-dose at the beginning of cycle 3, cycle 4 and then every other cycle (cycle 6, cycle 8, cycle 10….).These samples will be taken at the same time as the translational blood samples.
Finally at disease progression, 3 further blood samples (2mls) will be taken at the following time points: pre-consultation, post-consultation and 30-60 minutes later.

Pharmacokinetic blood samples will be sent to Oxford University for analysis. Please refer to the INTERIM Laboratory Manual for details of sample collection and processing procedures.

14 Statistics

14.1 Number of Patients to be enrolled

It is planned to recruit 150 patients (75 patients in each arm) in 18 months with a minimum of 9 months follow up from around 20 UK sites. This will provide reliable information and evidence to inform the design of a definitive trial which will be powered to test the hypothesis that intermittent dosing of BRAF+MEKi combination will prolong progression-free survival compared with standard continuous dosing, with fewer side effects and better quality of life for patients.

<u>Recruitment</u>
The planned recruitment period is 18 months. Recruitment will be assessed once the trial has been open for 15 months, or 15 centres have been open for 6 months, whichever is the sooner. Recruitment will be considered acceptable if 15 of the target 20 sites are entering an average of 1 patient every 2 months.

The targeted recruitment rate per site is, on average, 6 patients per year. If this target is achieved, around 1000 patients could be recruited from 50 sites in 4 years indicating that a phase III trial fully powered (see appendix 6) to detect a median improvement in progression-free survival from 12 to 15 months trial (a hazard ratio of 0.8, being less than the 50% relative reduction in death reported in the mouse model) will be feasible.

Treatment compliance

Approximately 13% of patients stop treatment early due to intolerable toxicity with continuous dosing schedules. An intermittent dosing schedule will not be considered feasible if the treatment compliance at 6 months is less than 60%; it will be considered feasible if it is over 75%. With a 5% significance level (one-sided), and 80% power, 65 patients[40] are required in the intermittent dosing arm to detect a difference of ≤60% versus ≥75%. A patient leaving the trial to move to continuous dosing will constitute a failure of intermittent treatment, as will stopping for intolerable toxicity or disease progression.

Quality of life

QoL improvement will be assessed primarily using the global health status derived from the EORTC QLQ-C30 questionnaire at 6 months from baseline (change from baseline in global health status score) between the standard and the experimental arms. This will be calculated as per scoring instructions in the EORTC QLQ-C30 manual[41–43]. Considering 80% patients will complete QoL at 6 months, a total of 150*80%= 120 patients' data will be available. With the estimated standard deviation of 12, which is based on 465 patients at 24 weeks from the COMBI-V trial[44], 120 patients will provide us a one-sided 90% confidence interval of a 5 points[45] improvement (a minimum clinical meaningful improvement) under the 0-100 scale excluding 0 (5 – 1.28*12*(1/60**0.5 + 1/60**0.5) = 1.0 >0).

Estimate the hazard ratio for progression-free survival

The estimated median PFS is 12 months for the standard continuous arm. Assuming a hazard ratio (HR) of 0.8 and 150 patients randomised in 18 months with a further 9 months follow up, approximately 90 PFS events will be observed based on estimated median PFS of 12 months for the standard continuous dosing schedule. This will generate a 1-sided 90% confidence interval of the estimated HR (exp(log(0.8) + 1.28*(4/90)**0.5 = 0.995)<1 in favour of the intermittent dosing schedule should the assumption be correct.

Assuming the anticipated 3 months improvement in median PFS from 12 in continuous dosing to 15 months in intermittent dosing is true, the estimated HR will be obtained based on at least 90 PFS events. If the estimated HR is less than 0.8, there is over 72% confidence (predictive power) that the planned phase III trial will test the hypothesis successfully. If the estimated HR is less than 0.75, there is over 81% confidence that the definitive phase III trial will test the hypothesis successfully (see appendix 6).

14.2 Statistical analysis methods

14.2.1 Analysis population

The following populations will be defined for efficacy and safety analyses

- Intention-to-treat Population (ITT)

The ITT population is defined as all patients randomised in the trial, regardless of whether they actually received treatment. The treatment group will be analysed as randomised.

- Minimum treatment population

Minimum treatment population is defined as all patients who received at least two cycles of allocated protocol treatment. The treatment group will be analysed as treated.

- Safety Population

The safety population comprises all patients randomised and having received at least one dose of trial treatment. The treatment group will be analysed as treated.

14.2.2 Statistical analysis

Statistical analyses for this feasibility trial will be mainly descriptive. A detailed statistical analysis plan will be drafted before any analyses are performed. Briefly, recrutiment rate will be estimated based on all patients randomised and summarised as an average number of patients recruited per month per site. Treatment compliance will be analysed based on patients who have received at least one dose of protocol treatment. The treatment compliance will be compared between the arms in an exploratory manner. Initial evidence of intermittent dosing benefit in quality of life (the estimated confidence interval of the difference of change from baseline in global health status score at 6 months between arms) and progression-free survival (estimated hazard ratio, together with the confidene interval) will be analysed based on intention-to-treat population and minimum treatment population. Safety analyses will be based on safety population and summarised using the frequency tables and listings.

14.2.2.1 Statistical analysis PROMs

Descriptive statistics will be produced, using medians and interquartile ranges (IQRs) instead of means and standard deviations in cases of heavily skewed data. The standardized Skindex-16 questionnaire and NCI-PRO-CTCAE data will be analysed and missing data handled in accordance with their respective guidelines[29,33]. Proportion of patients experiencing a change from baseline for each measure as well as mean group changes will be calculated for skin toxicity. Associations between the reporting of skin toxicity between clinician and patients at the same timepoints will be explored. Associations between Skindex-16 and PRO-CTCAE scores with reported manifestations of skin toxicity will be explored. In addition, sub-group analyses based on age, gender, treatment arm, will be undertaken. Statistical significance tests will be carried out if clinically significant differences are observed. Independent samples t-tests will be used to compare means, and the nonparametric equivalent will be used to compare medians in the case of skewed data. Proportions will be compared using the chi-square test. Associations will be explored using multivariate regression analyses if sample size allows.

14.2.2.2 Statistical analysis Patient Experience Survey

Quantitative:
Data analysis of Patient Experience will be undertaken (obtained both from those patients who have declined to enter the trial and those who have participated). Descriptive results will be reported and statistics will be used where relevant, using medians and IQRs instead of means and standard deviations in cases of heavily skewed data. In addition for participants, sub-group analyses based on age, gender and treatment arm, will be undertaken. Statistical significance tests will be carried out if clinically significant differences are observed. Independent samples t-tests will be used to compare means, and the nonparametric equivalent will be used to compare medians in the case of skewed data. Proportions will be compared using the chi-square test.

Associations will be explored using multivariate regression analyses if sample size allows.

Qualitative:
All interviews will be recorded using Olympus DSS digital recorder and transcribed verbatim. A framework analysis approach will be undertaken which will be developed from the interview schedule and from themes that emerge during the interviews and will be conducted using NVivo V.10 qualitative analysis software. All coding will be performed by the Qualitative Researcher. Qualitative data from the interviews will be integrated with the responses from the questionnaires and used to evaluate patient experience for patients who have participated in the INTERIM trial.

14.3 Interim analyses

An Independent Safety Data Monitoring Committee (ISDMC) will review trial progression and trial data, by treatment group, on the safety of patients in the trial. The ISDMC will meet approximately every 6 months while patients are receiving protocol treatment or until end of the trial. Interim progress reports will be produced for each ISDMC meeting.

14.4 Definition of the end of the trial

The trial will be considered closed for regulatory purposes 9 months from the date of randomisation of the last patient. Further observational follow-up on survival of all patients enrolled in the trial will be performed for a minimum of 9 months to a maximum of 5 years from the date of randomisation of the last patient, as survival beyond this point is unlikely.This will initially be via hospitals and clinics, but in the longer term may exploit national registers.

15 Data handling and record keeping

15.1 Case Report Form (CRF)

All anonymous data will be transferred into a CRF which will be anonymised. All trial data in the CRF must be extracted from and be consistent with the relevant source documents. The CRFs must be completed, dated and signed by the investigator or designee in a timely manner. It remains the responsibility of the investigator for the timing, completeness, legibility and accuracy of the CRF pages. The CRF will be accessible to trial coordinators, data managers, the investigators, Clinical Trial Monitors, Auditors and Inspectors as required.

Completed originals of the CRFs should be posted within two weeks of the trial visit to the trial coordination centre:

INTERIM Trial Coordinator
Cambridge Clinical Trials Unit – Cancer Theme (CCTU-CT)
Box 279 (S4)
Addenbrooke's Hospital
Hills Road
Cambridge
CB2 0QQ

The investigator will retain a copy of each completed CRF page at site. The investigator will also supply the trial coordination centre with any required, anonymised background information from the medical records as required.

The investigators must ensure that the CRFs and other trial related documentation is sent to the trial coordination centre containing no patient identifiable data.

All CRF pages must be clear, legible and completed in black ink. Any errors should be crossed with a single stroke so that the original entry can still be seen. Corrections should be inserted and the change dated and initialled by the investigator or designee. If it is not clear why the change has been made, an explanation should be written next to the change. Typing correction fluid must not be used.

15.2 Source Data

To enable peer review, monitoring, audit and/or inspection the investigator must agree to keep records of all participating patients (sufficient information to link records e.g., CRFs, hospital records and samples), all original signed informed consent forms and copies of the CRF pages.

Source data include, but are not limited to:

- Patient Medical Records
- Online Medical Records eg. medical records, prescribing records, results/reports from clinical investigations such as blood tests or scans
- Signed and dated informed consent forms
- Baseline Skin Report
- Pharmacy records
- Worksheets for sample collection, processing storage and shipment
- QoL questionnaires
- Clinician Skin Toxicity Questionnaire
- Patient Skin Toxicity Questionnaire
- Patient Diary Card
- Patient Experience surveys (Consent and Trial Treatment)
- Qualitative research interview recordings and transcripts

15.3 Data Protection & Patient Confidentiality

All investigators and trial site staff involved in this trial must comply with the requirements of the Data Protection Act 1998 and Trust Policy with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

16 Trial Committees

16.1 Trial management Group (TMG)

The TMG will meet approximately monthly by teleconference to oversee the running of the trial. TMG members will review SAEs which have occurred in the trial. If there are specific safety concerns these may be raised with the TSC and ISDMC. TMG members will include all INTERIM trial co-investigators, trial statistician, trial pharmacist, and the Trial co-ordinator.

16.2 Independent Safety Data Monitoring Committee (ISDMC)

The ISDMC is independent of investigators and the Cambridge Clinical Trials Unit-Cancer Theme. The group will meet approximately every 6 months while patients are receiving trial treatment or until end of trial. The ISDMC will review reports from the CCTU-CT and give advice on continuing recruitment. There are no formal stopping rules

for efficacy. A recommendation to discontinue recruitment (in all patients or in selected subgroups) will be made only if the emerging safety data indicate that the safety of the patients is not maintained. If a decision is made to continue, the ISDMC will advise on the frequency of future reviews of the data on the basis of accrual and event rates. The ISDMC will make recommendations to the TSC as to the continuation of the trial. The ISDMC will also be monitoring compliance of patients randomised to the intermittent arm of the trial and outcomes of both arms on a 6 monthly basis throughout the trial.

16.3 Trial Steering Committee (TSC)

The TSC includes members who are independent of the trial investigators and the CCTU-CT. It will provide overall supervision of the trial. It will meet at approximately 6-monthly intervals and will receive reports from the CCTU-CT, TMG and ISDMC.

17 Ethical & Regulatory considerations

17.1 Consent

The Informed Consent form must be approved by the REC and must be in compliance with GCP, local regulatory requirements and legal requirements. The investigator must ensure that each trial participant, or his/her legally acceptable representative, is fully informed about the nature and objectives of the trial and possible risks associated with their participation.

The investigator will obtain written informed consent from each patient or the patient's legally acceptable representative before any trial-specific activity is performed. The informed consent form used for this trial and any change made during the course of this trial, must be prospectively approved by the REC. The investigator will retain the original of each patients signed informed consent form.

Should a patient require a verbal translation of the trial documentation by a locally approved interpreter/translator, it is the responsibility of the individual investigator to use locally approved translators.

Any new information which becomes available, which might affect the patient's willingness to continue participating in the trial will be communicated to the patient as soon as possible. If the patient's next trial visit is imminent the new information will be communicated in person at that trial visit. Otherwise, the patient will be contacted over the telephone by a member of the trial team, eg. Investigator or Research Nurse.

17.2 Ethical committee review

Before the start of the trial or implementation of any amendment we will obtain approval of the trial protocol, protocol amendments, informed consent forms and other relevant documents e.g., advertisements and GP information letters if applicable from the REC. All correspondence with the REC will be retained in the Trial Master File/Investigator Site File.

Annual reports will be submitted to the REC in accordance with national requirements. It is the Chief Investigator's responsibility to produce the annual reports as required.

17.3 Regulatory Compliance

The trial will not commence until a CTA under the Notification Scheme for Type A trials is obtained from the MHRA. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

Development Safety Update Reports (DSURs) will be submitted to the MHRA in accordance with national requirements. It is the Chief Investigators responsibility to produce the annual reports as required.

17.4 Protocol Amendments

Protocol amendments must be reviewed and agreement received from the Sponsor for all proposed amendments prior to submission to the HRA, REC and/or MHRA.

The only circumstance in which an amendment may be initiated prior to REC and/or MHRA approval is where the change is necessary to eliminate apparent, immediate risks to the patients (Urgent Safety Measures). In this case, accrual of new patients will be halted until the HRA, REC and/or MHRA approval has been obtained.
In the event of an urgent safety measure, the chief investigator (or delegate) will cascade the information verbally and/or by email to each participating site within 24 hours.

17.5 Peer Review

This clinical trial has been peer reviewed by the National Institute for Health Research (NIHR) Research for Patient Benefit (RfPB) funding committee.

17.6 Declaration of Helsinki and Good Clinical Practice

The trial will be performed in accordance with the spirit and the letter of the declaration of Helsinki, the conditions and principles of Good Clinical Practice, the protocol and applicable local regulatory requirements and laws.

17.7 GCP Training

All trial staff must hold evidence of appropriate GCP training or undergo GCP training prior to undertaking any responsibilities on this trial. This training should be updated every 2 years or in accordance with your Trust's policy.

18 Sponsorship, Financial and Insurance

The trial is sponsored by Cambridge University Hospitals NHS Foundation Trust. The main trial will be funded by an NIHR RfPBgrant. The translational research and Pharmacokinetics will be funded by a CRUK grant.

Cambridge University Hospitals NHS Foundation Trust, as a member of the NHS Clinical Negligence Scheme for Trusts, will accept full financial liability for harm caused to participants in the clinical trial caused through the negligence of its employees and honorary contract holders. There are no specific arrangements for compensation should a participant be harmed through participation in the trial, but no-one has acted negligently.

19 Monitoring, Audit & Inspection

The investigator must make all trial documentation and related records available should an MHRA Inspection occur. Should a monitoring visit or audit be requested, the investigator must make the trial documentation and source data available to the Sponsor's representative. All patient data must be handled and treated confidentially.

The Sponsor's monitoring frequency will be determined by an initial risk assessment performed prior to the start of the trial. A detailed monitoring plan will be generated

detailing the frequency and scope of the monitoring for the trial. Throughout the course of the trial, the risk assessment will be reviewed and the monitoring frequency adjusted as necessary.

Remote monitoring will be conducted for all participating sites. The scope and frequency of the monitoring will be determined by the risk assessment and detailed in the Monitoring Plan for the trial.

20 Protocol Compliance and Breaches of GCP

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used.

Protocol deviations, non-compliances, or breaches are departures from the approved protocol. They can happen at any time, but are not planned. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

Deviations from the protocol which are found to occur constantly again and again will not be accepted and will require immediate action and could potentially be classified as a serious breach.

Any potential/suspected serious breaches of GCP must be reported immediately to the Sponsor without any delay.

21 Publications policy

Ownership of the data arising from this trial resides with the TMG. On completion of the trial the data will be analysed and tabulated and a Final Trial Report prepared.

The main trial results will be presented at national and international conferences and published in a peer-reviewed journal, on behalf of all collaborators. All presentations and publications relating to the trial must be authorised by the TMG.

The manuscript will be prepared by a writing group appointed from amongst the TMG and high-accruing investigators. The CCTU-CT, NIHR, CRUK and all participating sites and Investigators will be acknowledged in publications and presentations. Senior authorship shall be shared between members of the TMG according to their leadership role in the trial. Priority will be given to the lead sites (Cambridge and Oxford) co-ordinating the trial, then to participating sites, ordered by recruitment.

In addition patients who have consented to receive updates on trial progress and results of the trial, will be provided with trial updates and summary of the results in lay terms.

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23 Appendices

23.1 Appendix 1 – RECIST Version 1.1

For the full RECIST version 1.1, please refer to Eisenhauer E.A. et al.[46].
A summary of the criteria applicable for INTERIM is given below.

Methods of Assessment

Tumour assessments for response and progression require CT scan (or MRI if allergic to intravenous contrast) of thorax/abdomen/pelvis/head or measured by photography including a ruler. The same assessment technique should be used to characterise each identified and reported lesion at baseline and throughout the trial.

Measurable Disease

Patients will be classified as having measurable or non-measurable disease at baseline and at each imagining assessment.

Definition of Measurable Disease lesions
Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of 10 mm by CT scan (CT scan slice thickness no greater than 5 mm; when CT scans have slice thickness >5 mm, the minimum size should be twice the slice thickness).

Cutaneous lesions measured by photography including a ruler to indicate size, must be a minimum of 10mm in diameter.

Malignant lymph nodes: To be considered pathologically enlarged and measured, a lymph node must be ≥15 mm in short axis when assessed by CT scan. At baseline and in follow-up, only the short axis will be measured and followed.

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

Baseline Tumour Assessment

The baseline tumour assessment evaluation should be performed within 4 weeks of date of randomisation.

Baseline Documentation of "Target" and "Non-Target" Lesions

Target Lesions

- All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline.

- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, as well as their suitability for reproducible, repeated measurements.

- Pathological nodes which are defined as measureable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan.

Sum of the Diameters
Sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters.

Non-target Lesions
All lesions (or sites of disease) not identified as target lesions, including pathological lymph nodes and all non-measurable lesions, should be identified as non-target lesions and be recorded at baseline. Measurements of these lesions are not required and they should be followed as 'present', 'absent' or in rare cases, 'unequivocal progression'.

Response Criteria

Evaluation of Target Lesions

Complete Response (CR):
Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

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

Progressive Disease (PD):
At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on trial (this may include the baseline sum). The sum must also demonstrate an absolute increase of at least 5 mm.

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

Evaluation of Non-target Lesions

Complete Response (CR):
Disappearance of all non-target lesions and normalisation of tumour marker levels. All lymph nodes must be non-pathological in size (<10 mm short axis).

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

Progressive Disease (PD):

Unequivocal progression of existing non-target lesions.

- When patient has measurable disease. To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is not usually sufficient to qualify for unequivocal progression status.

- When patient has only non-measurable disease. There is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified, a useful test that can be applied is to consider if the increase in overall disease burden based on change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease. Examples include an increase in a pleural effusion from 'trace' to 'large' or an increase in lymphangitic disease from localized to widespread.

New lesions

The appearance of new malignant lesions denotes disease progression:

- The finding of a new lesion should be unequivocal (i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour, especially when the patient's baseline lesions show partial or complete response).

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

- A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and disease progression.

Time Point Response

The table below provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

Time point response: patients with target (=/- non-target) disease

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

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

23.2 Appendix 2 – Karnofsky and ECOG Performance Status Scale

Karnofsky Performance Status Scale[47]

Condition	PS %	Comments
Able to carry on normal activity and to work. No special care needed.	100	Normal. No complaints. No evidence of disease.
	90	Able to carry on normal activity. Minor signs or symptoms of disease.
	80	Normal activity with effort; Some signs or symptoms of disease.
Unable to work. Able to live at home, care for most personal needs. A varying amount of assistance needed.	70	Cares for self. Unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self. Requires equivalent of institutional or hospital care. Disease may be progressing rapidly.	40	Disabled. Requires special care and assistance.
	30	Severely disabled. Hospitalisation is indicated although death not imminent.
	20	Hospitalisation necessary, very sick; active supportive treatment necessary.
	10	Moribund. Fatal processes progressing rapidly.
	0	Dead

ECOG Performance Status Scale[48]

Scale	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light 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 disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Comparisons[49]

ECOG 0-1 equals Karnofsky 80-100
ECOG 2 equals Karnofsky 60-70
ECOG 3-4 equals Karnofsky 10-50

23.3 Appendix 3 – NYHA Functional Classification

The **New York Heart Association (NYHA) Functional Classification**[50] provides a simple way of classifying the extent of heart failure. It places patients in one of four categories based on how much they are limited during physical activity; the limitations/symptoms are in regards to normal breathing and varying degrees in shortness of breath and or angina pain:

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while *at rest*. Mostly bedbound patients.

23.4 Appendix 4 - Trial Management / Responsibilities

23.4.1 Patient registration/ Randomisation procedure

A web-based central randomisation system, supplied by Sealed Envelope, will allocate patient randomisation numbers sequentially in the order in which the patients are enrolled. At the site initiation, the trial coordinator will arrange for the member of trial team who is authorised to randomise patients to be provided with a unique system username and password, which will allow them to access the central randomisation system. The trial coordinator will also train site staff in how to access and use the randomisation system.

Using the web-base central randomisation system authorised site staff should randomise patients using their unique system username and password. Data required in order to randomise a patient is outlined in section 8.5. The treatment arm will be allocated and a unique trial number will be assigned by the randomisation system.

23.4.2 CRF Completion & Data management

CRFs should be completed by the site and sent to the coordinating centre in a timely manner, please refer to the CRF completion guidelines for more information. Data management at the coordinating centre will include CRF checking and raising data queries as required, for further information please refer to the Data Management Plan.

23.4.3 Data protection/ confidentiality

Individual patient medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below.

Case report forms will contain the patient's initials, Date of Birth and unique trial number. Medical information may be given to the 's medical team and all appropriate medical personnel responsible for the patient's welfare.

This transfer of identifiable data is disclosed in the Patient Information Sheet. The trial team will preserve the confidentiality of patients taking part in the trial.

23.4.4 Trial documentation & archiving

Each participating site is responsible for archiving their own trial data including source data, the Investigator Site File (ISF) for the appropriate time period as determined by the regulations governing clinical trials in place at the time of archival. The archiving facility may be at the participating site or at another appropriate location off-site as per local policy. The trial team will advise when the site may commence archiving. The site will need to provide the name and address of the archival facility to the Trial team. In case of audit or inspection following archival, the participating site will be expected to retrieve the relevant documentation within a reasonable timeframe.

23.5 Appendix 5 – Authorisation of Participating Sites

23.5.1 Required Documentation

The following documentation must be in place prior to a site being opened to recruitment by the CCTU-CT trial team:

- Trial specific registration of interest form (identifying relevant local trial team)
- All relevant institutional approvals (e.g. local NHS confirmation)
- A signed participating site agreement (PSA) or Statement of Activities between the Sponsor and the relevant institution (typically the sites local NHS Trust)
- CV signed and dated and GCP certificates for the site trial team
- An example of patient documentation (PIS/ICF etc) and GP Letter on local Trust-headed paper and with local contact details added.
- Example of IMP prescription
- Local Laboratory accreditation (or equivalent) and reference ranges for the protocol-specified paramaters
- Completed and signed Trial Initiation Form

The Principal Investigator (PI), other delegated site investigators and all staff involved in the conduct of the trial at site must be identified on the site delegation log held at site and copied to CCTU-CT prior to site activation

23.5.2 Procedure for initiating/opening a new site

Once the trial team at CCTU-CT have confirmed that all documentation is in place, a site activation letter will be issued to the PI, at which point the site may start to approach patients.

23.5.3 Principal Investigator Responsibilities

Once the site has been activated by CCTU-CT, the PI at each site is responsible for ensuring the following:

- Attendance at the site initiation meeting
- Adherence to the most recent version of the protocol
- All relevant staff are trained in protocol requirements
- Delegation of activities to appropriately trained staff (this must be documented on the delegation of responsibility and signature log)
- Appropriate recruitment and medical care of patients in the trial
- Timely completion and return of CRFs
- Accurate maintenance of the ISF
- Dissemination of all trial related information
- Ensuring appropriate attendance at the TMG teleconferences if required and ensure appropriate safety information is made available to the CCTU-CT in advance of the meeting.
- Dissemination of important safety or trial related information to all stakeholders at the participating site
- Safety reporting within the timelines and assessment of causality and expectedness of all SAEs

23.6 Appendix 6 Sample size ouput and predictive power

Sample size for a planned phase III trial: sample size N=~1000, number of PFS events m=846

Sample size with a 5% significance level and 90% power for a hazard ratio = 0.80, a median PFS of 12 months, a 4-year recruitment, a 2-year follow up.

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ART - ANALYSIS OF RESOURCES FOR TRIALS (version 1.0.7, 19 October 2009)

A sample size program by Abdel Babiker, Patrick Royston & Friederike Barthel,
MRC Clinical Trials Unit, London NW1 2DA, UK.

Type of trial	Superiority - time-to-event outcome
Statistical test assumed	Unweighted logrank test (local)
Number of groups	2
Allocation ratio	Equal group sizes
Total number of periods	6
Length of each period	One year
Baseline median survival time	1 year
Survival probs per period (group 1)	0.500 0.250 0.125 0.063 0.031 0.016
Survival probs per period (group 2)	0.574 0.330 0.189 0.109 0.063 0.036
Number of recruitment periods	4
Number of follow-up periods	2
Method of accrual	Uniform
Recruitment period-weights	1 1 1 1 0 0
Hazard ratios as entered (groups 1,2)	1, 0.8
Alpha	0.050 (two-sided)
Power (designed)	0.900

Total sample size (calculated) 949
Expected total number of events 846

Predictive power for a successful phase III trial

$$prior,\ \mu = \log(HR) \sim N(\mu_0,\ \sigma_0^2),$$

$$data\ X_n \mid \mu \sim N\left(\mu, \frac{4}{n}\right), n = \text{total no. of PFS events observed in the fesiblity study}$$

$$posterior,\ p(\mu|x_n) = N(\mu_{(n)},\ \sigma_{(n)}^2),\ \ \frac{1}{\sigma_{(n)}^2} = \frac{1}{\sigma_0^2} + \frac{n}{4},\ \ \ \mu_{(n)} = \sigma_{(n)}^2\left(\frac{\mu_0}{\sigma_0^2} + \frac{nx_n}{4}\right)$$

$$predictive\ likelihood\ X_m|X_n \sim N\left(\mu_{(n)},\ \sigma_{(n)}^2 + \frac{4}{m}\right), m = total\ no.of\ PFS\ events$$

The preditive power $PP(m)$ to reject H_0 (hazard ratio (HR) ≥1, or log (HR) ≥0 (δ=0)) of no PFS benefit of intermittent dosing schedul is

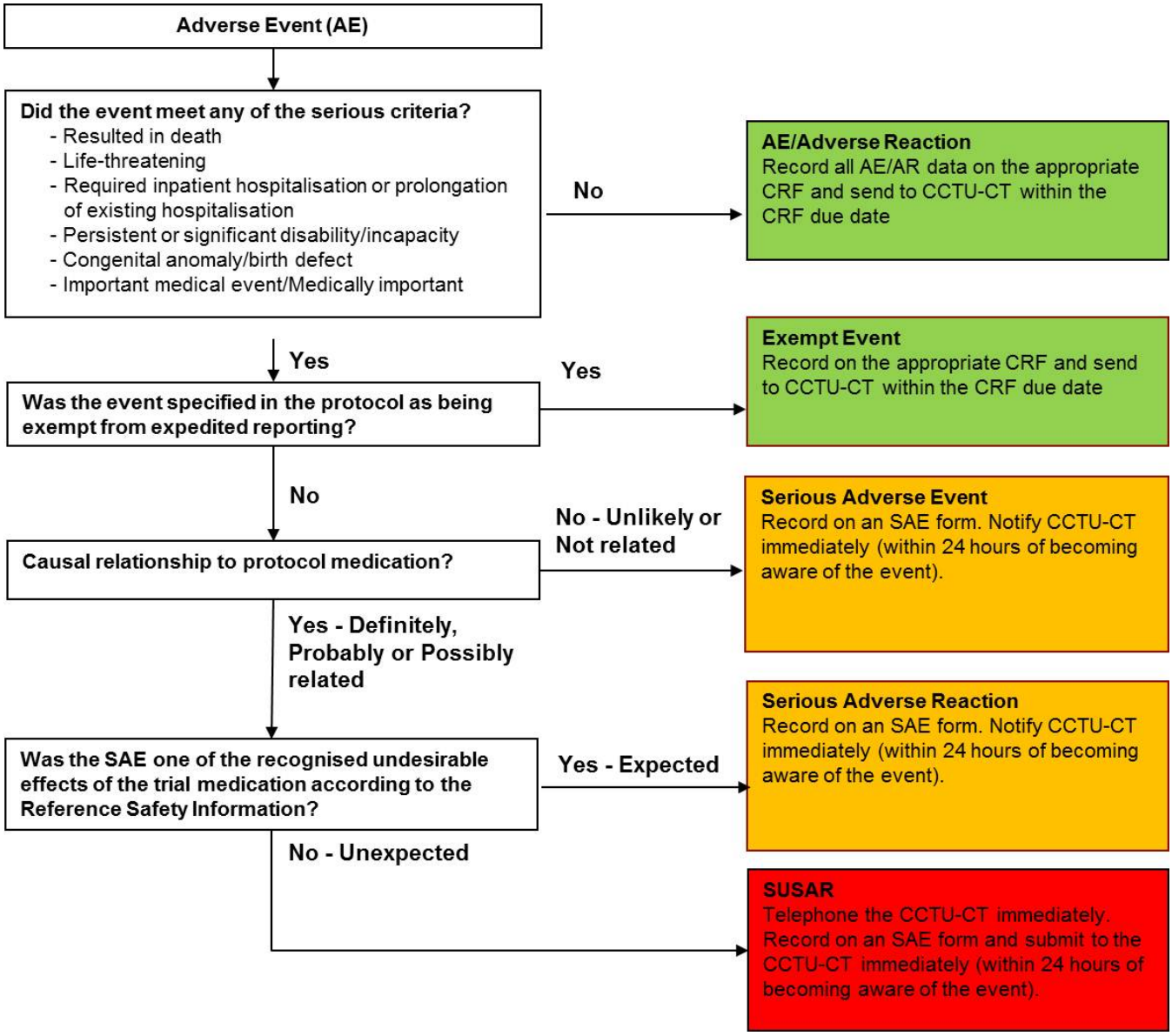
$$PP(m) = \Phi\left(\frac{\delta - \frac{nx_n + m\mu_{(n)}}{n+m} - z_{1-\alpha}\sqrt{\frac{4}{n+m}}}{\sqrt{\left(\frac{m}{n+m}\right)^2\left(\sigma_{(n)}^2 + \frac{4}{m}\right)}}\right).$$

With a prior of no difference and 1 PFS event, that is $\log(HR) \sim N(0,\ 4)$, significance level $\alpha = 5\%$, n=90 PFS events observed in the feasiblity study,

- if the observed HR=0.80 (an improvement in median PFS from 12 to 15 months) in the phase II trial, the predictive power to reject the null hypothesis of no PFS benefit of intermittent dosing schedule under the planned phase III trial (m=846) is 72%.

- If the observed HR=0.75 (an improvement in median PFS from 12 to 16 months) in the phase II trial, the predictive power to reject the null hypothesis of no PFS benefit of intermittent dosing schedule under the planned phase III trial (m=846) is 81%.

23.7 Appendix 7 - Safety reporting flowchart



23.8 Appendix 8 – Reference Safety Information (RSI)

Data taken from:
Debrafenib - Summary of Product Characteristics - updated 19 April 2017.
Trametinib - Summary of Product Characteristics - updated 19April 2017.

Tabulated summary of adverse reactions

ADRs which were reported are listed below by MedDRA body system organ class and by frequency. The following convention has been utilised for the classification of frequency:

Very common ≥1/10

Common ≥1/100 to <1/10

Uncommon ≥1/1,000 to <1/100

Rare ≥1/10,000 to <1/1,000

Not known (cannot be estimated from the available data)

For SUSAR reporting use the following tables to determine expectedness:

- **Table 1:** To determine expectedness in relation to dabrafenib in patients taking dabrafenib monotherapy
- **Table 2:** To determine expectedness in relation to trametinib in patients taking trametinib monotherapy
- **Table 3:** To determine expectedness in relation to dabrafenib in patients taking dabrafenib in combination with trametinib
- **Table 4:** To determine expectedness in relation to trametinib in patients taking trametinib in combination with dabrafenib

Table 1:Adverse reactions reported in the integrated safety population of dabrafenib monotherapy (n=578)

System Organ Class	Frequency (all grades)	Adverse Reactions
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Very common	Papilloma
	Common	Cutaneous squamous cell carcinoma
		Seborrhoeic keratosis
		Acrochordon (skin tags)
		Basal cell carcinoma
	Uncommon	New primary lesions
Immune system disorders	Uncommon	Hypersensitivity
Metabolism and nutrition disorders	Very common	Decreased appetite
	Common	Hypophosphataemia
		Hyperglycaemia
Nervous system disorders	Very common	Headache
Eye disorders	Uncommon	Uveitis
Respiratory, thoracic and mediastinal disorders	Very common	Cough
Gastrointestinal disorders	Very common	Nausea
		Vomiting
		Diarrhoea
	Common	Constipation
	Uncommon	Pancreatitis
Skin and subcutaneous tissue disorders	Very common	Hyperkeratosis
		Alopecia
		Rash
		Palmar-plantar erythrodysaesthesia
	Common	Dry skin
		Pruritus
		Actinic keratosis
		Skin lesion
		Erythema
		Photosensitivity Reaction
	Uncommon	Panniculitis
Musculoskeletal and connective tissue disorders	Very common	Arthralgia
		Myalgia
		Pain in extremity
Renal and urinary disorders	Uncommon	Renal failure, acute renal failure
		Nephritis
General disorders and administration site conditions	Very common	Pyrexia
		Fatigue
		Chills
		Asthenia
	Common	Influenza-like illness

Table 2 Adverse reactions reported in the integrated safety population of trametinib monotherapy (n=329)

System Organ Class	Frequency (all grades)	Adverse Reactions
Infections and infestation	Common	Folliculitis
		Paronychia
		Cellulitis
		Rash pustular
Blood and lymphatic system disorders	Common	Anaemia
Immune system disorders	Common	Hypersensitivity[a]
Metabolism and nutrition disorders	Common	Dehydration
Eye disorders	Common	Vision blurred
		Periorbital oedema
		Visual impairment
	Uncommon	Chorioretinopathy
		Papilloedema
		Retinal detachment
		Retinal vein occlusion
Cardiac disorders	Common	Left ventricular dysfunction
		Ejection fraction decreased
		Bradycardia
	Uncommon	Cardiac failure
Vascular disorders	Very common	Hypertension
		Haemorrhage[b]
	Common	Lymphoedema
Respiratory, thoracic and mediastinal disorders	Very common	Cough
		Dyspnoea
	Common	Pneumoniti
	Uncommon	Interstitial lung disease
Gastrointestinal disorders	Very common	Diarrhoea
		Nausea
		Vomiting
		Constipation
		Abdominal pain
		Dry mouth
	Common	Stomatitis
	Uncommon	Gastrointestinal perforation
		Colitis
Skin and subcutaneous disorders	Very common	Rash
		Dermatitis acneiform
		Dry skin
		Pruritus
		Alopecia
	Common	Erythema
		Palmar-plantar erythrodysaesthesia syndrome
		Skin fissures
		Skin chapped

Musculoskeletal and connective tissue disorders	Uncommon	Rhabdomyolysis
General disorders and administration site conditions	Very Common	Fatigue
		Oedema peripheral
		Pyrexia
	Common	Face oedema
		Mucosal inflammation
		Asthenia
Investigations	Very common	Aspartate aminotransferase increased
	Common	Alanine aminotransferase increased
		Blood alkaline phosphatase increased
		Blood creatine phosphokinase increased
[a] May present with symptoms such as fever, rash, increased liver transaminases, and visual disturbances [b] Events include but are not limited to: epistaxis, haematochezia, gingival bleeding, haematuria, and rectal,haemorrhoidal, gastric, vaginal, conjunctival, intracranial and post procedural haemorrhage.		

Table 3 Adverse reactions reported in the integrated safety population of dabrafenib in combination with trametinib (n=641)

System Organ Class	Frequency (all grades)	Adverse Reactions
Infections and infestations	Very common	Urinary tract infection
		Nasopharyngitis
	Common	Cellulitis
		Folliculitis
		Paronychia
		Rash pustular
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Common	Cutaneous squamous cell carcinoma[a]
		Papilloma[b]
		Seborrhoeic keratosis
	Uncommon	New primary melanoma
		Acrochordon (skin tags)
Blood and lymphatic system disorders	Very common	Neutropenia
	Common	Anaemia
		Thrombocytopenia
		Leukopenia
Immune system disorders	Uncommon	Hypersensitivity[c]
Metabolism and nutrition disorders	Very common	Decreased appetite
	Common	Dehydration
		Hyponatraemia
		Hypophosphataemia
		Hyperglycaemia

Nervous system disorders	Very common	Headache
		Dizziness
Eye disorders	Common	Vision blurred
		Visual impairment
		Chorioretinopathy
		Uveitis
		Retinal detachment
		Periorbital oedema
Cardiac disorders	Common	Ejection fraction decreased
	Uncommon	Bradycardia
	Not Know	Myocarditis
Vascular disorders	Very common	Hypertension
		Haemorrhaged
	Common	Hypotension
		Lymphoedema
Respiratory, thoracic and mediastinal disorders	Very common	Cough
	Common	Dyspnoea
		Pneumonitis
Gastrointestinal disorders	Very common	Abdominal pain
		Constipation
		Diarrhoea
		Nausea
		Vomiting
	Common	Dry mouth
		Stomatitis
	Uncommon	Pancreatitis
Skin and subcutaneous disorders	Very common	Dry skin
		Pruritus
		Rash
		Erythema
	Common	Dermatitis acneiform
		Actinic keratosis
		Night sweats
		Hyperkeratosis
		Alopecia
		Palmar-plantar erythrodysaesthesia Syndrome
		Skin lesion
		Panniculitis
		Skin fissures
		Photosensitivity Reaction
Musculoskeletal and connective tissue disorders	Very common	Arthralgia
		Myalgia
		Pain in extremity
		Muscle spasms
Renal and urinary disorders	Common	Renal failure
	Uncommon	Nephritis

General disorders and administration site conditions	Very common	Fatigue
		Chills
		Asthenia
		Oedema peripheral
		Pyrexia
	Common	Mucosal inflammation
		Influenza-like illness
		Face oedema
Investigations	Very common	Alanine aminotransferase increased
		Aspartate aminotransferase increased
	Common	Blood alkaline phosphatase increased
		Gamma-glutamyltransferase increased
		Blood creatine phosphokinase increased
[a] cu SCC: SCC, SCC of the skin, SCC in situ (Bowen's disease) and keratoacanthoma [b] Papilloma, skin papilloma [c] Includes drug hypersensitivity [d] Bleeding from various sites, including intracranial bleeding and fatal bleeding		

Table 4 Adverse reactions reported in the integrated safety population of trametinib in combination with dabrafenib (n=641)

System Organ Class	Frequency (all grades)	Adverse Reactions
Infections and Infestations	Very Common	Urinary tract infection
		Nasopharyngitis
	Common	Cellulitis
		Folliculitis
		Paronychia
		Rash pustular
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Common	Cutaneous squamous cell carcinoma[a]
		Papilloma[b]
		Seborrhoeic keratosis
	Uncommon	New primary melanoma
		Acrochordon (skin tags)
Blood and lymphatic system disorders	Very common	Neutropenia
	Common	Anaemia
		Thrombocytopenia
		Leukopenia
Immune system disorders	Uncommon	Hypersensitivity[c]

Metabolism and nutrition disorders	Very common	Decreased appetite
	Common	Dehydration
		Hyponatraemia
		Hypophosphataemia
		Hyperglycaemia
Nervous system disorders	Very common	Headache
		Dizziness
Eye disorders	Common	Vision blurred
		Visual impairment
	Uncommon	Chorioretinopathy
		Uveitis
		Retinal detachment
		Periorbital oedema
Cardiac disorders	Common	Ejection fraction decreased
	Uncommon	Bradycardia
	Unknown	Myocarditis
Vascular disorders	Very common	Hypertension
		Haemorrhage[d]
	Common	Hypotension
		Lymphoedema
Respiratory, thoracic and mediastinal disorders	Very common	Cough
	Common	Dyspnoea
		Pneumonitis
Gastrointestinal disorders	Very common	Abdominal pain
		Constipation
		Diarrhoea
		Nausea
		Vomiting
	Common	Dry mouth
		Stomatitis
	Uncommon	Pancreatitis
		Gastrointestinal perforation
		Colitis
Skin and subcutaneous disorders	Very common	Dry skin
		Pruritus
		Rash
		Erythema
	Common	Dermatitis acneiform
		Actinic keratosis
		Night sweats
		Hyperkeratosis
		Alopecia
		Palmar-plantar erythrodysaesthesia syndrome
		Skin lesion
		Hyperhidrosis
		Panniculitis
		Skin fissures
		Photosensitivity Reaction

Musculoskeletal and connective tissue disorders	Very common	Arthralgia
		Myalgia
		Pain in extremity
		Muscle spasms
Renal and urinary disorders	Common	Renal failure
	Uncommon	Nephritis
General disorders and administration site conditions	Very common	Fatigue
		Chills
		Asthenia
		Oedema peripheral
		Pyrexia
	Common	Mucosal inflammation
		Influenza-like illness
		Face oedema
Investigations	Very common	Alanine aminotransferase increased
		Aspartate aminotransferase increased
	Common	Blood alkaline phosphatase increased
		Gamma-glutamyltransferase increased
		Blood creatine phosphokinase increased

[a] cu SCC: SCC, SCC of the skin, SCC in situ (Bowen's disease) and keratoacanthoma
[b] Papilloma, skin papilloma
[c] Includes drug hypersensitivity
[d] Bleeding from various sites, including intracranial bleeding and fatal bleeding