Division: Worldwide Development
Information Type: Clinical Protocol

Title:	Phase II biomarker study evaluating the upfront combination of BRAF inhibitor dabrafenib with MEK inhibitor trametinib versus the combination after eight weeks of monotherapy with dabrafenib or trametinib in patients with metastatic and unresectable stage III or IV melanoma harbouring an activating BRAF mutation

Compound Number: GSK1120212+GSK2118436

Development Phase II

Effective Date: 28-OCT-2013

Protocol Amendment Number: 01

Description: Three-arm, open-label, randomised Phase II study to evaluate whether the different sequencing of dabrafenib and trametinib monotherapies and the upfront combination has an impact on translational or clinical activity in patients with BRAF mutant metastatic unresectable stage IIIc or IV melanoma.

Subject: Oncology, trametinib, dabrafenib, MEK, BRAF, melanoma

Author(s): GlaxoSmithKline: PPD

PPD Institut Gustave Roussy

Revision Chronology:

2012N132406_00	2013-APR-15	Original
2012N132406_01	2013-OCT-28	Amendment 01

1. Update to figure 1 Trial design to better reflect the design of the study
2. Replaced “treatment vials” with Treatment bottles” as the study drugs are tablets.
3. Change of brain MRI from 4 weeks to 5 weeks before Day 1
4. Amendment and further clarification around the biopsies taken for this study as requested by the ANSM. This includes: a) That the biopsies will only be done on cutaneous and subcutaneous lesions only if they are easily accessible; b) confirmation that no deep lesion biopsies will be performed; c) clarification of who is qualified to perform the biopsies;
5. Clarification regarding the confirmation of response
6. Clarification to the PK blood sampling
7. New France specific Appendix 6 added to reflect the monitoring required for Cutaneous Squamous Cell Carcinoma (CuSCC), new primary melanoma and non-cutaneous secondary/recurrent malignancy as reqested by ANSM

SPONSOR SIGNATORY:

PPD

28-October-2013

Michael Arning
VP Oncology Medical Affairs

Date

SPONSOR INFORMATION PAGE

Clinical Study Identifier: BRF116613

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In some countries, the clinical trial sponsor may be the local GlaxoSmithKline affiliate company (or designee). Where applicable, the details of the Sponsor and contact person will be provided to the relevant regulatory authority as part of the clinical trial submission.

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European Drug Regulatory Authorities Clinical Trials (EudraCT) Number 2012-004577-12

INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receive the appropriate information throughout the study.

Investigator Name: _____

_____ _____

Investigator Signature Date

TABLE OF CONTENTS

PAGE

LIST OF ABBREVIATIONS

AE	Adverse event
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase (SGPT)
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase (SGOT)
ATP	Adenosine triphosphate
BCRP	Breast cancer resistance protein
BID	Twice a day
BUN	Blood urea nitrogen
cfDNA	Circulating cell free DNA
CI	Confidence interval
CPK	Creatine phosphokinase
CR	Complete response
$_{Cr}$ CL	Creatinine clearance
CRP	C-reactive protein
CSR	Central serous retinopathy
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DBP	diastolic blood pressure
dL	Deciliter(s)
DMSO	dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DoR	Duration of Response
DTIC	dacarbazine
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EGFR	Epidermal growth factor receptor
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose positron emission tomography
FSH	Follicle-stimulating hormone
g	Gram
G6PD	glucose-6-phosphate dehydrogenase
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transpeptidase
GSK	GlaxoSmithKline
HBV	Hepatitis B Virus
HCG	Human chorionic gonadotropin
HCV	Hepatitis C Virus
HFSR	Hand-foot skin reaction
HIV	Human Immunodeficiency Virus
HPLC	High-performance liquid chromatography

HR	Hazard ratio
HRT	Hormone-replacement therapy
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committees
IHC	Immunohistochemistry
INR	International normalized ratio
ITT	Intent-to-treat
IVRS	Interactive voice response system
KA	Keratoacanthoma
L	Liter(s)
LDH	lactate dehydrogenase
LLN	Lower limit of normal
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mL	Milliliter
mm	Millimeter
MRI	Magnetic resonance imaging
MSDS	Material Safety Data Sheet
NA	Not applicable
NCI	National Cancer Institute
NE	Not evaluable
NED	no evidence of disease
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression free survival
Pg	Picogram
Pgp	P-glycoprotein
PK	Pharmacokinetic
Pmol	Picomole
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
QTc	Corrected QT interval on electrocardiogram
RAMOS	Registration and Medication Ordering System
RAP	Reporting and analysis plan
RECIST	Response Evaluation Criteria In Solid Tumours
RNA	Ribonucleic acid
RR	response rate
RVO	Retinal vein occlusion
s.d.	Standard deviation
SAE	Serious adverse event
SBP	Systolic blood pressure

SCC	Squamous cell carcinoma
SD	Stable disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SPF	Skin protection factor
SPM	Study Procedures Manual
ULN	Upper limit of normal

Trademark Information

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None

PROTOCOL SUMMARY

Rationale

Both dabrafenib and trametinib have demonstrated clinical activity as monotherapies and in combination in BRAF-mutant melanoma. However, duration of responses seem to be limited due to acquired drug resistance.

Anti-BRAF treatments are associated with skin side effects like squamous cell carcinoma and keratoacanthoma as well as rash and hyperkeratosis.

Clinical data from the combination study BRF113220 suggests that both resistance and secondary skin tumours might be reduced by using both inhibitors simultaneously.

The goal of this protocol is to study the sequential effects of BRAF and MEK inhibition on skin, blood and tumour biomarkers and to study the correlation between biomarkers and response to treatment and intrapatient toxicity.

Objectives

Primary objective:

- To evaluate biomarkers linked to treatment response, resistance and toxicity including skin toxicity when dabrafenib and trametinib combination is given upfront or as monotherapy before the combination treatment.

Secondary objectives:

- To evaluate the clinical response (ORR)
- To characterise the safety profile of dabrafenib and trametinib in monotherapy and/or in combination including incidences of squamous cell carcinoma (SCC) and other proliferative cutaneous lesions as well as the papulo-pustular rash.
- To evaluate dabrafenib, trametinib and combination exposures in connection to clinical response and toxicity.

Exploratory objectives:

- To evaluate changes in inflammation
- To evaluate the impact of the two drugs, separately and in combination on immune system
- To evaluate the progression-free survival (PFS) and duration of response (DoR).

Study Design

This is a three-arm, open label, randomised, Phase II study comparing the upfront combination of dabrafenib (GSK2118436) with trametinib (GSK1120212) versus the combination after eight weeks of monotherapy treatment with dabrafenib or trametinib.

Approximately 54 eligible patients with histologically confirmed cutaneous melanoma that is either metastatic or unresectable (stage IIIc or IV) and BRAF V600E/K mutation positive as determined by a local laboratory will be randomised, 1:1:1 to one of the three treatment arms.

- Arm A: dabrafenib 150mg BID continuously during eight weeks followed by the combination of trametinib 2mg once daily with dabrafenib 150mg BID until disease progression, death or unacceptable toxicity.
- Arm B: trametinib 2mg/day continuously during eight weeks followed by the combination of trametinib 2mg once daily with dabrafenib 150mg BID until disease progression, death or unacceptable toxicity.
- Arm C: trametinib 2mg/day plus dabrafenib 150mg BID continuously until disease progression, death or unacceptable toxicity.

Biomarker analysis will be performed on blood, tumour and skin samples.

Study Assessments

The ORR, PFS and duration of response endpoints will be determined using investigator's lesion assessments as evaluated by the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1. Safety will be evaluated by clinical assessments including vital signs and physical examinations, 12-lead electrocardiograms (ECG), echocardiograms (ECHO), chemistry and haematology laboratory values and adverse events (AEs). Exposure to dabrafenib, dabrafenib metabolites, and trametinib will be evaluated by measuring drug and metabolite plasma concentrations.

1. INTRODUCTION

1.1. Background

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

The RAS/RAF/MEK/ERK pathway (i.e., the MAP kinase pathway) is a critical proliferation pathway in many human cancers. Oncogenic mutations in both RAS and BRAF signal through the extracellular signal regulated kinases MEK1 and MEK2. BRAF mutations have been identified at a high frequency in specific cancers, including up to 60% of melanoma tumours (Davies, 2002). In melanoma, more than 80% of the BRAF mutations cause a substitution of the amino acid glutamate (E) for valine (V) at position 600 (V600E) of the BRAF protein, whereas approximately 3-20% of melanoma mutations are a substitution of lysine (K) for valine at position 600 (V600K) (Gorden, 2003; Libra, 2005). Both mutations cause constitutive activation of BRAF, which in turn activates the MAP kinase pathway.

Dabrafenib is a potent and selective RAF kinase inhibitor of human wild type BRAF and CRAF enzymes as well as the mutant forms BRAFV600E, BRAFV600K and BRAFV600D. The mode of action of dabrafenib is consistent with competitive inhibition of adenosine triphosphate (ATP) binding. By contrast, trametinib is a reversible, highly selective, allosteric inhibitor of MEK1 and MEK2. Trametinib is non-competitive towards ATP and inhibits both MEK activation and kinase activity. Because BRAF and MEK are in the same pathway, and because MEK is a substrate of activated BRAF, inhibiting both proteins simultaneously rather than individually could provide more effective pathway inhibition and also decrease the likelihood of developing resistance. Data generated in cell line, mouse xenograft, and rat safety models with BRAF and MEK inhibitor combinations suggest enhanced effects on efficacy and less potential for proliferative skin lesions or stimulation of dormant tumours containing RAS mutations compared to treatment with a BRAF inhibitor alone.

Based on the demonstrated efficacy of both dabrafenib and trametinib as monotherapies along with preliminary clinical data suggesting that the combination may prevent resistance and improve efficacy, phase III clinical studies of the dabrafenib/trametinib combination are being initiated in advanced melanoma and as adjuvant therapy for high-risk Stage III disease.

1.1.1. The BRAF Inhibitor Dabrafenib as Monotherapy

Dabrafenib, a selective BRAF inhibitor, has shown activity with a manageable safety profile in phase 1 and 2 studies in patients with BRAF V600E/K-mutation positive metastatic melanoma. The BREAK-3 (BRF113683) global phase III trial was conducted

in patients with BRAF V600E mutation-positive advanced or metastatic melanoma randomised (3:1) to receive treatment with either dabrafenib (150 mg , twice daily [BID]) or dacarbazine (DTIC) (Hauschild, 2012). Patients were randomised by disease stage (unresectable Stage III, IVM1a and IVM1b versus IVM1c). Patients randomised to the DTIC arm were allowed to crossover to receive dabrafenib after confirmation of progressive disease (PD). The primary endpoint was progression free survival (PFS) based on investigator assessment in the intent-to-treat (ITT) population comprised of all randomised patients, regardless of whether or not treatment was administered. Secondary endpoints were overall survival (OS), overall response rate (ORR) in both groups and after crossover, PFS for patients randomised to the DTIC treatment groups after crossover, duration of response, safety/tolerability and BRAF mutation assay validation.

Two hundred and fifty patients were enrolled; including 187 that were randomised to dabrafenib and 63 to DTIC. At the time of data cut-off for the primary analysis, 141 patients were on study treatment (dabrafenib n=127; DTIC n=14) including 21/28 DTIC patients that crossed over to dabrafenib. Median age was 52 years; 31% had an Eastern Cooperative Oncology Group (ECOG) performance status ≤1, 66% were M1c, and 33% lactate dehydrogenase (LDH) greater than the upper limit of normal (>ULN) (Hauschild, 2012).

At the time of the primary analysis, there were 118 events (77 dabrafenib and 41 DTIC). The hazard ratio (HR) for PFS was 0.30 (95% confidence interval (CI): 0.18-0.53; p<0.0001). Median PFS was 5.1 months for dabrafenib and 2.7 months for DTIC by investigator assessment. OS data were immature. Confirmed response rate (RR) was 53% for dabrafenib and 19% for DTIC. Benefits in PFS and RR were observed in all subgroups evaluated.

The most frequent adverse events (AEs) (≥20%) in the dabrafenib arm were hyperkeratosis (37%), headache (32%), pyrexia (28%), arthralgia (27%), skin papillomas (24%), alopecia (22%), palmar-plantar erythrodysaesthesia syndrome (2%). Serious adverse events (SAEs) (>1%) on the dabrafenib arm included pyrexia (4%), squamous cell carcinomas (6%), and new primary melanomas (2%).

Further evidence for the safety and efficacy of dabrafenib has been established in a large (N=172) study of patients (BREAK-MB) with both controlled and uncontrolled brain metastases (Long, 2012). Activity in patients with the V600K mutation was also seen.

1.1.2. The MEK Inhibitor Trametinib as Monotherapy

Trametinib is a reversible, highly selective allosteric inhibitor of MEK1/2 activation and kinase activity. A Phase 3 trial, METRIC (MEK114267), was conducted in patients with BRAF V600E/K mutation positive advanced or metastatic melanoma. Patients were randomised 2:1 to trametinib (2mg once daily) or chemotherapy (DTIC or paclitaxel). Patients were stratified by baseline LDH level and prior chemotherapy; patients in the chemotherapy arm were allowed to crossover to receive trametinib after confirmation of PD. The primary endpoint was PFS in patients with BRAF V600E mutation-positive metastatic melanoma and no prior brain metastases; PFS was also evaluated in the ITT

population. Secondary endpoints were OS, ORR in the primary and ITT population and safety in the safety population (Flaherty, 2012b).

Three hundred and twenty-two patients were randomised to trametinib (n=214) or chemotherapy (n=108); 273 patients were BRAF V600E mutation-positive with no prior brain metastases. Median age was 54 years; all had an ECOG performance status of 0 (64%) or 1 (36%), and 65% were M1c (Flaherty, 2012b).

The HR for the primary population for PFS by investigator was 0.44 (95% CI 0.31–0.64; p<0.0001) in favour of trametinib with a median PFS of 4.8 months vs. 1.4 months with chemotherapy. The confirmed ORR was 24% with trametinib and 7% with chemotherapy. HR for interim OS was 0.53 (95% CI 0.30–0.94; p=0.0181), in favour of trametinib.

The most frequent AEs (≥20%) with trametinib were skin rash (57%), diarrhoea (43%), fatigue (26%), and oedema (26%). Known MEK inhibitor class effects were observed in this study including chorioretinopathy (<1%) and decreased ejection fraction (7%).

1.1.3. BRAF and MEK Inhibitors as Combination Therapy

A 4-part Phase I/II study (BRF113220) investigating the dabrafenib/trametinib combination is being conducted in patients with V600 BRAF mutation-positive solid tumours.

In Part B, patients were treated on 4 escalating dose levels of dabrafenib/trametinib (mg BID/mg once daily): 75/1, 150/1, 150/1.5, 150/2. Demographic and efficacy data for the melanoma patients and safety data for all 125 Part B patients were reported (Flaherty, 2012a).

Among 77 treatment-naïve patients with BRAF V600 mutation-positive melanoma and measurable disease according to Response Evaluation Criteria in Solid Tumours version 1.1(RECIST 1.1), median age was 52 years, 61% male, 57% ECOG performance status of 0, 91% V600E, 65% M1c stage, 26% prior brain metastases, and 52% LDH > ULN. Confirmed ORR was 56% (95% CI: 44.1%-67.2%) with 4 complete response (CR), 39 partial response (PR), 29 stable disease (SD) and3 PD. Confirmed response rates for each dose level tested in Part B were 67% (n=6), 64% (n=22), 44% (n=25), and 63% (n=24), respectively. Median PFS was 7.4 months overall (95% CI: 5.5-9.2), and 10.8 months (95% CI: 5.3, not reached) in the cohort treated with 150/2. Median duration of response for the entire cohort was 11.3 months (95% CI: 9.2, not reached) with a median duration on treatment of 10.7 months (including 38% of patients ongoing at the time of the analysis). The most common adverse events (AE) were pyrexia (52%), rash (45%), chills (38%), fatigue (37%), and nausea (34%). There were two grade 5 adverse events (AEs), pneumonia and hyponatraemia. The most common Grade 3/4 AEs were pyrexia (n=6, 5%), fatigue (n=6, 5%) and dehydration (n=6, 5%). Skin toxicity ≥ Grade 2 occurred in 17 (14%) patients. Cutaneous squamous cell carcinoma occurred in 3 (2%) patients and actinic keratoses in 2 (2%). The most common treatment related AEs (≥20%, all grades) among patients in Part B receiving 150 mg BID dabrafenib and 2 mg once daily

trametinib (n=79) were pyrexia (58%), skin toxicities including rash (42%), chills (37%), fatigue (38%) and nausea (34%).

The Part C data for the randomised comparison of two of dabrafenib/trametinib combination schedules versus dabrafenib monotherapy in 162 patients were reported (Flaherty, 2012a). The data showed that the combination of the full dose of dabrafenib (150 mg BID) and trametinib (2 mg once daily) is well tolerated and is more efficacious than dabrafenib monotherapy or a combination of 150 mg BID dabrafenib and 1 mg once daily trametinib in BRAF mutation-positive melanoma patients who have not been previously treated with a BRAF-inhibitor.

1.2. Study Rationale

Both dabrafenib and trametinib have demonstrated clinical activity as monotherapies and in combination in BRAF-mutant melanoma. However, duration of responses seem to be limited due to acquired drug resistance (Flaherty, 2012b; Hauschild, 2012).

Anti-BRAF treatments are associated with skin side effects like squamous cell carcinoma and keratoacanthoma as well as rash and hyperkeratosis (Chapman, 2011; Hauschild, 2012).

Clinical data from the combination study BRF113220 suggests that both resistance and secondary skin tumours might be reduced by using both inhibitors simultaneously (Flaherty, 2012a).

The goal of this protocol is to study the sequential effects of BRAF and MEK inhibition on skin, blood and tumour biomarkers and to study the correlation between biomarkers and response to treatment and intrapatient toxicity.

1.3. Dose Rationale

Dabrafenib and trametinib will be co-administered at their recommended monotherapy doses of 150 mg BID and 2.0 mg once daily, respectively. As monotherapies, these dose levels achieved > 80% target inhibition, and in the Phase III setting demonstrated confirmed response rates of 50% and 22%, respectively, in patients with V600 mutation-positive melanoma (Flaherty, 2012b; Hauschild, 2012). This combination dose is further supported by the PK and safety data obtained in Parts A, B and C of the combination study BRF113220 which showed no clinically meaningful drug-drug interaction and showed an acceptable safety profile for the proposed combination dose level (Flaherty, 2012a).

2. OBJECTIVES AND ENDPOINTS

Table 1 lists the study objectives and corresponding endpoints.

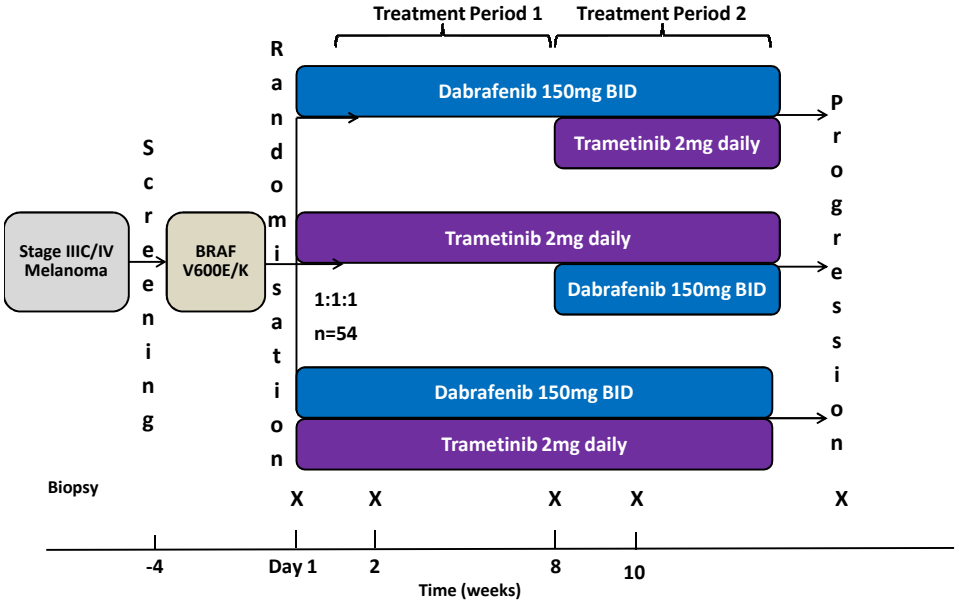
Table 1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate biomarkers linked to treatment response, resistance and toxicity including skin toxicity when dabrafenib and trametinib combination is given upfront or as monotherapy before the combination treatment.	Percentage Change of of Erk phosphorylation score from baseline
Secondary	
1. To evaluate the clinical response (ORR) 2. To characterise the safety profile of dabrafenib and trametinib in monotherapy and/or in combination including incidences of squamous cell carcinoma (SCC) and other proliferative cutaneous lesions as well as the papulo-pustular rash. 3. To evaluate dabrafenib, trametinib and combination exposures in connection to clinical response and toxicity.	4. Overall response rate (ORR; defined as the percentage of patients with a confirmed complete response [CR] or partial response [PR] at any time per Response Evaluation Criteria in Solid Tumours [RECIST], version 1.1. 5. Safety as measured by clinical assessments including vital signs and physical examinations, ECOG performance status, 12-lead electrocardiograms (ECG), echocardiogram (ECHO), chemistry and haematology laboratory values, incidence of squamous cell carcinoma and keratoacanthoma (KA), and adverse events (AEs) graded according to the Common Terminology Criteria for Adverse Events (CTC-AE), version 4.0 6. Plasma PK/PD evaluation
Exploratory	
7. To evaluate changes in inflammation 8. To evaluate the impact of the two drugs, separately and in combination on immune system 9. To evaluate the progression-free survival (PFS) and duration of response (DoR).	10. Inflammatory markers 11. T cell function by blood immunomonitoring and lymphocyte infiltration of tumours and skin 12. Progression-free survival (PFS; defined as the time from randomisation until the earliest date of disease progression or death due to any cause) and Duration of response (DoR; defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause among patients who achieve an overall response).

Refer to Section 9 for further details on endpoint definitions.

3. STUDY DESIGN

Figure 1 Study Schema



This is a three-arm, open label, randomised, Phase II study comparing the upfront combination of dabrafenib (GSK2118436) with trametinib (GSK1120212) versus the combination after eight weeks of monotherapy treatment with dabrafenib or trametinib.

Approximately 54 eligible patients with histologically confirmed cutaneous melanoma that is either metastatic or unresectable (stage IIIc or IV) and BRAF V600E/K mutation positive as determined by a local laboratory will be randomised, 1:1:1 to one of the three treatment arms.

- Arm A: dabrafenib 150mg BID continuously during eight weeks followed by the combination of trametinib 2mg once daily with dabrafenib 150mg BID until disease progression, death or unacceptable toxicity.
- Arm B: trametinib 2mg/day continuously during eight weeks followed by the combination of trametinib 2mg once daily with dabrafenib 150mg BID until disease progression, death or unacceptable toxicity.
- Arm C: trametinib 2mg/day plus dabrafenib 150mg BID continuously until disease progression, death or unacceptable toxicity.

Monitoring will be performed throughout the study according to the Time and Events Table (Table 19). Protocol specified guidelines for dose adjustments, interruptions and discontinuation due to AEs/liver toxicity are provided in Section 5.8, and Section 5.9, respectively. The visits allow a window of +/- 7 days. Dose interruptions should not alter the assessment schedule for any subsequent treatment period.

Biomarker analysis will be performed on blood, tumour and skin samples according to the Time and Events Table (Table 19).

Clinical responses will be evaluated using RECIST 1.1 criteria every 8 weeks. The response evaluation may be performed earlier if clinically indicated (for example, if patient has symptomatic deterioration suggesting rapid disease progression or to confirm clinical response at 4 weeks after achieving response).

Patients who show either radiographic or clinical progression of disease according to the investigator during the monotherapy treatment period in arm A or B will be able to go on to the combination treatment before completion of the 8 weeks monotherapy treatment. Patients will be treated with the combination treatment until disease progression, unacceptable toxicity or withdrawal from study whichever comes first.

The study will be considered completed when all patients ended study treatment either through progression, death or withdrawal from study for any reason.

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table (Table 19), are essential and required for study conduct.

Supplementary study conduct information not mandated to be present in this protocol will be provided in the Study Procedures Manual (SPM). The SPM will provide the site personnel with administrative and detailed technical information that does not impact patient safety.

4. PATIENT SELECTION AND DISCONTINUATION/ COMPLETION CRITERIA

4.1. Patient Selection Criteria

4.1.1. Number of Patients

Approximately 54 patients will be randomised 1:1:1 into the three treatment arms. See Section 9.2.1 for sample size assumptions.

4.1.2. Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational products dabrafenib (GSK2118436) and trametinib (GSK1120212) that may impact patient eligibility is provided in the Investigator Brochures (IBs).

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or patient safety. Therefore, adherence to the criteria as specified in the protocol is essential.

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

1. Signed written informed consent;
2. ≥18 years of age;
3. Histologically confirmed cutaneous melanoma that is either Stage IIIc (unresectable) or Stage IV (metastatic) (according to American Joint Committee on Cancer (AJCC) staging 7th edition).
4. BRAF V600E/K mutation-positive confirmed by a local laboratory.
5. Accessible melanoma tumours for biopsies (locally advanced primary melanoma or metastases)
6. Measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST 1.1) (Eisenhauer, 2009) on not biopsied lesions. Refer to Section 7.3.3.1 for the definition of a measureable lesion.
7. All prior anti-cancer treatment-related toxicities (except alopecia) must be ≤ Grade 1 according to the Common Terminology Criteria for Adverse Events version 4 (CTCAE version 4.0) at the time of randomisation.
8. Able to swallow and retain orally administered medication and does not have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels.
9. Women of childbearing potential must have a negative serum pregnancy test within 14 days prior to randomisation and agree to use effective contraception, as defined in Section 7.4.3.1, throughout the treatment period, and for 4 months after the last dose of study treatment.

10. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1. Refer to Appendix 1 for details.
11. Adequate baseline organ function as defined in Table 2.

Table 2 Definitions for Adequate Baseline Organ Function

System	Laboratory Values
Hematologic	
ANC	≥ 1.2 × 10^9/L
Haemoglobin	≥ 9 g/dL
Platelet count	≥ 75 x 10^9/L
PT/INR and PTT[a]	≤ 1.5 x ULN
Hepatic	
Albumin	≥ 2.5 g/dL
Total bilirubin	≤ 1.5 x ULN
AST and ALT	≤ 2.5 x ULN
Renal	
Calculated creatinine clearance[b]	≥50 mL/min
Cardiac	
Left Ventricular Ejection fraction (LVEF)[c]	≥ LLN by ECHO

a. Abbreviations: ALT = alanine transaminase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; INR = international normalized ratio; LLN = lower limit of normal; PT = prothrombin time; PTT = partial thromboplastin time; ULN = upper limit of normal.
b. Patients receiving anticoagulation treatment may be allowed to participate with INR established within the therapeutic range prior to randomisation. PT and PTT >1.5 ULN are permitted in these patients.
c. Calculate creatinine clearance using standard Cockcroft-Gault formula (Appendix 2). Creatinine clearance must be ≥50 mL/min to be eligible.
d. ECHO scans must be used throughout the study

12. In France, a patient will be eligible for inclusion in this study only if either affiliated to, or a beneficiary of, a social security category.

4.1.3. Exclusion Criteria

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or patient safety. Therefore, adherence to the criteria as specified in the protocol is essential.

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

1. Prior treatment with a BRAF or MEK inhibitor
2. Any major surgery, extensive radiotherapy, chemotherapy with delayed toxicity, biologic therapy, or immunotherapy within 21 days prior to randomisation and/or daily or weekly chemotherapy without the potential for delayed toxicity within 14 days prior to randomisation.
3. Taken an investigational drug within 28 days or 5 half-lives (minimum 14 days), whichever is shorter, prior to randomisation
4. Current use of a prohibited medication as described in Section 6.2.

5. Refusal of tumour and skin biopsies.
6. History of another malignancy.

   Exception: Patients, who have been disease-free for 3 years, or patients with a history of completely resected non-melanoma skin cancer, and/or patients with indolent second malignancies are eligible.

7. Any serious and/or unstable pre-existing medical conditions (aside from malignancy exceptions specified above), psychiatric disorders, or other conditions that could interfere with the patient's safety, obtaining informed consent, or compliance with study procedures.
8. Known Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection (with the exception of chronic or cleared HBV and HCV infection which will be allowed).
9. A history of glucose-6-phosphate dehydrogenase (G6PD) deficiency.
10. Brain metastases are excluded unless:

    a. All known lesions were previously treated with surgery or stereotactic surgery (whole-brain radiation is not allowed unless given after definitive treatment with surgery or stereotactic surgery), OR
    b. Brain lesion(s), if still present, must be confirmed stable (i.e., no increase in lesion size) for ≥ 12 weeks prior to randomisation (stability must be confirmed with two consecutive magnetic resonance image (MRI) or computed tomography (CT) scans with contrast, AND
    c. Asymptomatic with no corticosteroid requirements for ≥ 4 weeks prior to randomisation, AND
    d. No enzyme inducing anticonvulsants for ≥ 4 weeks prior to randomisation

    In addition, for patients that had brain metastases but currently have no evidence of disease (NED), NED for ≥12 weeks is required and must be confirmed by two consecutive scans, separated by ≥6 weeks, prior to randomisation.

11. A history or evidence of cardiovascular risk including any of the following:

    a. LVEF < LLN
    b. A QT interval corrected for heart rate using the Bazett's formula (QTcB; Appendix 3) ≥480 msec;
    c. A history or evidence of current clinically significant uncontrolled arrhythmias;

       Exception: Patients with atrial fibrillation controlled for > 30 days prior to randomisation are eligible.

    d. A history (within 6 months prior to randomisation) of acute coronary syndromes (including myocardial infarction or unstable angina), coronary angioplasty;

e. A history or evidence of current ≥Class II congestive heart failure as defined by the New York Heart Association (NYHA) guidelines (Appendix 4);

f. Treatment refractory hypertension defined as a blood pressure of systolic> 140 mmHg and/or diastolic > 90 mm Hg which cannot be controlled by anti-hypertensive therapy;

g. Patients with intra-cardiac defibrillators or permanent pacemakers;

h. Known cardiac metastases;

i. Abnormal cardiac valve morphology (≥grade 2) documented by echocardiogram (patients with grade 1 abnormalities [i.e., mild regurgitation/stenosis] can be entered on study). Patients with moderate valvular thickening should not be entered on study.

12. A history or current evidence/risk of retinal vein occlusion (RVO) or central serous retinopathy (CSR) including:

    a. Presence of predisposing factors to RVO or CSR (e.g., uncontrolled glaucoma or ocular hypertension, uncontrolled hypertension, uncontrolled diabetes mellitus, or a history of hyperviscosity or hypercoagulability syndromes); or

    b. Visible retinal pathology as assessed by ophthalmic examination that is considered a risk factor for RVO or CSR such as:

        i. Evidence of new optic disc cupping;

        ii. Evidence of new visual field defects on automated perimetry;

        iii. Intraocular pressure >21 mmHg as measured by tonography.

13. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to the study treatments, their excipients, and/or dimethyl sulfoxide (DMSO).

14. Pregnant or lactating females

15. Interstitial lung disease or pneumonitis

4.2. Permanent Discontinuation from Study Treatment and Patient Completion Criteria

4.2.1. Permanent Discontinuation from Study Treatment

Patients will receive study treatment when on combination therapy until disease progression, death or unacceptable adverse event, including haematologic or other non-haematologic toxicity, and/or meeting stopping criteria for liver chemistry defined in Section 5.9.1. A patient will be allowed to continue on monotherapy (either dabrafenib or trametinib) if only one study drug is permanently discontinued.

Note: Continuation of combination study treatment beyond radiographic or clinical disease progression (as defined by RECIST 1.1) may be possible if the investigator determines that patient has clear evidence of clinical benefit from study treatment, continuing study drugs may be in the best interest for the patient and the patient is willing to continue on study drugs. In this case, consultation between the investigator and the GSK Medical Monitor is mandatory. If continuing the patient on study treatment is agreed then all study procedures, including tumour assessments, must be followed as scheduled (Table 19). In addition, after each tumour assessment, the investigators must confirm with the GSK Medical Monitor that the patient is still benefiting from study treatment and therefore can continue receiving study treatment.

In addition study treatment may be permanently discontinued for any of the following reasons:

- deviation(s) from the protocol
- request of the patient or proxy
- investigator's discretion
- patient is lost to follow-up
- study is closed or terminated.

The primary reason study treatment was permanently discontinued must be documented in the patient's medical records and in the electronic case record form (eCRF).

If the patient voluntarily discontinues from treatment due to toxicity, 'adverse event' will be recorded as the primary reason for permanently discontinuation on the eCRF.

Once a patient has permanently discontinued from study treatment, the patient will not be allowed to be retreated.

All patients who discontinue from study treatment will have safety assessments as specified in Time and Events Table (Table 19) under End-of-study visit.

4.2.2. Patient Completion and Withdrawal

A patient will be considered to have completed the study if the patient has disease progression or dies during the study treatment.

A patient will be considered to have withdrawn from the study if the patient has stopped study treatment due to toxicity, has withdrawn consent or if the study is

closed/terminated. The investigator should attempt to complete the End-of-study assessments as detailed in the Times and Events Table (Table 19).

There is no survival follow-up on patients. For patients who did not progress on study drug but withdrew due to toxicity the individual's observation will be censored.

5. STUDY TREATMENTS

The term 'study treatment' is used throughout the protocol to describe any combination of products received by the patient as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

5.1. GSK Investigational Products

5.1.1. Dabrafenib

Dabrafenib will be provided as 50 mg and 75 mg capsules. Each capsule will contain 50 mg or 75 mg of free base (present as the mesylate salt). Dabrafenib will be provided to sites by GSK. The contents of the label will be in accordance with all applicable regulatory requirements.

5.1.2. Trametinib

Trametinib study medication will be provided as 0.5 mg and 2.0 mg tablets. Each tablet will contain 0.5 mg or 2.0 mg of trametinib parent (present as the DMSO solvate). Trametinib will be provided to sites by GSK. The contents of the label will be in accordance with all applicable regulatory requirements.

Under normal conditions of handling and administration, investigational product is not expected to pose significant safety risks to site staff. Material Safety Data Sheets (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from GSK upon request.

5.2. Dosage and Administration

Please refer to Section 5.8 for rules for dose modifications.

No special preparation of study medication is required.

Study treatments will be administered as follows:

- Dabrafenib, 150 mg, BID
- Trametinib, 2.0 mg, once daily

Both study treatments should be administered **in the morning** at approximately the same time every day. The second dose of dabrafenib (150 mg) should be administered approximately 12 hours after the morning dose. Study medication should be taken orally with approximately 200 mL of water under fasting conditions, either 1 hour before or 2 hours after a meal. During the combination therapy, if administration of trametinib is interrupted or permanently discontinued, administration of dabrafenib may be continued. If administration of dabrafenib is interrupted, administration of trametinib may continue.

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

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

Patients should abstain from ingestion of any food or drink containing grapefruit and grapefruit juice, Seville oranges, or pomelos within 7 days prior to randomisation until treatment discontinuation, as these have been shown to inhibit CYP3A4 activity.

Patients should start treatment as soon as possible after randomisation but no later than 72 hours post-randomisation.

5.3. Handling and Storage of Study Treatment

Dabrafenib, trametinib must be dispensed and administered in accordance with the protocol, and only to patients enrolled in the study. Dabrafenib and trametinib must be stored in a secure area under the appropriate physical conditions for the product. Study medication is to be stored at the temperature specified on the label. Maintenance of a temperature log (manual or automated) is required. Access to and administration of dabrafenib and trametinib will be limited to the investigator and authorized site staff.

Procedures for final disposition of unused study treatments will be provided in the SPM.

5.4. Treatment Assignment

Patients will be identified by a unique patient number that will remain consistent for the duration of the study.

Upon completion of all the required screening assessments, eligible patients will be registered into RAMOS (Registration and Medication Ordering System), the GSK interactive voice response system (IVRS), by the investigator or authorized site staff. RAMOS allows study sites to register and randomise patients, and also records stratification information.

Randomisation will be done centrally using a randomisation schedule generated by the GSK Biostatistical Department, which will assign patients in a 1:1:1 ratio to:

- Dabrafenib monotherapy followed by dabrafenib and trametinib combination therapy;
- Trametinib monotherapy followed by dabrafenib and trametinib combination therapy;
- Dabrafenib and trametinib combination therapy

Once a randomisation number has been assigned it must not be re-assigned even in cases of errors.

5.5. Blinding

This is an open-label study

5.6. Product Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of investigational product dispensed and/or administered to study patients, the amount returned by study patients, and the amount received from and returned to GSK, when applicable. Product accountability records must be maintained throughout the course of the study. Refer to the SPM for further detailed instructions on product accountability.

5.7. Treatment Compliance

Patients will be instructed to return treatment bottles at each visit. Compliance with dabrafenib and trametinib will be assessed through querying the patient during the site visits and documented in the source documents and eCRF.

A record of the number of dabrafenib and trametinib tablets dispensed to and taken by each patient must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the CRF. The investigator will make every effort to bring non-compliant patients into compliance.

5.8. Dose Modification Guidelines

The severity of AEs will be graded using the CTCAE, version 4.0. The section includes:

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

Note: With the exception of pyrexia (likely related to dabrafenib), the guidance suggests that both therapies be reduced simultaneously in response to toxicities that are considered by the investigator to be treatment related.

Table 3 Categories of Dose Modification Guidelines

Adverse Event	Dabrafenib	Trametinib	Section
General Guidelines for Clinically Significant Toxicities	X	X	Section 5.8.2
Guidelines for Specific Adverse Events			
Cardiovascular Adverse Events			
LVEF	X	X	Section 5.8.3.1
Hypertension	X	X	Section 5.8.3.2
Prolonged QTc	X	X	Section 5.8.3.3
Skin –Related Adverse Events (Except cuSCC)[a]			
Rash	X	X	Section 5.8.4.1
Hand-Foot Skin Reaction	X	X	Section 5.8.4.2
Other Adverse Events			
Pyrexia	X		Section 5.8.5.1
Diarrhea	X	X	Section 5.8.5.2
Renal Insufficiency	X	X	Section 5.8.5.3
Visual Changes	X	X	Section 5.8.5.4
Pneumonitis	X	X	Section 5.8.5.5
Liver Chemistry Stopping Criteria	X	X	Section 5.9

e. [a]Refer to Section 5.8.4.3 for management of cuSCC

5.8.1. Dose Levels of dabrafenib and trametinib

The dose levels for this study are provided in Table 4.

Table 4 Dose Level Reduction Guidelines

Dose Level	Dabrafenib Dose/Schedule	Trametinib Dose/Schedule
Starting Dose	150 mg BID	2 mg once daily
-1 (1st Dose reduction)	100 mg BID	1.5 mg once daily
-2 (2nd Dose reduction)	75 mg BID	1.0 mg once daily

Abbreviation: BID = twice daily

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

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

Note: Approval from the GSK Medical Monitor is required to restart study treatment after ≥21 days of interruption.

5.8.2. General Guidelines for Clinically Significant Toxicities

General guidelines regarding management and dose reduction for adverse events that are considered by the investigator to be related to study treatment and which do not have specific guidelines (Table 3) are provided in Table 5.

Table 5 Dose Modification Guidelines for Events Considered Related to Study Treatment

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

5.8.3. Guidelines for Cardiovascular Adverse Events

Cardiovascular adverse events have been seen in patients receiving either dabrafenib, trametinib or both in combination. (See the IBs for additional information.)

5.8.3.1. Left Ventricular Ejection Fraction (LVEF)

Decreases of the left-ventricular-ejection-fraction (LVEF) have been observed in patients receiving trametinib monotherapy and in combination with dabrafenib. Therefore, ECHOs must be performed to assess cardiac ejection fraction at regular intervals as outlined in the Time and Events Table (Table 19). If possible ECHO assessment should be performed by the same operator throughout the study. Dose modification guidance and stopping criteria for LVEF decrease are provided in Table 6.

Table 6 Dose Modification Guidelines and Stopping Criteria for LVEF Decrease

Clinic	LVEF-drop (%) or CTCAE grade	Action and Dose Modification
Asymptomatic	Absolute decrease of >10% in LVEF compared to baseline and ejection fraction below the institution's LLN	Interrupt study treatment and repeat ECHO within 2 weeks[a] If the LVEF **recovers** within 4 weeks (defined as LVEF ≥LLN and absolute decrease ≤10% compared to baseline) Consult with the GSK medical monitor and request approval for restart Restart with trametinib or placebo reduced by one dose level Restart dabrafenib at previous dose level Repeat ECHO 2 , 4 , 8 and 12 weeks after re-start; continue in intervals of 12 weeks thereafter If LVEF **does not recover** within 4 weeks Consult with cardiologist **Permanently discontinue study treatment** Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution Consult with GSK medical monitor
Symptomatic[b]	Grade 3: resting LVEF 39-20% or >20% absolute reduction from baseline	**Permanently discontinue study treatment.** **Consult with cardiologist** Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution
	Grade 4: resting LVEF <20%	

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

a. If ECHO does not show LVEF recovery after 2 weeks, repeat ECHO 2 weeks later.

b. Symptoms may include: dyspnea, orthopenea, and other signs and symptoms of pulmonary congestion and oedema.

5.8.3.2. Hypertension

Increases in blood pressure have been observed in patients receiving trametinib. Recommendations for blood pressure monitoring and management are provided in this section.

Monitoring of Hypertension

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

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

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

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

Asymptomatic hypertension is defined as an increase of SBP >140 mm Hg and/or DBP >90 mm Hg in the absence of headache, light-headedness, vertigo, tinnitus, episodes of fainting or other symptoms indicative of hypertension that resolve after the blood pressure is controlled within the normal range.

Management of Hypertension

For patients experiencing an increase in systolic and/or diastolic blood pressure that is persistent and may be associated with the study treatment, recommendations for the clinical management of hypertension are described in Table 7.

Table 7 Management and Dose Modification Guidelines for Hypertension

Hypertension	Action and Dose Modification
Scenario A: Asymptomatic and persistent[a] SBP of ≥140 and <160 mmHg, or DBP ≥90 and <100 mmHg, or Clinically significant increase in DBP of 20 mmHg (but still below 110 mmHg).	Continue study treatment at the current dose Adjust current or initiate new antihypertensive medication Titrate antihypertensive medication(s) during the next 2 weeks as indicated to achieve well-controlled[b] BP If BP is not well controlled within 2 weeks, consider referral to a specialist and go to scenario (B).
Scenario B: Asymptomatic SBP ≥160 mmHg, or DBP ≥100 mmHg, or Failure to achieve well-controlled BP within 2 weeks in Scenario A	Interrupt study treatment if clinically indicated Adjust current or initiate new antihypertensive medication(s) Titrate antihypertensive medication(s) during the next 2 weeks as indicated to achieve well-controlled BP Once BP is well controlled[b], restart study treatment **reduced by one dose level**
Scenario C: Symptomatic[c] hypertension or Persistent[d] SBP ≥160 mmHg, or DBP ≥100 mmHg, despite antihypertensive medication and dose reduction of study treatment	Interrupt study treatment Adjust current or initiate new antihypertensive medication(s) Titrate antihypertensive medication during the next 2 weeks as indicated to achieve well-controlled BP Referral to a specialist for further evaluation and follow-up is recommended Once BP is well controlled, restart study treatment **reduced by one dose level**
Scenario D: Refractory hypertension unresponsive to above interventions or hypertensive crisis.	Permanently discontinue study treatment Continue follow-up per protocol.

Abbreviations: BP = blood pressure; DBP = diastolic blood pressure; mmHg = millimetres mercury; SBP = systolic blood pressure;

a. Hypertension detected in two separate readings during up to three consecutive visits
b. Well-controlled blood pressure defined as SBP ≤140 mm Hg and DBP ≤90 mm Hg in two separate readings during up to three consecutive visits.
c. Symptomatic hypertension defined as hypertension aggravated by symptoms (e.g., headache, light-headedness, vertigo, tinnitus, episodes of fainting) that resolve after the blood pressure is controlled within the normal range.
d. Persistent hypertension is defined as asymptomatic hypertension after initially successful anti-hypertensive intervention.

5.8.3.3. Guidelines for Prolonged QTc

Guidelines for dose modification and stopping criteria due to QTC-prolongation are provided in Table 8.

Table 8 Withholding and Stopping Criteria for QTc-Prolongation

QTc-Prolongation[a]	Action and Dose Modification
QTcB ≥501 msec	• Interrupt study treatment until QTcB prolongation resolves to grade 1 or baseline • Restart at current dose level[b] • If event recurs, permanently discontinue study treatment

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

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

b. If the QTc prolongation resolves to grade 1 or baseline, the patient may resume study treatment if the investigator and GSK medical monitor agree that the patient will benefit from further treatment.

5.8.3.4. Guidelines for Valvular Toxicity

- Patients who have an asymptomatic, moderate regurgitation or stenosis by ECHO (Grade 2 mitral/tricuspid/aortic valvular toxicity per CTCAE v4.0) should temporarily discontinue study treatment and have a repeat evaluation by ECHO within 1 week. ECHO should be repeated every 1-2 weeks for 4 weeks or until valve recovery to baseline.

    o If the valve recovers to baseline any time during the next 4 weeks, after consultation and approval of the GSK medical monitor, the patient may be restarted on dabrafenib at a reduced dose(s). For such patients, monitoring of the valve via ECHO will then be performed 2 and 4 weeks after rechallenge, and every 4 weeks thereafter for 12 weeks and then per protocol.

    o If repeat ECHO does not reveal valve recovery to baseline within 4 weeks, then the patient should permanently discontinue study treatment. The valve should continue to be monitored via ECHO every 4 weeks for 16 weeks or until resolution.

- Patients with a Grade 3 or 4 (symptomatic, severe regurgitation/stenosis by imaging, with symptoms controlled by medical intervention) valvular toxicity must discontinue study treatment. Valvular toxicity should continue to be monitored every 4 weeks for 16 weeks or until resolution. If recovery occurs (return to baseline via imaging AND symptom resolution) within 4 weeks, the patient may restart dabrafenib at a reduced dose after consultation and approval of the GSK medical monitor. For such patients, monitoring of the valve via ECHO will then be performed 2 and 4 weeks after rechallenge, and every 4 weeks thereafter for 12 weeks and then per protocol.

ECHO must be performed at baseline and at follow-up visit(s). Copies of all ECHO(s) and cardiology consultations performed on patients who experience a valvular toxicity will be required by GSK for review.

5.8.4. Guidelines for Skin-related Adverse Events

Cutaneous adverse events have been observed in patients receiving dabrafenib, trametinib or both therapies in combination (see the Investigator Brochures for more information). Recommendations for supportive care and guidelines for dose modifications are provided (Section 5.8.4.1, Section 5.8.4.2 , and Section 5.8.4.3). The institutional standards for the management of skin-related AEs can differ from these guidelines. In this case, best clinical judgment should be applied and a consultation with the GSK Medical Monitor may be required. In addition, biopsies of any new skin lesions especially those suspicious of cuSCC for further study should be taken at the investigator's discretion.

5.8.4.1. Rash

Rash is a frequent AE observed in patients receiving trametinib, dabrafenib, or the combination of both therapies. Guidelines for rash management are based on experience with other MEK inhibitors and epidermal growth factor receptor (EGFR) inhibitors and are provided below (Table 9 and Table 10).

Table 9 Guidelines for Supportive Care of Rash

Type of Care	Action
Prevention/Prophylaxis[a]	• Avoid unnecessary exposure to sunlight • Apply broad-spectrum sunscreen (containing titanium dioxide or zinc oxide) with a skin protection factor (SPF) ≥15 at least twice daily. • Use thick, alcohol-free emollient cream (e.g., glycerine and cetomacrogol cream) on dry areas of the body at least twice daily.
Symptomatic Care[b]	• Pruritic lesions: cool compresses and oral antihistamine therapies • Papulopustular rash: topical steroids and antibiotics and antibiotics • Fissuring lesions: , silver nitrate, or zinc oxide cream • Desquamation: thick emollients and mild soap • Paronychia: antiseptic bath, local potent corticosteroids in addition to oral antibiotics; if no improvement, consult dermatologist or surgeon • Infected lesions: appropriate bacterial/fungal culture-driven systemic or topical antibiotics

Abbreviations: BID = twice daily; SPF = skin protection factor

a. Rash prophylaxis is recommended for the first 6 weeks of study treatment

b. Patients who develop rash/skin toxicities should be seen by a qualified physician and should receive evaluation for symptomatic/supportive care management

Guidelines for management and dose reduction for rash considered to be related to study treatment are provided in Table 10.

Table 10 Management and Dose Modification Guidelines for Rash

CTCAE Grade	Adverse Event Management	Action and Dose Modification
Grade 1	• Initiate prophylactic and symptomatic treatment measures[a] • Use moderate strength topical steroid[b] • Reassess after 2 weeks	• Continue study treatment • If rash does not recover to baseline within 2 weeks despite best supportive care, continue topical steroid, consider using more potent topical steroids
Grade 2	• Initiate prophylactic and symptomatic treatment measures • Use moderate strength topical steroid[b] • Use systemic tetracycline • Reassess after 2 weeks	• Continue study treatment • If no recovery to ≤grade 1 within 2 weeks, reduce study treatment by one dose level. If rash recovers to ≤grade 1 within 2 weeks, increase dose to previous dose level
Grade ≥3	• Use moderate strength topical steroids[b] PLUS oral • Use antibiotic • Consult dermatologist	• Interrupt study treatment until rash recovers to grade ≤1 • **Restart[c] with study treatment reduced by one dose level[d]** • If no recovery to grade ≤2 within 4 weeks**, permanently discontinue study treatment**

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events
a. Rash prophylaxis is recommended for the first 6 weeks of study treatment
b. Moderate-strength topical steroids: hydrocortisone 2.5% cream or fluticasone prioprionate 0.5% cream
c. Approval of GSK medical monitor is required to restart study treatment after >4 weeks of interruption.
d. Escalation of study treatment to previous dose level may be considered if no rash is evident 4 weeks after restarting study treatment

5.8.4.2. Guidelines for Hand-foot Skin Reactions (HFSR)

Episodes of Hand-foot Skin Reaction (HFSR) have been observed in patients receiving dabrafenib. Guidelines for management of HFSR are based on experience with other kinase inhibitors (Lacouture, 2008; McLellan, 2011) and are listed Table 11.

Table 11 Management and Dose modification Guidelines for Hand-Foot Skin Reaction (HFSR)

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

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events

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

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

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

c. Symptoms usually resolve within 2-4 weeks of treatment cessation. Approval of GSK medical monitor is required to restart study treatment after ≥21 days of interruption

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

5.8.4.3. Guidelines for cuSCC

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

5.8.5. Guidelines for Other Adverse Event of Special Interest

5.8.5.1. Guidelines for Pyrexia

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

Pyrexia accompanied by hypotension, dehydration requiring IV fluids, or severe rigors/chills should be reported as an SAE per Section 7.4.2.2.

Patients should be instructed on the importance of immediately reporting febrile episodes. In the event of a fever, the patient should be instructed to take non-steroidal anti-pyretics as appropriate to control fever. In patients experiencing pyrexia associated with rigors, severe chills, dehydration, hypotension, etc., renal function should be monitored carefully (see Section 5.8.5.3).

Guidelines regarding management and dose reduction for pyrexia considered to be related to study treatment are provided in Table 12.

Table 12 Management and Dose Modification Guidelines for Pyrexia

Adverse Event	Adverse Event Management	Action and Dose Modification

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

a. Pyrexia is defined as a body temperature equal to or above 38.5° Celsius or 101.3° Fahrenheit.
b. For patients experiencing pyrexia complicated by rigors, severe chills, etc., a clinical evaluation and laboratory work-up is mandatory for each event; anti-pyretic treatment should be started immediately at the first occurrence and prophylactic anti-pyretic treatment is recommended
c. Thorough clinical examination for signs and symptoms of infection or hypersensitivity is required; laboratory work-up should include full-blood-count, electrolytes, creatinine, blood urea nitrogen (BUN), C-reactive protein (CRP), liver-function tests, blood culture, and urine culture.
d. Oral hydration should be encouraged in patients without evidence of dehydration. Intravenous hydration is recommended in patients experiencing pyrexia complicated by dehydration/hypotension.
e. Anti-pyretic treatment may include acetaminophen, ibuprofen, or suitable anti-pyretic medication according to institutional standards. Prophylactic anti-pyretic treatment may be discontinued after three days in the absence of pyrexia
f. In patient experiencing pyrexia complicated by rigors, severe chills, etc., which cannot be controlled with anti-pyretic medication, oral corticosteroids should be started at the 2nd event and doses should be gradually increased for subsequent events.
g. Dabrafenib should be reduced by one dose level after three episodes of pyrexia complicated by rigors, severe chills, etc., which cannot be managed by best supportive care and increasing doses of oral steroids. Escalation of dabrafenib is allowed if no episode of pyrexia is observed in the 4 weeks subsequent to dose reduction.

5.8.5.2. Guidelines for Diarrhoea

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

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

Table 13 Management and Dose Modification Guidelines for Diarrhoea

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

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events

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

5.8.5.3. Guidelines for Renal Insufficiency

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

Guidelines regarding management and dose reduction for renal insufficiency considered to be related to study treatment by the investigator are provided in Table 14.

Table 14 Management and Dose Modification Guidelines for Renal Insufficiency

Serum Creatinine Level	Adverse Event Management	Action and Dose Modification
Serum creatinine increase >0.2 mg/dL (18 umol/L) but ≤0.5 mg/dL (44 umol/L) above baseline	Recheck serum creatinine within 1 week Serum creatinine increase > 1 week: contact GSK Medical Monitor If pyrexia is present, treat pyrexia as per guidelines[a]	Continue study treatment at the same dose level
Serum creatinine increase >0.5 mg/dL (44 umol/L) above baseline or serum creatinine >2 mg/dL (> 177 umol/L)	Monitor serum creatinine ≥ 2-times per week Hospitalization may be necessary if serum creatinine cannot be monitored frequently If pyrexia is present, treat pyrexia per guidelines[a] Consult nephrologist if clinically indicated Perform renal biopsy if clinically indicated, for example: Renal insufficiency persists despite volume repletion Patient has new rash or signs of hypersensitivity (such as elevated eosinophil count)	Interrupt study treatment until serum creatinine recovers to baseline Restart with study treatment[b]

Abbreviations: GSK = GlaxoSmithKline; NSAIDS = non-steroidal anti-inflammatory drugs

a. NSAIDs can induce renal insufficiency, especially in patients with dehydration; encourage oral fluids or consider intravenous fluids as clinically indicated. See guidelines for pyrexia 5.8.5.1.

b. Investigator may restart at either the same or a reduced dose level. Escalation of study treatment to previous dose level is allowed if another episode of renal insufficiency does not occur after 4 weeks of dose reduction. Consultation with GSK Medical Monitor is required before restarting study treatment if there is evidence of thrombotic microangiography.

5.8.5.4. Guidelines for Visual Changes

Episodes of visual changes have been observed in patients receiving dabrafenib, trametinib or the combination of both therapies. The causal relationship between a change in vision and the study treatment should be carefully explored and an ophthalmologist should be consulted. Special attention should be given to retinal (e.g., CSR) or retinal vein abnormalities (e.g., RVO). For events of visual changes regardless of severity, a blood sample for PK analysis must be drawn as close as possible to the time of the event.

Guidelines regarding management and dose reduction for visual changes considered to be related to study treatment are provided in Table 15.

Table 15 Management and Dose Modification Guidelines for Visual Changes

CTCAE Grade[a]	Adverse Event Management	Action and Dose Modification
Grade 1	Consult ophthalmologist within 7 days of onset Exclude CSR or RVO Consult retinal specialist in case of CSR or RVO Report RVO as SAE Continue follow up examination(s) by retinal specialist for CSR and RVO	Continue study treatment at the same dose level until ophthalmologic examination can be conducted[b] If ophthalmologic examination cannot be performed within 7 days of onset, interrupt study treatment until CSR and RVO can be excluded and symptoms resolve Restart study treatment at same dose level CSR: Interrupt study treatment until symptoms resolve and exam by retinal specialist shows resolution Restart with study treatment reduced by one dose level RVO: **Permanently discontinue study treatment**
Grade 2 and Grade 3	Consult ophthalmologist immediately Exclude CSR and RVO Consult retinal specialist in case of RVO or CSR for follow-up exam Report RVO as SAE Continue follow up examination(s) by retinal specialist for CSR and RVO	Interrupt study treatment until signs and symptoms have resolved to baseline Restart with study treatment reduced by one dose level CSR: Interrupt study treatment until symptoms resolve and exam by retinal specialist shows resolution Restart study treatment **reduced by one dose level** RVO: **Permanently discontinue study treatment**
Grade 4	Consult ophthalmologist immediately Exclude CSR and RVO Report RVO as SAE Continue follow up examination(s) by retinal specialist for CSR and RVO	**Permanently discontinue study treatment**

Abbreviations: CSR = central serous retinopaty; CTCAE = Common Terminology Criteria for Adverse Events; RVO = retinal vein occlusion; SAE = serious adverse event

a. Refers to CTCAE Version 4.0 'Eye disorders – Other, specify

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

5.8.5.5. Guidelines for Pneumonitis

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

Table 16 Management and Dose Modification Guidelines for Pneumonitis

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

Abbreviations: BAL= broncioalveolar lavage; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events

5.9. Stopping, Follow-up, and Monitoring Criteria for Hepatobiliary Events

5.9.1. Liver Chemistry Stopping Criteria

These liver chemistry stopping and follow-up criteria have been designed to assure patient safety and evaluate liver event etiology in alignment with the FDA Guidance for Industry – Drug-Induced Liver Injury: Premarketing Clinical Evaluation (July 2009, www.fda.gov). **Liver chemistry stopping criteria 1-5 are defined as:**

1. ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin) (or ALT≥3xULN and INR>1.5, if INR measured)

   NOTE: If serum bilirubin fractionation is not immediately available, study treatment should be discontinued if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.

2. ALT ≥5xULN.

3. ALT ≥3xULN if associated with symptoms (new or worsening) believed to be related to hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).

4. ALT ≥3xULN persists for ≥4 weeks

5. ALT ≥3xULN and cannot be monitored weekly for 4 weeks

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

- **Immediately discontinue patient from** study treatment
- Report the event to GSK **within 24 hours** of learning its occurrence
- Complete the liver event CRF and SAE data collection tool if the event also meets the criteria for an SAE All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) (or ALT≥3xULN and INR>1.5, if INR measured; INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants), termed 'Hy's Law', **must be reported as an SAE**.

  NOTE: if serum bilirubin fractionation is not immediately available, study treatment should be discontinued if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury
- Complete the liver imaging and/or liver biopsy CRFs if these tests are performed
- Perform liver event follow up assessments, and monitor the patient until liver chemistries resolve, stabilize, or return to baseline values as described below

- Withdraw the patient from the study after completion of the liver chemistry monitoring (unless further safety follow up is required or GSK Medical Governance approval of drug restart is granted, as described in Section 5.9.1.3).
- Do not restart investigational product unless written approval is granted by GSK Medical Governance (details for restarting investigational product are described in Section 5.9.1.3), whereupon the patient continues in the study after completion of the liver chemistry monitoring described in Section 5.9.1.2).

In addition, for patients meeting liver stopping criterion 1:

- Make every reasonable attempt to have patients return to clinic **within 24 hours** for repeat liver chemistries, liver event follow up assessments (refer to Section 5.9.1.1), and close monitoring
- A specialist or hepatology consultation is recommended
- Monitor patients twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

For patients meeting any of the liver stopping criteria 2-5:

- Make every reasonable attempt to have patients return to clinic **within 24-72 hrs** for repeat liver chemistries and liver event follow up assessments (refer to Section 5.9.1.1)
- Monitor patients weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values;
- Patients meeting criterion 5 should be monitored as frequently as possible.

5.9.1.1. Liver Event Follow-up Assessments

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

- Viral hepatitis serology including:
  - Hepatitis A IgM antibody
  - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM)
  - Hepatitis C RNA
  - Cytomegalovirus IgM antibody
  - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing)
  - Hepatitis E IgM antibody.
- Blood sample for pharmacokinetic (PK) analysis, obtained within 10 days of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the patient's best approximation. If the date/time of

the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM.

- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin ≥2xULN.
- Obtain complete blood count with differential to assess eosinophilia.
- Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, pyrexia, rash or eosinophilia as relevant on the AE form. Please note that treatment with trametinib often associates with rash which is usually acneiform and affects the scalp, face, neck, chest, and upper back. Discuss with GSK Medical Monitor as needed.
- Record use of concomitant medications such as acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications form.
- Record alcohol use on the liver event alcohol intake form.

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

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies and quantitative total immunoglobulin G (IgG or gamma globulins).
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.
- Serum acetaminophen adduct high-performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in patients with definite or likely acetaminophen use in the preceding week (James, 2009).
- Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen): quantitative hepatitis B DNA and hepatitis delta antibody. **NOTE**: if hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) – as outlined in: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1153793/.

5.9.1.2. Liver Chemistry Monitoring Criteria

For patients with ALT ≥3xULN **but** <5xULN **and** bilirubin <2xULN, without hepatitis symptoms or rash, and who can be monitored weekly for 4 weeks, the following actions should be taken:

- Notify the GSK Medical Monitor within 24 hours of learning of the abnormality to discuss patient safety
- Continue study treatment

- Return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline values
- If at any time the patient meets any of the liver chemistry stopping criteria 1 – 5, proceed as described above
- If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor patients twice monthly until liver chemistries normalize or return to within baseline values.
- Refer to Appendix 5 for an algorithm of liver chemistry monitoring, stopping, and follow-up criteria.

5.9.1.3. Drug Restart/Rechallenge Following Liver Events that are Possibly Related to Study Treatment

Approval by GSK for study treatment restart can be considered where:

The patient is receiving compelling benefit, benefit of drug restart exceeds risk, and no effective alternative therapy is available. Ethics Committee or Institutional Review Board approval of study treatment restart/rechallenge must be obtained, as required.

If the restart/rechallenge is approved by GSK in writing, the patient must be provided with a clear description of the possible benefits and risks of drug administration, including the possibility of recurrent, more severe liver injury or death.

The patient must also provide signed informed consent specifically for the study treatment restart/rechallenge. Documentation of informed consent must be recorded in the study chart.

Study treatment must be administered at the dose specified by GSK.

Patients approved by GSK for restart/rechallenge of study treatment must return to the clinic twice a week for liver chemistry tests until stable, liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.

5.9.1.4. Drug Restart Following Transient Resolving Liver Events Not Related to Study Treatment

Approval by GSK for drug restart can be considered where:

- Liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN). Ethics Committee or Institutional Review Board approval of study treatment restart/rechallenge must be obtained, as required.
- If restart of study treatment is approved by GSK in writing, the patient must be provided with a clear description of the possible benefits and risks of drug administration, including the possibility of recurrent, more severe liver injury or death.

- The patient must also provide signed informed consent specifically for the restart. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Patients approved by GSK for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated, and then laboratory monitoring may resume as per protocol. If protocol defined stopping criteria for liver chemistry elevations are met, study treatment must be stopped.

6. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

6.1. Permitted Medications and Non-drug Therapies

The investigator must be informed as soon as possible about any medication taken from the time of screening until 30 days after the last dose of study treatment with the exception of new anti-cancer therapy, if taken after study treatment discontinuation; these will be documented until study completion/withdrawal or death. Any concomitant medication(s), including dietary supplements, taken during the study will be recorded in the eCRF. The minimum requirement is that drug name, dose, the dates of administration and reason for medications are to be recorded. Additionally, a complete list of all prior anti-cancer therapies will be recorded in the eCRF.

Patients should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrhoeals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines. Use of anticoagulants such as warfarin is permitted provided that INR is monitored in accordance with local institutional practice.

While patients are on study treatment, palliative radiation therapy is permitted for non-target lesions that are either new or present at baseline. The total dose may not exceed 30 Gy.

6.2. Prohibited Medications and Non-drug Therapies

The use of certain medications and illicit drugs within 28 days or 5 half lives, whichever is shorter, prior to randomisation and for the duration of the study will not be allowed. The GSK medical monitor can approve the use of a prohibited medication if it is required for a single use (such as for a procedure) while treatment with study drug is interrupted.

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

- Other anti-cancer therapies;
- Other investigational drugs;
- Antiretroviral drugs (Note: Patients with known HIV are ineligible for study participation);
- Herbal remedies (e.g., St. John’s wort);
- Drugs that are strong inhibitors or inducers of CYP3A and CYP2C8 (for examples see Table 17) may only be used under special circumstances (e.g. as a single use for a procedure) while treatment with study drug is interrupted as they may alter dabrafenib and/or trametinib concentrations; consider therapeutic substitutions for these medications. Approval of the GSK medical monitor is required in these situations. A partial list of these medications is provided in Table 17. The list may be modified based on emerging data. Refer to the SPM for the most current list.

Table 17 Drugs that are Strong Inhibitors or Inducers of CYP3A and CYP2C8

Class/Therapeutic Area	Drugs/Agents
Antibiotics	Clarithromycin, rifamycin class agents (e.g., rifampin, rifabutin, rifapentine), telithromycin, troleandomycin
Antidepressant	Nefazodone
Antifungals	Itraconazole, ketoconazole, posaconazole, voriconazole
Hyperlipidemia	Gemfibrozil
Miscellaneous	Amiodarone, bosentan, carbamazepine, conivaptan, mibefranil, phenobarbital, phenytoin, s-mephenytoin

6.3. Medications to be used with Caution

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

- Drugs that are mild/moderate inhibitors or inducers of CYP3A and CYP2C8 as they may alter concentrations of dabrafenib.
- Dabrafenib has been shown to induce CYP3A4 in vivo and may induce CYP2B6. Other enzymes such as CYP2C8, CYP2C9, and CYP2C19 may also be affected. Co-administration of dabrafenib and medications which are affected by the induction of these enzymes (including warfarin) may result in loss of efficacy. If co-administration of these medications is necessary, investigators should monitor patients for loss of efficacy or consider substitutions of these medications. A partial list of these medications is provided in Table 18 and in the SPM.

Table 18 Medications to be used with Caution

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

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

Questions regarding concomitant medications should be directed to the GSK Medical Monitor for clarification.

6.4. Treatment after Discontinuation of Study Treatment or Withdrawal from/Completion of Study

The investigator is responsible for ensuring that consideration has been given for the post-study care of the patient's medical condition whether or not GSK is providing specific post-study treatment.

Post-study treatment will not be provided as part of the protocol. Upon discontinuation from assigned study treatment, patients may receive additional (non-protocol) anti-cancer therapy at the discretion of the treating physician.

6.5. Treatment of Study Treatment Overdose

In the event of a dabrafenib overdose, defined as administration of more than 300 mg as a single dose or 600 mg per day (the highest dose tested in clinical studies to date), and/or a trametinib overdose, defined as administration of more than 3.0 mg once daily (the maximum tolerated dose defined in the MEK111054 Study), the investigator should contact the GSK Medical Monitor immediately and closely monitor the patient for AEs/SAEs and laboratory abnormalities. GSK does not recommend specific treatment. The investigator will use clinical judgment to treat any overdose.

Decisions regarding dose modifications or interruptions should be made by the investigator in consultation with the GSK Medical Monitor based on the clinical evaluation of the patient.

A plasma sample for PK analysis may be requested by the GSK Medical Monitor on a case-by-case basis. This plasma sample should be collected as soon as possible.

Information regarding the quantity of the excess dose as well as the duration of the overdosing should be documented in the eCRF.

7. STUDY ASSESSMENTS AND PROCEDURES

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

Procedures conducted as part of the patient's routine clinical management (e.g., imaging) and obtained prior to signing of informed consent may be used for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe specified in the protocol.

Refer to the Time and Events Table (Table 19) for the timing of all assessments. Assessments must be performed on a calendar schedule; delays in treatment administration will not delay performance of assessments. Details on efficacy and safety assessments are presented in Section 7.3 and Section 7.4, respectively. Further details of study procedures and assessments can be found in the SPM

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

The investigator may discuss with the GSK Medical Monitor the possibility of continuing study treatment for a patient who is receiving benefit but has met the RECIST 1.1 criteria for disease progression.

Table 19 Time and Events

Study Assessments[1]	**Screening** (≤ 28 days except where noted)[2]	**Day 1**	**Every 4 Weeks** (± 7 days)	**Every 8 Weeks** (± 7 days)	**Every 12 Weeks** (± 7 days)	**End of Study**[20]
Clinical assessments						
Informed consent[3]	X					
Inclusion/Exclusion criteria	X	X				
Demographic data	X					
Past and current medical conditions including cardiovascular medical and family history, risk factors	X					
Disease characteristics[4]	X					
Prior anti-cancer therapies	X					
Performance status (ECOG)	X		X			X
Brain MRI/CT[5]	X (5 weeks)					
Lesion assessment (including skin lesion photography)[6]	X (5 weeks)			Week 8 and every 8 weeks thereafter through week 56 and then every 12 weeks thereafter until determination of progressive disease		
Randomisation[7]		X				
Safety Assessments						
Vital signs[8]	X		X			X
Physical examination[9,23]	X		X (short)			X
Ophthalmic examination[10]	X					
Adverse events[11]	X	X	X			X
ECG[12]	X (5 weeks)		X (only at Week 4)		X	X
ECHO[13]	X (5 weeks)		X (only at Week 4)		X	
Dermatology assessment[23]	X		X (only at week 2, 8, 10)			X (at PD)
Concomitant medications[14]	X	X	X			X
Laboratory Assessments						
Chemistry and Haematology[15]	X		X			X

Study Assessments[1]	**Screening** (≤ 28 days except where noted)[2]	**Day 1**	**Every 4 Weeks** (± 7 days)	**Every 8 Weeks** (± 7 days)	**Every 12 Weeks** (± 7 days)	**End of Study**[20]
Serum pregnancy test[16]	X					
Coagulation	X					
Study Treatments						
Dispensation of medication[17]		X	X			
Assessment of compliance[18]			X			
Biomarker Samples						
Tumour biopsy[21, 22,]		X	X (only at week 2, 8, 10)			X (at PD)
Skin biopsy[21, 22]		X	X (only at week 2, 8, 10)			X (at PD)
Blood sample for biomarker		X	X (only at week 2, 8, 10)			X (at PD)
Blood sample for PK[19]			X (only at week 2, 8, 10)			X (at PD)
Blood sample for cfDNA[21]		X				

Abbreviations: cfDNA = cell-free deoxyribonucleic acid; CNS = central nervous system; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; LLN = lower limit of normal; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; PD = progressive disease; PK = pharmacokinetics; RAMOS = Registration and Medication Ordering System; RECIST = Response Evaluation Criteria in Solid Tumours; SPM = study procedures manual.

1. All assessments mandated throughout the study must be performed on a calendar schedule; delays in treatment administration will not delay performance of assessments.
2. Screening procedures may be performed up to 28 days prior to randomisation. Screening procedures that have a larger visit window are indicated in parentheses.
3. Informed consent must be given prior to performance of any study-related procedures. Informed consent can be obtained at any time before Day 1.
4. Disease characteristics will include date of diagnosis, primary tumour type, histology, stage, etc.
5. Baseline MRI (preferred) or CT (only if MRI contraindicated or unavailable) of the brain must be performed on all patients to rule out current leptomeningeal metastases, brain metastases, or spinal cord compression secondary to metastasis. Post-baseline scans should be performed in all patients with documented metastases at baseline and as clinically indicated (e.g., symptoms suggestive of CNS progression) in all patients.
6. Lesion assessments must be done for chest, abdomen, pelvis, and any area of known disease. Lesion assessment by contrast CT (preferred) or MRI must be performed within 5 weeks prior to randomisation and at the times indicated until disease progression, death, or withdrawal of consent, whichever occurs first. (See Section 7.3.3 for instructions regarding chest X-Rays and CT assessment.) Target and non-target lesions must be identified at the time of screening and the same lesions must be re-assessed at each timepoint in a consistent manner according to RECIST, version 1.1. The same diagnostic method, including use of contrast when applicable, must be used throughout the study to evaluate each lesion. Lesion measurements will be taken using ruler or calipers. The Week 8 assessment for patients in arms A & B should be done before starting the combination treatment. If the last assessment was > 8 weeks prior to study withdrawal and disease progression had not been documented, a disease assessment should be obtained.

7. Randomisation will occur via RAMOS on Day 1.
8. Refer to Section 7.4.6 for details regarding vital sign measurements.
9. A complete physical examination will be performed at Screening and End-of-study; brief physical examinations will be performed at all other timepoints as indicated. In females, genitourinary exam should include a visual inspection of the cervix. If the patient has had a genitourinary and rectal exam within 6 months of screening the genitourinary and rectal exam do not need to be repeated. Refer to Section 7.4.7 for details.
10. An ophthalmic examination will be performed at Screening; additional ophthalmic examinations will be performed only as symptomatically warranted. Refer to Section 7.4.5 for details.
11. Adverse events will be recorded from the time the first dose of study treatment is administered until 30 days after discontinuation of study treatment. Serious adverse events will be collected over the same time period as AEs except SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy), study treatment, or a GSK concomitant medication which must be recorded from the time a patient consents to participate in the study up to and including any follow-up contact.
12. At each timepoint listed, a single 12-lead ECG will be performed by qualified site personnel after the patient has rested in a semi-recumbent or supine position for at least 5 minutes.
13. While on treatment, patients who have an asymptomatic, absolute decrease in LVEF of > 10% compared to screening and whose ejection fraction is below the institution's LLN, must be followed according to LVEF guidelines for study drug management and requirements for subsequent ECHO.
14. All medications the patient takes during the study from the time of screening until 30 days after the last dose of study treatment will be recorded.
15. Analysis of clinical chemistry and haematology samples will be performed by the local lab. Screening labs performed within 2 weeks prior to randomisation do not need to be repeated.
16. Serum pregnancy test is required at Screening. Subsequent tests may be urine tests, and should be performed as clinically indicated.
17. A 4-week supply of study medication should be dispensed at each scheduled study visit as of Day 1. Patients should be provided with dosing instructions. Patients should start treatment as soon as possible after randomisation but no later than 72 hours post-randomisation.
18. Patients should be instructed to return study drug vials at each visit; compliance will be assessed through querying the patient and through pill count at the time of new dispensation. Dose modifications and interruptions must be recorded.
19. The date and exact time of PK sample collection and most recent dose will be recorded. Details of collection procedures, including dosing instructions for morning and afternoon visits, will be provided in the SPM.
20. End of study assessments do not need to be repeated if performed within 4 weeks
21. Biomarker-related sampling to be conducted at randomisation to avoid biomarker sample collection for ineligible patients
22. Biopsies are to be taken at the judgement of the investigator at the various time-points to ensure that any potential risk or impact to the patients are kept to a minimum, All biopsies, be they from cutaneous or sub-cutaneous lesions, are to be performed only if the lesions are easily accessible.Biopsies are to be performed by either the investigator, a dermatologist, a surgeon or a physician qualified in radiology if an ultrasound-led biopsy is necessary.
23. For Subjects enrolled in France, refer to the Appendix 6: Additional Monitoring for Patients Enrolled in France

7.1. Critical Baseline Assessments

Baseline assessments comprise clinical examination with detailed skin examination and standardised skin photos (face, trunk, limbs, scalp, nails, hand and feet). The dermatologic assessment will be reproduced at each biomarker sampling at week 2, 8, 10 and at disease progression. Efficacy assessments conducted at baseline are described in Section 7.3.2, tumour tissue and biomarker assessments are described in Section 7.2. Safety assessments conducted at baseline and during treatment are described in Section 7.4. Cardiovascular medical history/risk factors will be assessed at baseline.

7.1.1. BRAF Mutation Determination

The conduct of the BRAF-mutation screening prior to the baseline assessments is the responsibility of the investigator and must be performed in a local laboratory. Testing for BRAF mutation for enrolment in the trial can occur any time prior to dosing.

7.1.2. Baseline Documentation of Target and Non-target Lesions

All baseline lesion assessments, including brain MRI/CT to rule out brain metastases, must be performed within 5 weeks prior to randomisation.

- Lymph nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.
- Pathological lymph nodes with a short axis of < 15 mm but ≥ 10 mm are considered non-measurable.
- Pathological lymph nodes with a short axis of ≥ 15 mm are considered measurable and can be selected as target lesions. Lymph nodes should not be selected as target lesions when other suitable target lesions are available.
- Measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions, and recorded and measured at baseline. These lesions should be selected on the basis of their size (i.e., lesions with the longest diameter) and their suitability for accurate repeated measurements (i.e., either by imaging techniques or clinically).

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

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

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI can be considered measurable. Bone scans, fluorodeoxyglucose positron emission tomography (FDG-PET) scans or X-rays are not considered adequate imaging techniques to measure bone lesions.

- All other lesions (or sites of disease) should be identified as non-target and should also be recorded at baseline. Non-target lesions will be grouped by organ. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

7.2. Biomarkers

Comparative examination of pre-dosing profiles of patients may uncover known or novel candidate biomarkers/profiles which could be used to predict response to study treatments or provide new insights into melanoma and medically related conditions. Comparative examination of post-dosing profiles in conjunction with pre-dosing profiles may yield known and novel candidate biomarkers/profiles and new insights which relate to the action of the study treatments and changes contributing to the development of resistance.

Novel candidate biomarkers and subsequently discovered biomarkers of the biological response associated with melanoma or medically related conditions and/or the action of the study treatments may be identified by application of DNA/gene, RNA and protein analysis of tumour tissue.

Unless stated otherwise, these investigations may be performed irrespective of whether a response to study treatment is observed.

Biopsies will be performed on cutaneous or sub-cutaneous lesions that are easily accessible and will NOT be performed on any deep lesions. If possible biopsies should be taken from the same lesion/location. Key biopsies are taken at randomisation, week 2, week 8, and week 10. Additional patients might be recruited to ensure a sufficient number of patients in each arm providing these three key biopsies.

7.2.1. Biomarkers on blood sample

Biomarkers include, but are not limited to:

- LDH
- CRP
- Osteopontin
- Circulating cell-free DNA (cfDNA)
- Protein S 100
- Lymphocyte subpopulations
- Inflammatory cytokines (e.g. TNF-α, IL-1)

7.2.2. Biomarkers on tumour sample

The exploratory research objectives of this study include further characterisation of the patient population through analysis of tumour DNA, RNA and protein, or other aberrations from tumour tissue and to determine whether these are associated with clinical outcome in response to therapy and/or to toxicity.

Biomarkers in the melanoma tumour samples:

Biomarkers include, but are not limited to:

Immunohistochemistry (IHC) on fixed tumour samples:

- P-ERK
- P-MEK
- Ki-67
- P-AKT
- P-S6
- PTEN
- eIF4E and P-eIF4E
- eIF4G
- CDK4
- c-Met
- EGFR
- P-EGFR

Mutations screening:

A panel of genes relevant in melanoma biology (up to 400 genes potentially involved ontogeny or resistance) such as *BRAF, MEK1 and 2, HRAS, NRAS,KRAS, PTEN, KIT, NRAS, STK11, TP53, MNK1 CDK4, CDKN2ATGFBR1, EGF* will be assessed on limited quantity of DNA using IonTorrent technology. This analysis should allow a sensitivity of mutation detection up to 10% of mutated DNA extracted from FFPE or frozen samples collected at base line or after (e.g. at recurrence).

For samples with sufficient amount of DNA, according to method available (currently 3µg) the whole exome analysis will be performed.

Additional analysis of chromosomal abnormalities by CGH array and transcriptome analysis with Gen Expression microarray will be performed on frozen samples

Biomarkers in skin tumours induced by kinase inhibitors (papillomas, KA and SCC):

Biomarkers include, but are not limited to:

- Fixed samples: P-ERK and P-MEK
- Mutations screening: mutational hotspot for the three *RAS* genes, *TGFBR1, TP53, BRAF*
- HPV DNA and RNA

7.2.3. Biomarkers on skin sample

Biomarkers include, but are not limited to:

- Fixes samples: P-ERK, P-MEK, P-AKT, eiF4E and P-eiF4E, P-S6, HPV DNA, Ki-67
- Frozen samples: kinome analysis

7.3. Efficacy

7.3.1. Efficacy Endpoints

The efficacy endpoints of this study are:

- Overall response rate (ORR), defined as the percentage of patients with a confirmed or unconfirmed CR or PR at any time per RECIST, version 1.1 (Eisenhauer, 2009).
- Progression-free survival (PFS), defined as the time from randomisation until the earliest date of disease progression or death due to any cause.
- Duration of response, defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause among patients who achieve an overall response (i.e., unconfirmed or confirmed CR or PR)

7.3.2. Efficacy Assessment

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

Refer to the Time and Events table (Table 19) for the schedule of efficacy assessments. Assessments must be performed on a calendar schedule and should not be affected by dose interruptions/delays.

The following scans/assessments are required at baseline: contrast CT (preferred method) of chest/abdomen/pelvis or MRI of abdomen/pelvis and any area of known disease, skin lesion photography, and clinical disease assessment for palpable lesions. Exception: If a chest CT cannot be performed, chest X-ray can be used only to document **the absence of disease** (no tumour lesions) or the **presence of new lesions**. If lesions are detected at baseline by chest X-ray, chest CT must be done to properly document these lesions at baseline and in follow-up tumour assessments. At each post-baseline assessment, evaluations of the sites of disease identified by these scans are required.

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

Confirmation of response (i.e., CR and PR) is not necessary per RECIST, version 1.1, as the primary endpoint of the study is not overall best response.

Scans will be assessed by investigators and will not be collected for central review.

7.3.2.1. Assessment Guidelines

Please note the following:

- The same diagnostic method, including use of contrast when applicable, must be used throughout the study to evaluate lesions.
- The same diagnostic method, including use of contrast when applicable, must be used throughout the study to evaluate a lesion. Contrast agents must be used in accordance with the Image Acquisition Guidelines.All measurements should be taken and recorded in millimeters (mm), using a ruler or calipers.
- Ultrasound is not a suitable modality of disease assessment. If new lesions are identified by ultrasound, confirmation by CT or MRI is required.
- Fluorodeoxyglucose-positron emission tomography (FDG-PET) is generally not suitable for ongoing assessments of disease. It can, however, be useful in confirming new sites of disease when a positive FDG-PET scan correlates with the new site of disease present on CT/MRI or when a baseline FDG-PET was previously negative for the site of the new lesion. Fluorodeoxyglucose (FDG)-PET may also be used in lieu of a standard bone scan providing coverage allows interrogation of all likely sites of bone disease and FDG-PET is performed at all assessments.
- If PET/CT is performed then the CT component can only be used for standard response assessments if performed to diagnostic quality, which includes the required anatomical coverage and prescribed use of contrast. The method of assessment should be noted as CT in the eCRF.

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

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

X-ray: In general, X-ray should not be used for target lesion measurements owing to poor lesion definition. Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung; however chest CT is preferred over chest X-ray [Eisenhauer, 2009].

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

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

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

7.3.2.2. Follow-up Assessments for Patients Permanently Discontinued from both Study Treatments

All patients who permanently discontinue both study treatments without disease progression will be withdrawn from study and progression data will be censored.

7.3.2.3. Assessment at Patient Completion

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

7.3.3. Guidelines for Evaluation of Disease

7.3.3.1. Measurable and Non-measurable Definitions

Measurable lesion(s):

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

- ≥10 mm with MRI or CT when the scan slice thickness is ≤ 5 mm. If the slice thickness is >5 mm, the minimum size of a measurable lesion must be at least double the slice thickness (e.g., if the slice thickness is 10 mm, a measurable lesion must be ≥20 mm).
- ≥10 mm caliper/ruler measurement by clinical exam or medical photography.
- ≥20 mm by chest x-ray.

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

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

Non-measurable lesion(s):

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

Measurable disease:

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

Non-measurable only disease:

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

7.3.4. Response Criteria

7.3.4.1. Evaluation of Target Lesions

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

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes must have a short axis of <10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the baseline sum of the diameters (i.e., percent change from baseline).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD).
- Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (i.e., percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of ≥5 mm.
- Not Applicable (NA): No target lesions at baseline.
- Not Evaluable (NE): Cannot be classified by one of the 5 preceding definitions.

Note:

- If lymph nodes are documented as target lesions the short axis is added into the sum of the diameters (i.e., sum of diameters is the sum of the longest diameters for non-nodal lesions and the short axis for nodal lesions). When lymph nodes decrease to non-pathological size (short axis < 10 mm), they should still have a measurement reported in order not to overstate progression.
- If at a given assessment timepoint all target lesions identified at baseline are not assessed, the sum of the diameters cannot be calculated for purposes of assessing CR, PR, or SD, or for use as the nadir for future assessments. The sum of the diameters of the assessed lesions and the percent change from nadir should, nevertheless, be calculated to ensure that PD has not been documented. If an assessment of PD cannot be made, the response assessment should be NE.
- All lesions (nodal and non-nodal) should have their measurements recorded even when very small (e.g., 2 mm). If lesions are present but too small to measure, 5 mm should be recorded and should contribute to the sum of the diameters, unless it is likely that the lesion has disappeared in which case 0 mm should be reported.
- If a lesion disappears and reappears at a subsequent timepoint it should continue to be measured. The response at the time when the lesion reappears will depend upon the status of the other lesions. For example, if the disease had reached a CR status then PD would be documented at the time of reappearance; if the response status was PR or SD, the diameter of the reappearing lesion should be added to the remaining diameters and response determined based on percent change from baseline and percent change from nadir.

7.3.4.2. Evaluation of Non-target Lesions

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

- Complete Response (CR): The disappearance of all non-target lesions. All lymph nodes identified as a site of disease at baseline must be non-pathological (i.e., a short axis of <10 mm).
- Non-CR/Non-PD: The persistence of 1 or more non-target lesion(s) or lymph nodes identified as a site of disease at baseline with a short axis of ≥10 mm.
- Progressive Disease (PD): Unequivocal progression of existing non-target lesions.
- Not Applicable (NA): No non-target lesions at baseline.
- Not Evaluable (NE): Cannot be classified by one of the 4 preceding definitions.

Note:

- In the presence of measurable disease, progression on the basis of solely non-target disease requires substantial worsening such that even in the presence of

SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy.

- Sites of non-target lesions, which are not assessed at a particular timepoint based on the assessment schedule, should be excluded from the response determination (i.e., non-target response does not have to be NE).

7.3.4.3. New Lesions

New malignancies denoting disease progression must be unequivocal. Lesions identified in follow-up in an anatomical location not scanned at baseline are considered new lesions.

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

7.3.4.4. Evaluation of Overall Response

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

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

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

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

Note:

- Patients with a global deterioration of health status requiring treatment discontinuation without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Objective response

status is determined by evaluations of disease burden. Every effort should be made to document the objective progression even after treatment discontinuation.

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

7.3.4.5. Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression, death, or withdrawal of consent, whichever occurs first. Best overall response will be determined programmatically by GSK based on the investigator's assessment of response at each timepoint.

- To be assigned a status of SD, follow-up disease assessment must have met the SD criteria at least once after randomisation for a minimum of 49 days.
- If the minimum time for SD is not met, best response will depend on the subsequent assessments. For example, if an assessment of PD follows the assessment of SD and SD does not meet the minimum time requirement, the best response will be PD. Alternatively, patients lost to follow-up after an SD assessment not meeting the minimum time criteria will be considered NE.

7.4. Safety

7.4.1. Safety Endpoints

The secondary objectives of the study include characterising the safety of dabrafenib and trametinib combination therapy. As a consequence, clinical assessments including vital signs and physical examinations, ECOG, 12-lead ECG, ECHO, chemistry and haematology laboratory values, and AEs will be monitored and evaluated.

7.4.2. Adverse Events

The investigator or site staff will be responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as outlined in Section 7.4.2.1 and Section 7.4.2.2, respectively.

7.4.2.1. Definition of an AE

Any untoward medical occurrence in a patient or clinical investigation patient, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this

also includes failure to produce expected benefits, abuse, or misuse. Examples of events meeting the definition of an AE include:

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

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

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

7.4.2.2. Definition of an SAE

A serious adverse event (SAE) is any untoward medical occurrence that, at any dose:

a. Results in death;

b. Is life-threatening;

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

c. Requires hospitalization or prolongation of existing hospitalization;

   Note: In general, hospitalisation signifies that the patient has been detained (i.e., usually involving at least one overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalisation are AEs.

If a complication prolongs hospitalisation or fulfills any other serious criteria, the event is serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.

Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity; and/or

Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and/or accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

f. Protocol-specific SAEs:

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

  Note: Bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a patient meets the criterion of total bilirubin ≥2 x ULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. International normalized ratio (INR) elevations >1.5 suggest severe liver injury.

- Any new malignancy with a histology different from the primary tumour, including cutaneous squamous cell carcinoma
- Laboratory abnormalities as referenced in Section 7.4.2.3.
- LVEF that meets stopping criteria Section 5.8.3.1
- CSR or RVO

- Pyrexia accompanied by ≥ Grade 3 hypotension or hypotension that is clinically significant in the judgement of the investigator, or dehydration requiring IV fluids, or severe rigors/chills.

7.4.2.3. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

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

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

Any new primary cancer must be reported as an SAE.

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

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

An event which is part of the natural course of the disease under study (i.e., disease progression or hospitalisation due to disease progression) does not need to be reported as an SAE. Death due to disease under study is to be recorded on the Death eCRF form and does not need to be reported as an SAE. If however, if the underlying disease (i.e., progression) is greater than that which would normally be expected for the patient, or if the investigator considers that there was a causal relationship between treatment with study medication(s) or protocol design/procedures and disease progression, then this must be reported as an SAE.

7.4.2.5. Time Period and Frequency for Detecting AEs and SAEs

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

Adverse events (AEs) will be collected from the time the first dose of study treatment is administered until 30 days after discontinuation of study treatment regardless of initiation of a new anti-cancer therapy or transfer to hospice.

Serious adverse events (SAEs) will be collected over the same time period as stated above for AEs. In addition, any SAE assessed as **related** to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy), study treatment, or a GSK concomitant medication, must be recorded from the time a patient consents to participate in the study up to and including any follow-up contact. All SAEs will be reported to GSK within 24 hours, as indicated in Section 7.4.2.6.

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

7.4.2.6. Prompt Reporting of SAEs and Other Events to GSK

Serious adverse events (SAEs), pregnancies, and liver function abnormalities meeting pre-defined criteria will be reported promptly by the investigator to GSK as described in Table 21 once the investigator determines that the event meets the protocol-definition for that event.

Table 21 Time Frames for Reporting SAEs and Other Events

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	SAE data collection tool	24 hours	Updated SAE data collection tool "CV events" and/or "death" data collection tool(s) if applicable
Pregnancy	2 weeks	Pregnancy notification form	2 weeks	Pregnancy follow-up form
Liver Chemistry Abnormalities:				
ALT ≥ 3 x ULN **PLUS** total bilirubin ≥ 2 x ULN (> 35% direct) or ALT ≥ 3 x ULN and INR > 1.5, if INR measured[a]	24 hours[b]	SAE data collection tool, liver event eCRF form, and liver imaging and/or biopsy eCRFs, if applicable[c]	24 hours	Updated SAE data collection tool and updated liver event eCRF form[c]
ALT ≥ 8 x ULN; ALT ≥ 3 x ULN with hepatitis or rash or ≥ 3 x ULN but < 5 x ULN that persists ≥ 4 weeks	24 hours[b]	Liver event eCRF form[c]	24 hours	Updated liver event eCRF form[c]
ALT ≥ 5 x ULN **PLUS** total bilirubin < 2 x ULN	24 hours[b]	Liver event eCRF form does not need completing unless elevations persist for 2 weeks or patient cannot be monitored weekly for 2 weeks[c]	24 hours	
ALT ≥ 5 x ULN **PLUS** total bilirubin < 2 x ULN that persists ≥ 2 weeks	24 hours[b]	Liver event eCRF form[c]	24 hours	Updated liver event eCRF form[c]
ALT ≥ 3 x ULN but < 5 x ULN **PLUS** total bilirubin < 2 x ULN	24 hours[b]	Liver event eCRF form does not need completing unless elevations persist for 4 weeks or patient cannot be monitored weekly for 4 weeks[c]		

Abbreviations: ALT = alanine transaminase; AST = aspartate aminotransferase; eCRF = electronic case report form; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal.

a. INR measurement is not required; if measured, the threshold value stated will not apply to patients receiving anticoagulants.
b. GSK to be notified at onset of liver chemistry elevations to discuss patient safety.
c. Liver Event Documents (i.e., "Liver Event CRF" and "Liver Imaging CRF" and/or "Liver Biopsy CRF", as applicable) should be completed as soon as possible.

Liver chemistry stopping, follow-up, and monitoring criteria are provided in Section 5.9. Methods for detecting, recording, evaluating, and following-up on AEs and SAEs and procedures for completing and transmitting SAE reports to GSK are provided in the SPM. Procedures for post-study AEs and SAEs are provided in the SPM.

7.4.2.7. Regulatory Reporting Requirements for SAEs

Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of patients are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country-specific regulatory requirements relating to safety reporting to regulatory authorities, Independent Ethics Committees (IEC) and investigators.

Investigator safety reports will be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and will be forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

7.4.3. Pregnancy Testing, Prevention, and Reporting

7.4.3.1. Pregnancy Testing and Prevention

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

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

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

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

If a female patient is of childbearing potential, she must have a serum β-human chorionic gonadotropin (HCG) pregnancy test performed within 14 days prior to randomisation. Patients with a positive pregnancy test result must be excluded from the study. Patients with a negative pregnancy test result must agree to use an effective contraception method

as described below throughout the treatment period and until 4 months after the last dose of study treatment.

- GSK acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of the physician, are as follows:
- An intrauterine device with a documented failure rate of less than 1% per year.
- Vasectomised partner who is sterile prior to the female patient's entry and is the sole sexual partner for that female.
- Complete abstinence from sexual intercourse for 14 days prior to randomisation, throughout the treatment period, and for at least 4 months after the last dose of study treatment.

  Note: Abstinence is acceptable only when in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

- Double-barrier contraception: condom and occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/cream/suppository).

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

Female patients who are nursing must discontinue prior to randomisation and must refrain from nursing throughout the treatment period and for 4 months after the last dose of study treatment.

7.4.3.2. Pregnancy Reporting

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure patient safety, each pregnancy must be reported to GSK within 2 weeks of learning of its occurrence. The pregnancy must be followed-up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

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

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

7.4.4. Laboratory Assessments

All protocol-required laboratory assessments must be conducted in accordance with the Time and Events Schedule (Table 19). Only local laboratory assessments are undertaken during the course of the trial and its data must be recorded in the patients CRF.

Clinical chemistry and haematology parameters to be tested are listed in Table 22. Female patients of child-bearing potential will have a serum pregnancy test at Screening; urine pregnancy testing may be done during study treatment, if necessary.

Table 22 Clinical Chemistry and Haematology Parameters

Clinical Chemistry Parameters
• Albumin • Alkaline Phosphatase • Alanine Transaminase (ALT) or Serum Glutamic Pyruvic Transaminase (SGPT) • Aspartate Aminotransferase (AST) or Serum Glutamic Oxaloacetic Transaminase (SGOT) • Gamma-Glutamyl Transpeptidase (GGT) • Blood Urea Nitrogen (BUN) or urea • Calcium • Creatinine[c] • Lactate Dehydrogenase (LDH) • Phosphate • Potassium • Sodium • Total Bilirubin[b] • Total Protein
Haematology Parameters

• White Blood Cell (WBC) Count
• Hemoglobin
• International Normalized Ratio (INR; at Screening only)[a]
• Platelet Count
• Prothrombin Time (PT; at Screening only)[a]
• Partial Thromboplastin Time (PTT; at Screening only)[a]
• Automated WBC Differential (expressed as %):
  ○ Basophils
  ○ Eosinophils
  ○ Lymphocytes
  ○ Monocytes
  ○ Neutrophils

a. Coagulation panel to be done at Screening only.
b. Bilirubin fractionation is recommended if total bilirubin is > 2 x the upper limit of normal (ULN).
c. If serum creatinine is > 1.5 mg/dL, creatinine clearance should be calculated using the standard Cockcroft-Gault formula (Appendix 2).

For patients with a history of chronic HBV and/or HCV, the following tests will be performed at Screening:

- Viral hepatitis serology;
- Hepatitis B surface antigen and Hepatitis B core antibody (IgM); and/or
- Hepatitis C RNA.

7.4.5. Ophthalmic Examination

Patients are required to have a standard ophthalmic examination performed by an ophthalmologist at baseline and as clinically warranted per protocol's guidance (Section 5.8.5.4). The exam will include indirect and/or direct fundoscopic examination, visual acuity (with correction), visual field examination, and tonometry, with special attention to retinal abnormalities that are predisposing factors for RVO or CSR.

In patients with clinical suspicion of RVO or CSR, fluorescent angiography and/or optical coherence tomography are highly recommended.

7.4.6. Vital Signs

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

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

7.4.7. Physical Examinations

Complete physical examination will include assessments of eyes, neurological and cardiovascular systems, lungs, abdomen, and any other areas with signs and symptoms of disease, and of the head, neck, ears, nose, mouth, throat, thyroid, lymph nodes, extremities, and a full skin exam to assess cutaneous malignancies and proliferative skin diseases. Complete physical examinations will also include thorough genitourinary (pelvic) and rectal exams to assess secondary malignancies. In females, the pelvic exam must visualize the cervix. Pap smear and colposcopy are performed at the investigator's discretion. Rectal exam must include digital rectal exam and visual inspection of the anus and perianal area. Brief physical examinations will include assessment of head, neck, eyes, skin, neurological and cardiovascular systems, lungs, abdomen, and any other areas with signs and symptoms of disease. Refer to the Time and Events Table (Table 19) for when to perform a complete or a brief physical examination.

Dermatologic skin exams may be referred to a dermatologist, if needed.

If possible, the same physician should perform each examination for the duration of the study to ensure consistency between evaluations (i.e., if the patient is referred to a Dermatologist for the Screening examination, the Dermatologist should do all follow-up dermatologic skin assessments).

7.4.8. Electrocardiograms (ECG)

Twelve (12)-lead ECGs will be obtained using an ECG machine that automatically calculates heart rate and measures PR, QRS, QT, RR and QTcB intervals.

At each assessment, a single 12-lead ECG will be performed by qualified site personnel after the patient has rested in a semi-recumbent or supine position for at least 5 minutes.

See Section 5.8.3.3 for instructions if QTc withholding criteria are met.

7.4.9. Echocardiograms (ECHO)

Echocardiograms (ECHO) will be performed to assess cardiac ejection fraction and cardiac valve morphology. If possible, ECHO should be performed by the same person throughout the study for a patient. The echocardiographer's evaluation should include an evaluation for left ventricular ejection fraction and both right and left-sided valvular lesions.

7.5. Pharmacokinetics

As part of the secondary objectives of this study, concentrations of trametinib and of dabrafenib and its metabolites (GSK2285403, GSK2298683, and GSK2167542) will be determined at each time point during treatment when the skin and tumour biopsies are performed. During the monotherapy treatment in arm A and B, only trametinib or dabarafenib and its metabolites will be measured. During combination, both drugs and metabolites will be measured.

7.5.1. Blood Sample Collection for Pharmacokinetics

Blood samples for PK analyses of dabrafenib, trametinib, and metabolites of dabrafenib will be collected at the same day as the tumour and skin biopsies are performed during treatment (Week 2, 8 and 10). Patients with morning clinic visits will be instructed to withhold their morning dose, and samples will be collected prior to dabrafenib and trametinib administration; for patients with afternoon clinic visits, patients will take their morning doses as usual, and samples will be collected 4-8 hours following dabrafenib and trametinib administration. Date and exact time of pharmacokinetic sample and of most recent dose will be recorded.. No more than 25 mL of blood will be collected over the duration of the study for PK blood sample collection, including any extra assessments that may be required.

Details of PK blood sample collection (including volume to be collected), processing, storage, and shipping procedures will be provided in the SPM.

8. DATA MANAGEMENT

For this study, patient data will be entered into GSK defined Inform eCRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events, concomitant medications terms and other anti-cancer therapies will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and an internal validated medication dictionary, GSKDrug.

eCRFs (including queries and audit trails) will be retained by GSK and copies will be sent to the investigator to maintain as the investigator copy. In all cases, patient initials will not be collected or transmitted to GSK in accordance with GSK policy.

9. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

9.1. Hypotheses

The primary objective of this trial is to evaluate the percentage reduction of pERK score from baseline and characterise safety and efficacy of different treatment sequence with the pERK score changes. The primary end point will be analysed with a descriptive intent only. Hence no hypothesis testing will be performed.

9.2. Study Design Considerations

9.2.1. Sample Size Assumptions

Based on feasibility a sample size of 54 patients will be enrolled in this trial in 1:1:1 ratio to one of the three treatment arms allowing a total of 20% early dropout rate. Assuming as large as 30% standard deviation (s.d.) of percentage reduction of pERK score from baseline, 15 patients per treatment arm will be sufficient to ensure that the 95% confidence interval (CI) will be the mean ±16.61%. With 15 patients per treatment arm, the study will have >97% power to detect 80% reduction of pERK score from baseline to Week 2 within a treatment group (with s.d.=70%, alpha=0.05, two sided paired t-test).

9.2.2. Sample Size Sensitivity

The effect of changes in the assumed standard deviation on the precision (i.e., half-width of the 95% CI for percent reduction of pERK score from Baseline at Week 2 within a treatment group) is summarised in Table 23.

Table 23 Effects of changes in the assumption of standard deviation

Standard Deviation (%)	Precision (Half-width of 95% CI of % reduction of pERK score from baseline within a treatment group)
10	5.538
20	11.076
30	16.613
40	22.151
50	27.689

9.2.3. Sample Size Re-estimation

Sample size re-estimation is not planned for this study.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

The **Intent-to-Treat Population** (ITT) will consist of all randomised patients whether or not randomised treatment was administered. This population will be based on the

treatment to which the patient was randomised and will be the primary population for the analysis of efficacy data. Any patient who receives a treatment randomisation number will be considered to have been randomised.

The **Safety Population** will consist of all patients who received at least one dose of randomised treatment and will be based on the actual treatment received. This population will be used for the analysis of clinical safety data.

The **Biomarker Population** will consist of all patients with biopsy performed at screening and at least once during treatment.

9.3.2. Analysis Data Sets

The primary dataset for efficacy (ORR, PFS and DoR) will be comprised of the ITT population as defined in Section 9.3.1

The primary dataset for assessing safety will be the Safety Population as defined in Section 9.3.1.

The primary dataset for biomarker analysis will be the Biomarker Population as defined in Section 9.3.1.

Details on the handling of missing data are provided in the Reporting and analysis plan (RAP).

9.3.3. Treatment Comparisons

This is a descriptive study and there will be no treatment comparison. Biomarker, efficacy and safety endpoints will be evaluated for each treatment arm.

9.3.4. Interim Analysis

No interim analyses will be performed for this study.

9.3.5. Key Elements of Analysis Plan

The final analysis will be performed after the last patient has the week 16 efficacy assessment.

Data will be listed and summarised according to the GSK reporting standards, where applicable. Complete details will be documented in the RAP. Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the RAP and final study report.

Demographic and baseline characteristics will be summarised.

Percentage reduction in pERK biomarker score from baseline to Week 2 will be calculated within a treatment group.

ORR will be determined based on confirmed responses. Details on the determination of tumour response are given in Section 7.3.4.

PFS analysis will be performed if there is sufficient number of events at the time of final analysis. For the analysis of PFS, if the patient received subsequent anti-cancer therapy prior to the date of documented progression or death, progression free-survival will be censored at the last adequate assessment (e.g. assessment where visit level response is CR, PR, or SD) prior to the initiation of therapy. Otherwise, if the patient does not have a documented date of progression or death progression-free survival will be censored at the date of the last adequate assessment. Further details on rules for censoring will be provided in the RAP.

Duration of response analysis will be performed if there is sufficient number of responders.

Additional details on biomarker analyses are provided in Section 9.3.5.1. Similarly additional details on efficacy and safety analyses are provided in Section 9.3.5.2. and in Section 9.3.5.3 respectively.

9.3.5.1. Biomarker Analyses

Biomarker endpoints are defined in Section 2. Percentage reduction of pERK score from baseline is the primary endpoint of this study. Change in biomarker status is most prominent within two weeks of start of treatment. Patients from arm A and arm B will be given combination therapy starting from week 9 after completion of 8 weeks of monotherapy. Therefore, changes in biomarker between screening and week 2 as well as between week 8 and week 10 will be summarised. In addition, effect of change of biomarker status on ORR will be determined. Further details will be provided in the RAP.

9.3.5.2. Efficacy Analyses

Efficacy endpoints are described in Section 2 and Section 7.3. The ITT population will be used for the analysis of efficacy data.

The ORR endpoint will be tabulated based on number and percentage of patients attaining a confirmed overall best response of CR or PR in the ITT population. Patients with unknown or missing response data, including those who withdraw from the study without an assessment, will be treated as non-responders (i.e., they will be included in the denominator when calculating the percentage). No imputation will be performed for missing lesion assessment or tumour response data.

Overall response rates (ORR) for each treatment group will be provided along with the corresponding 95% CI. However, ORR will not be compared between treatment groups.

PFS and DoR are exploratory endpoints and will be analyzes provided there is sufficient number of events at the time of final analysis.

PFS will be evaluated for each treatment group. The date of objective disease progression will be defined as the earliest date of radiological or photographic disease progression as assessed by the investigator using RECIST, version 1.1. For patients who have not progressed or died at the time of the PFS analysis, censoring will be performed using the date of the last disease assessment. In addition, patients who start a new anti-cancer

therapy prior to a PFS event will be censored at the date of the last disease assessment prior start of new anti-cancer therapy, respectively. Further details on censoring rules will be outlined in the RAP.

DoR will include patients from the ITT population who achieve a confirmed best response of CR or PR and will only be analyzed provided a sufficient number of patients respond to warrant such an analysis. Censoring rules for duration of response will follow the rules for PFS and will be outlined in detail in the RAP.

9.3.5.3. Safety Analyses

Safety endpoints are described in Section 2 and Section 7.4.

The Safety Population will be used for the analysis of safety data. Complete details of the safety analyses will be provided in the RAP.

Extent of Exposure

The number of patients administered study treatment will be summarised according to the duration of therapy.

Adverse Events

Adverse events (AEs) will be coded using the standard GlaxoSmithKline Medical Dictionary for Regulatory Activities (MedDRA) and grouped by system organ class. AEs will be graded by the investigator according to the NCI-CTCAE (version 4).

Events will be summarised by frequency and proportion of total patients, by system organ class and preferred term. Separate summaries will be given for all AEs, drug-related AEs, serious AEs and AEs leading to discontinuation of study treatment.

If the AE is listed in the NCI CTCAE (version 4) table, the maximum grade will be summarised.

Characteristics (e.g. number of occurrences, action taken, grade, etc) of the following AEs of special interest (e.g. diarrhoea and dash) will be summarised separately as detailed in the RAP.

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

Clinical Laboratory Evaluations

Haematology and clinical chemistry data will be summarised at each scheduled assessment according to NCI CTCAE grade (version 4). The proportion of values lying outside the reference range will also be presented for laboratory tests that are not graded because there are no associated NCI CTCAE criteria. Summaries will include data from scheduled assessments only, and all data will be reported according to the nominal visit date for which it was recorded (i.e. no visit windows will be applied). Unscheduled data will be included in “overall” and “any post-screening” summaries which will capture a

worst case across all scheduled and unscheduled visits post first dose of study treatment. Further details will be provided in the RAP.

Other Safety Measures

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

9.3.5.4. Pharmacokinetic/Pharmacodynamic Analyses

If data warrant, exploratory analyses will be performed to examine the relationship between plasma concentration of dabrafenib and/or trametinib and pharmacodynamic endpoints such as tumour size, biomarker changes and other clinical and safety measures.

Initially, the relationships will be explored graphicially. If these exploratory graphical analyses suggest a relationship between pharmacodynamic endpoints and concentration or pharmacokinetic parameters, PK/PD models may be derived and evaluated. Additional exploratory analyses may be performed to further characterize biomarkers.

Further details of PK/PD analyses will be described under a separate RAP. Results of the PK/PD analyses may be included in a report separate from the clinical study report.

9.3.5.5. Translational Research Analyses

The results of translational research investigations will be reported separately from the main clinical study report. All endpoints of interest from all comparisons will be descriptively and/or graphically summarised as appropriate to the data.

Further details on the translational research analyses will described under a separate RAP.

10. STUDY CONDUCT CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of patients begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable patient privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008, including, but not limited to:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.
- Patient informed consent.
- Investigator reporting requirements.

GSK will provide full details of the above procedures, either verbally, in writing, or both.

Written informed consent must be obtained from each patient prior to participation in the study.

10.3. Quality Control (Study Monitoring)

In accordance with applicable regulations, GCP, and GSK procedures, the site will be contacted prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the CRF will serve as the source document.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents and to allocate their time and the time to their staff to monitor to discuss findings and any issues.

Monitoring visits will be conducted in a manner to ensure that the:

- Data are authentic, accurate, and complete.
- Safety and rights of patients are being protected.

- Study is conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.4. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified

10.5. Study and Site Closure

Upon completion or termination of the study, the monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, ICH GCP, and GSK Standard Operating Procedures.

GSK reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe noncompliance. If GSK determines that such action is required, GSK will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, GSK will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for **safety reasons**, GSK will promptly inform all investigators, heads of the medical institutions (where applicable),and/or institutions conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

10.6. Records Retention

Following closure of the study, the investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that

an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

GSK will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, GSK standard operating procedures, and/or institutional requirements.

The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study patients, as appropriate.

GSK aims to post a results summary to the GSK Clinical Study Register and other publicly available registers no later than 8 months after the last patient's last visit (LSLV) [this applies to each data analysis phase for studies with multiple phases, e.g., primary analysis, follow up analysis etc]. In addition, the aim is to submit a manuscript to a peer-reviewed journal for publication within 18 months of LSLV. GSK also aims to publish the full study protocol on the GSK Clinical Study Register at the time the results of the study are published as a manuscript in the scientific literature.

When manuscript publication in a peer-reviewed journal is not feasible, further study information will be posted to the GSK Clinical Study Register to supplement the results summary.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

10.8. Independent Data Monitoring Committee

No Independent Data Monitoring Committee (IDMC) will be utilized in this study.

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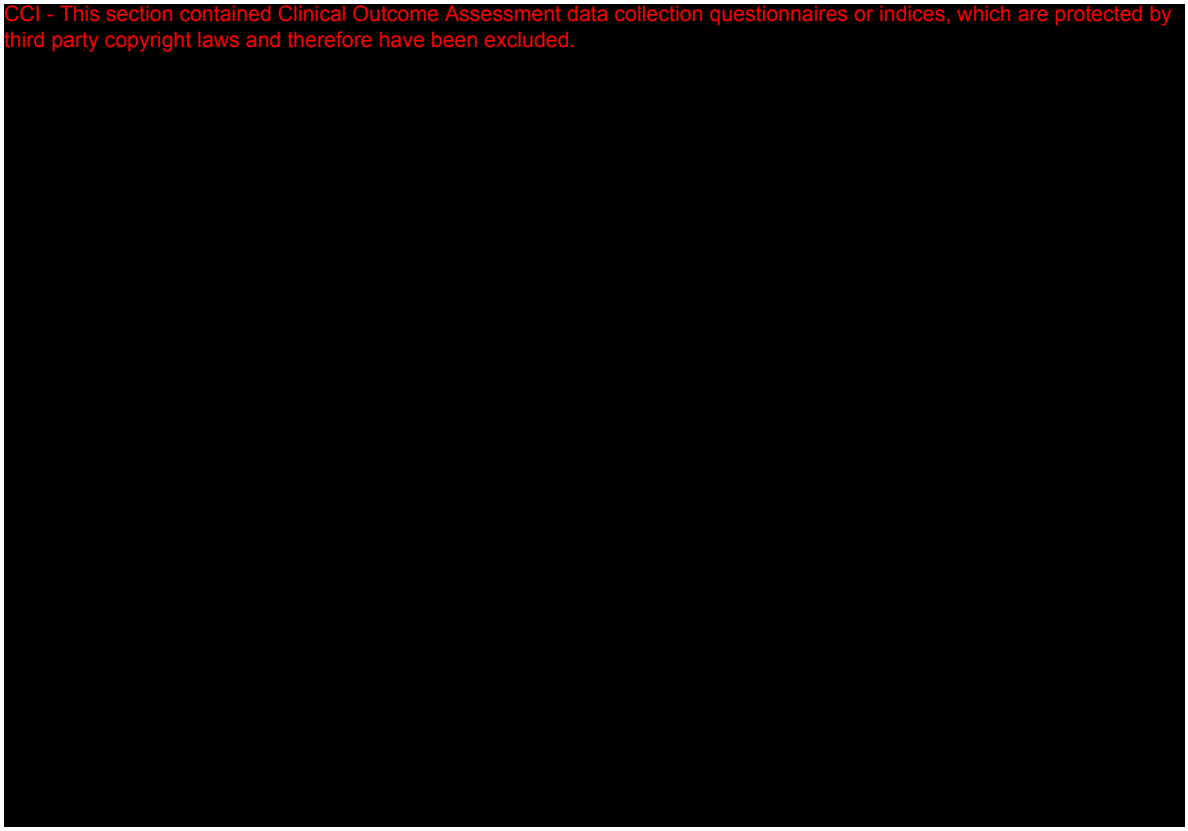
12. APPENDICES

Appendix 1 Eastern Cooperative Oncology Group (ECOG) Performance Status

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.



Appendix 2 Cockcroft-Gault Formula

To determine eligibility for the study, investigators should calculate a patient's creatinine clearance by the Cockcroft-Gault formula as follows [Cockcroft, 1976]:

$$\text{CrCl for males (mL/min)} = \frac{(140 - \text{age [years]}) \times (\text{weight [kg]})}{72 \times (\text{serum creatinine [mg/dL]})}$$

$$\text{CrCL for females (mL/min)} = \frac{0.85 \times (140 - \text{age [years]}) \times (\text{weight [kg]})}{72 \times (\text{serum creatinine [mg/dL]})}$$

For SI units:

$$\text{CrCl for males (mL/min)} = \frac{(140 - \text{age [years]}) \times (\text{weight [kg]}) \times 1.23}{(\text{serum creatinine [μmol/L]})}$$

$$\text{CrCL for females (mL/min)} = \frac{(140 - \text{age [years]}) \times (\text{weight [kg]}) \times 1.05}{(\text{serum creatinine [μmol/L]})}$$

CrCl = creatinine clearance; SI = Système International d'Unités.

Reference

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16(1):31-41.

Appendix 3 QT interval on electrocardiogram corrected using the Bazett's formula (QTcB)

Bazett's formula used to correct QT interval for heart rate is:

$$QTcB = \frac{QT}{\sqrt{RR}}$$

where QTcB is the QT interval corrected for heart rate, RR is the interval from the onset of one QRS complex to the onset of the next QRS complex, *measured in seconds*, often derived from the heart rate (HR) as 60/HR, and QT is the QT interval *measured in milliseconds*.

Reference

Bazett HC. An analysis of the time-relations of electrocardiograms. Heart 1920; 7: 353-370.

Appendix 4 New York Heart Association (NYHA) Guidelines

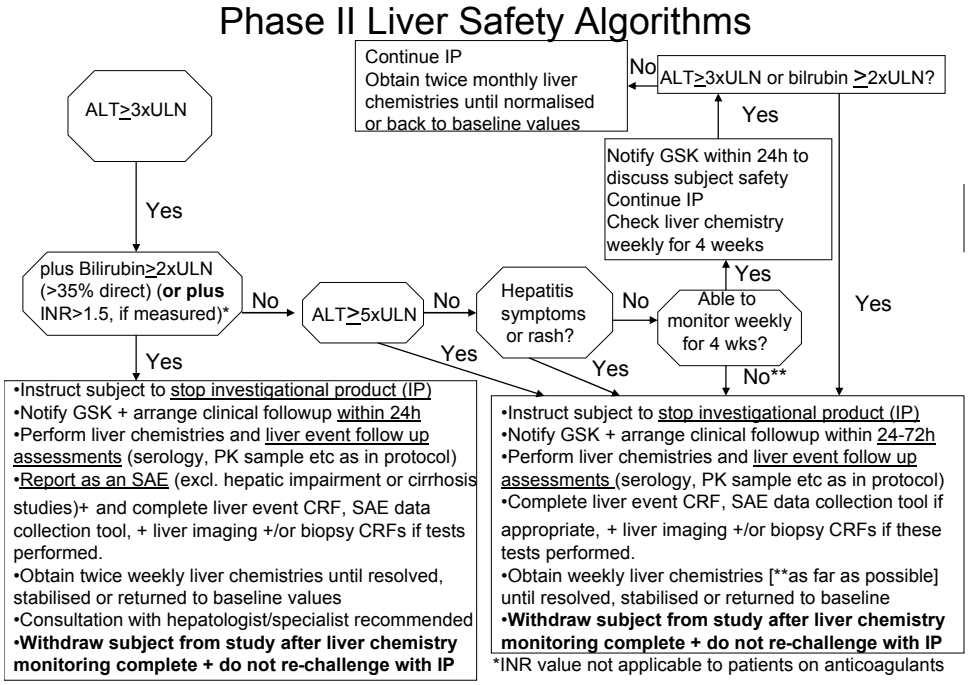
The New York Heart Association Functional Classification provides a simple way of classifying the extent of heart failure [The Criteria Committee of the New York Heart Association 1994]. It places patients in 1 of 4 categories based on the level of limitation experienced during physical activity:

Functional Capacity	Objective Assessment
Class I: Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	**A:** No objective evidence of cardiovascular disease.
Class II: Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	**B:** Objective evidence of minimal cardiovascular disease.
Class III: Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.	**C:** Objective evidence of moderately severe cardiovascular disease.
Class IV: Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	**D:** Objective evidence of severe cardiovascular disease.

Reference

The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, Mass: Little, Brown, & Co; 1994:253-256.

Appendix 5 Liver Chemistry Monitoring, Interruption Stopping and Follow-up Criteria



IP may be re-challenged if protocol provides this option.

Appendix 6 Additional Monitoring for Patients Enrolled in France

Evaluation for Cutaneous Squamous Cell Carcinoma (cuSCC), New Primary Melanoma, and Non-cutaneous Secondary/Recurrent Malignancy Following Discontinuation of Dabrafenib

Patients should be monitored for cuSCC, new primary melanoma, and non-cutaneous secondary/recurrent malignancies. Dermatological examinations should be performed prior to initiation of therapy with dabrafenib, monthly throughout treatment, and for 6 months following discontinuation of dabrafenib or until initiation of another anti-neoplastic therapy, whichever comes first. Cases should be managed by dermatological excision and dabrafenib treatment should be continued without any dose adjustment. Patients should be instructed to immediately inform their physician if new lesions develop.

Non-cutaneous secondary/recurrent malignancy

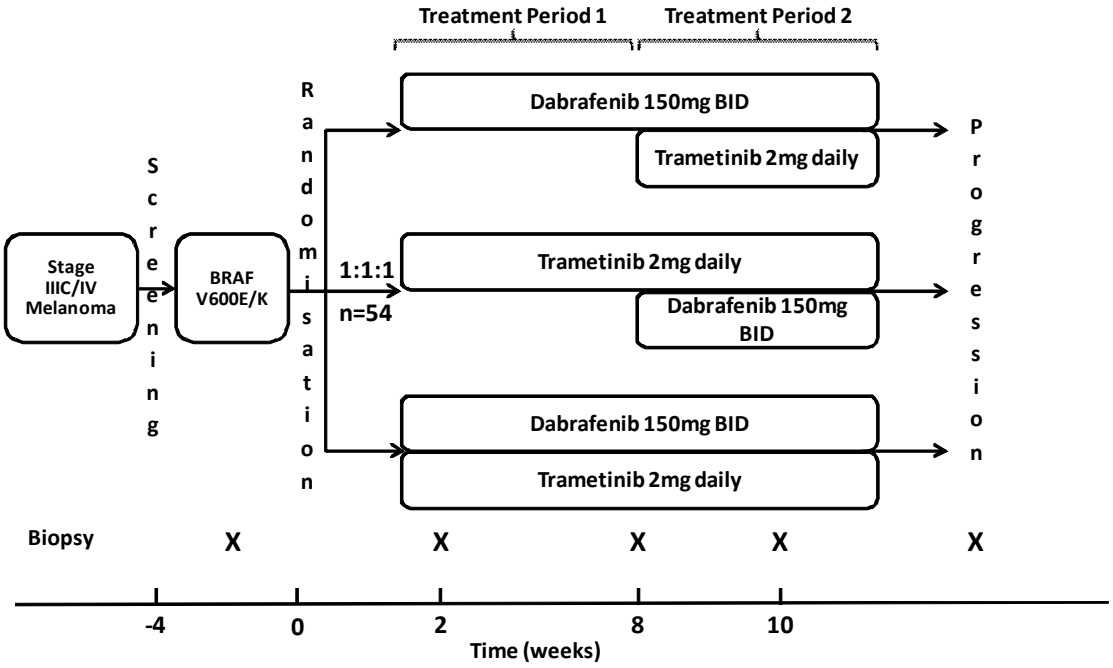
Prior to initiation of dabrafenib treatment patients should undergo a head and neck examination with minimally visual inspection of oral mucosa and lymph node palpation, as well as chest/abdomen Computerised Tomography (CT) scan. Refer to Section 7.47 and Time and events table (Table 19). During treatment patients should be monitored as clinically appropriate which may include a head and neck examination every 3 months and a chest/abdomen CT scan every 6 months. Anal examinations and pelvic examinations (for women) are recommended as per Section 7.4.7 and the Time and Events table (Table 19), or when considered clinically indicated. Complete blood cell counts should be performed as clinically indicated. Following discontinuation of dabrafenib and completion in study, monitoring for non-cutaneous secondary/recurrent malignancies should continue for up to 6 months or until initiation of another anti-neoplastic therapy, whichever comes first as per the SmPC fro Dabrafenib. Abnormal findings should be managed according to clinical practices.

Any cuSCC, new primary melanomas, and or non-cutaneous secondary/recurrent malignancy should be reported as a protocol-specific SAE~~s~~ and treated according to standard clinical practice. Refer to Section 7.4.2.2.

Appendix 7 Summary of Changes for Amendment 01

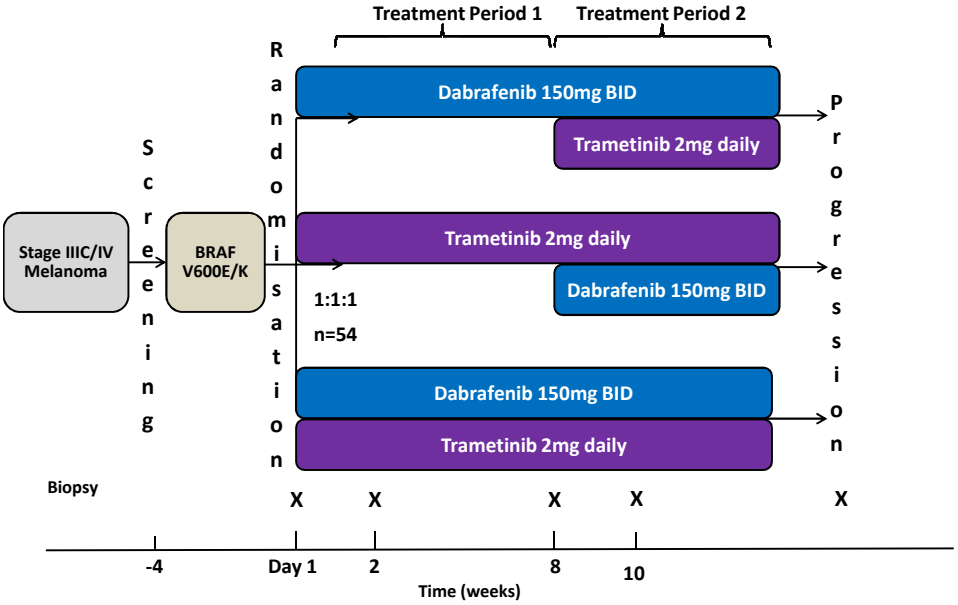
Previous - 3. STUDY DESIGN

Figure 2 Study Schema



Revised- 3. STUDY DESIGN

Figure 3 Study



Schema

Rationale: Amendment to figure 1.in order to be better aligned with the study design with regards to timelines.

Previous

5.7 Treatment Compliance

Patients will be instructed to return treatment vials at each visit.

Revised

5.7 Treatment Compliance

Patients will be instructed to return treatment bottles at each visit.

Rationale: Clarification of text. The study medication will be in bottles and not vials

Previous

7.2 Biomarkers

If possible biopsies should be taken from the same organ. Key biopsies are screening, week 2 and week 10. Additional patients might be recruited to ensure a sufficient number of patients in each arm providing these three key biopsies.

Revised

7.2 Biomarkers

Biopsies will be performed on cutaneous or sub-cutaneous lesions that are easily accessible and will NOT be performed on any deep lesions. If possible biopsies should be taken from the same lesion/location. Key biopsies are taken at randomisation, week 2, week 8, and week 10. Additional patients might be recruited to ensure a sufficient number of patients in each arm providing these three key biopsies.

Rationale: Amendment and further clarification around the biopsies taken for this study as requested by the ANSM.

Previous

7.3.2 Efficacy Assessment

Confirmation of response (i.e., CR and PR) is not necessary per RECIST, version 1.1, as the primary efficacy endpoint of the study is PFS.

Revised

7.3.2 Efficacy Assessment

Confirmation of response (i.e., CR and PR) is not necessary per RECIST, version 1.1, as the primary endpoint of the study is not overall best response.

Rationale: Clarification regarding the confirmation of response.

Previous

7.5.1 Blood Sample Collection for Pharmacokinetics

Blood samples for PK analyses of dabrafenib, trametinib, and metabolites of dabrafenib will be collected pre-dose and at the same time as the tumour and skin biopsies are performed during treatment (Week 2, 8 and 10). The actual date and time of each blood sample collection will be recorded. No more than 25 mL of blood will be collected over the duration of the study for PK blood sample collection, including any extra assessments that may be required.

Revised

7.5.1 Blood Sample Collection for Pharmacokinetics

Blood samples for PK analyses of dabrafenib, trametinib, and metabolites of dabrafenib will be collected at the same day as the tumour and skin biopsies are performed during treatment (Week 2, 8 and 10). Patients with morning clinic visits will be instructed to withhold their morning dose, and samples will be collected prior to dabrafenib and trametinib administration; for patients with afternoon clinic visits, patients will take their morning doses as usual, and samples will be collected 4-8 hours following dabrafenib and trametinib administration. Date and exact time of pharmacokinetic sample and of most recent dose will be recorded.. No more than 25 mL of blood will be collected over the duration of the study for PK blood sample collection, including any extra assessments that may be required.

Rationale: Clarification of the PK blood sampling.

Previous - Table 24 Time and Events

Table 25 Time and Events

Study Assessments[1]	**Screening** (≤ 28 days except where noted)[2]	**Day 1**	**Every 4 Weeks** (± 7 days)	**Every 8 Weeks** (± 7 days)	**Every 12 Weeks** (± 7 days)	**End of Study**[20]
Clinical assessments						
Informed consent[3]	X					
Inclusion/Exclusion criteria	X	X				
Demographic data	X					
Past and current medical conditions including cardiovascular medical and family history, risk factors	X					
Disease characteristics[4]	X					
Prior anti-cancer therapies	X					
Performance status (ECOG)	X		X			X
Brain MRI/CT[5]	X					
Lesion assessment (including skin lesion photography)[6]	X (5 weeks)			Week 8 and every 8 weeks thereafter through week 56 and then every 12 weeks thereafter until determination of progressive disease		
Randomisation[7]		X				
Safety Assessments						
Vital signs[8]	X		X			X
Physical examination[9]	X		X (short)			X
Ophthalmic examination[10]	X					
Adverse events[11]	X	X	X			X
ECG[12]	X (5 weeks)		X (only at Week 4)		X	X
ECHO[13]	X (5 weeks)		X (only at Week 4)		X	
Dermatology assessment	X		X (only at week 2, 8, 10)			X (at PD)
Concomitant medications[14]	X	X	X			X
Laboratory Assessments						

Study Assessments[1]	**Screening** (≤ 28 days except where noted)[2]	**Day 1**	**Every 4 Weeks** (± 7 days)	**Every 8 Weeks** (± 7 days)	**Every 12 Weeks** (± 7 days)	**End of Study**[20]
Chemistry and Haematology[15]	X		X			X
Serum pregnancy test[16]	X					
Coagulation	X					
Study Treatments						
Dispensation of medication[17]		X	X			
Assessment of compliance[18]			X			
Biomarker Samples						
Tumour biopsy[21]	X		X (only at week 2, 8, 10)			X (at PD)
Skin biopsy[21]	X		X (only at week 2, 8, 10)			X (at PD)
Blood sample for biomarker		X	X (only at week 2, 8, 10)			X (at PD)
Blood sample for PK[19]			X (only at week 2, 8, 10)			X (at PD)
Blood sample for cfDNA[21]	X					

Abbreviations: cfDNA = cell-free deoxyribonucleic acid; CNS = central nervous system; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; LLN = lower limit of normal; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; PD = progressive disease; PK = pharmacokinetics; RAMOS = Registration and Medication Ordering System; RECIST = Response Evaluation Criteria in Solid Tumours; SPM = study procedures manual.

1. All assessments mandated throughout the study must be performed on a calendar schedule; delays in treatment administration will not delay performance of assessments.
2. Screening procedures may be performed up to 28 days prior to randomisation. Screening procedures that have a larger visit window are indicated in parentheses.
3. Informed consent must be given prior to performance of any study-related procedures. Informed consent can be obtained at any time before Day 1.
4. Disease characteristics will include date of diagnosis, primary tumour type, histology, stage, etc.
5. Baseline MRI (preferred) or CT (only if MRI contraindicated or unavailable) of the brain must be performed on all patients to rule out current leptomeningeal metastases, brain metastases, or spinal cord compression secondary to metastasis. Post-baseline scans should be performed in all patients with documented metastases at baseline and as clinically indicated (e.g., symptoms suggestive of CNS progression) in all patients.
6. Lesion assessments must be done for chest, abdomen, pelvis, and any area of known disease. Lesion assessment by contrast CT (preferred) or MRI must be performed within 4 weeks prior to randomisation and at the times indicated until disease progression, death, or withdrawal of consent, whichever occurs first. (See Section 7.3.3 for instructions regarding chest X-Rays and CT assessment.) Target and non-target lesions must be identified at the time of screening and the same lesions must be re-assessed at each timepoint in a consistent manner according to RECIST, version 1.1. The same diagnostic method, including use of contrast when applicable, must be used throughout the study to evaluate each lesion. Lesion measurements will be taken using ruler or calipers. The Week 8 assessment for patients in arms A & B should be done before starting the

combination treatment. If the last assessment was > 8 weeks prior to study withdrawal and disease progression had not been documented, a disease assessment should be obtained.

7. Randomisation will occur via RAMOS on Day 1.
8. Refer to Section 7.4.6 for details regarding vital sign measurements.
9. A complete physical examination will be performed at Screening and End-of-study; brief physical examinations will be performed at all other timepoints as indicated. In females, genitourinary exam should include a visual inspection of the cervix. If the patient has had a genitourinary and rectal exam within 6 months of screening the genitourinary and rectal exam do not need to be repeated. Refer to Section 7.4.7 for details.
10. An ophthalmic examination will be performed at Screening; additional ophthalmic examinations will be performed only as symptomatically warranted. Refer to Section 7.4.5 for details.
11. Adverse events will be recorded from the time the first dose of study treatment is administered until 30 days after discontinuation of study treatment. Serious adverse events will be collected over the same time period as AEs except SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy), study treatment, or a GSK concomitant medication which must be recorded from the time a patient consents to participate in the study up to and including any follow-up contact.
12. At each timepoint listed, a single 12-lead ECG will be performed by qualified site personnel after the patient has rested in a semi-recumbent or supine position for at least 5 minutes.
13. While on treatment, patients who have an asymptomatic, absolute decrease in LVEF of > 10% compared to screening and whose ejection fraction is below the institution's LLN, must be followed according to LVEF guidelines for study drug management and requirements for subsequent ECHO.
14. All medications the patient takes during the study from the time of screening until 30 days after the last dose of study treatment will be recorded.
15. Analysis of clinical chemistry and haematology samples will be performed by the local lab. Screening labs performed within 2 weeks prior to randomisation do not need to be repeated.
16. Serum pregnancy test is required at Screening. Subsequent tests may be urine tests, and should be performed as clinically indicated.
17. A 4-week supply of study medication should be dispensed at each scheduled study visit as of Day 1. Patients should be provided with dosing instructions. Patients should start treatment as soon as possible after randomisation but no later than 72 hours post-randomisation.
18. Patients should be instructed to return study drug vials at each visit; compliance will be assessed through querying the patient and through pill count at the time of new dispensation. Dose modifications and interruptions must be recorded.
19. The date and exact time of PK sample collection and most recent dose will be recorded. Details of collection procedures, including dosing instructions for morning and afternoon visits, will be provided in the SPM.
20. End of study assessments do not need to be repeated if performed within 4 weeks
21. Biomarker-related sampling to be conducted at randomisation to avoid biomarker sample collection for ineligible patients

Revised - Table 26 Time and Events

Table 27 Time and Events

Study Assessments[1]	**Screening** (≤ 28 days except where noted)[2]	**Day 1**	**Every 4 Weeks** (± 7 days)	**Every 8 Weeks** (± 7 days)	**Every 12 Weeks** (± 7 days)	**End of Study**[20]
Clinical assessments						
Informed consent[3]	X					
Inclusion/Exclusion criteria	X	X				
Demographic data	X					
Past and current medical conditions including cardiovascular medical and family history, risk factors	X					
Disease characteristics[4]	X					
Prior anti-cancer therapies	X					
Performance status (ECOG)	X		X			X
Brain MRI/CT[5]	X (5 weeks)					
Lesion assessment (including skin lesion photography)[6]	X (5 weeks)			Week 8 and every 8 weeks thereafter through week 56 and then every 12 weeks thereafter until determination of progressive disease		
Randomisation[7]		X				
Safety Assessments						
Vital signs[8]	X		X			X
Physical examination[9,23]	X		X (short)			X
Ophthalmic examination[10]	X					
Adverse events[11]	X	X	X			X
ECG[12]	X (5 weeks)		X (only at Week 4)		X	X
ECHO[13]	X (5 weeks)		X (only at Week 4)		X	
Dermatology assessment[23]	X		X (only at week 2, 8, 10)			X (at PD)
Concomitant medications[14]	X	X	X			X

Study Assessments[1]	**Screening** (≤ 28 days except where noted)[2]	**Day 1**	**Every 4 Weeks** (± 7 days)	**Every 8 Weeks** (± 7 days)	**Every 12 Weeks** (± 7 days)	**End of Study**[20]
Laboratory Assessments						
Chemistry and Haematology[15]	X		X			X
Serum pregnancy test[16]	X					
Coagulation	X					
Study Treatments						
Dispensation of medication[17]		X	X			
Assessment of compliance[18]			X			
Biomarker Samples						
Tumour biopsy[21, 22,]		X	X (only at week 2, 8, 10)			X (at PD)
Skin biopsy[21, 22]		X	X (only at week 2, 8, 10)			X (at PD)
Blood sample for biomarker		X	X (only at week 2, 8, 10)			X (at PD)
Blood sample for PK[19]			X (only at week 2, 8, 10)			X (at PD)
Blood sample for cfDNA[21]		X				

Abbreviations: cfDNA = cell-free deoxyribonucleic acid; CNS = central nervous system; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; LLN = lower limit of normal; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; PD = progressive disease; PK = pharmacokinetics; RAMOS = Registration and Medication Ordering System; RECIST = Response Evaluation Criteria in Solid Tumours; SPM = study procedures manual.

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2. Screening procedures may be performed up to 28 days prior to randomisation. Screening procedures that have a larger visit window are indicated in parentheses.
3. Informed consent must be given prior to performance of any study-related procedures. Informed consent can be obtained at any time before Day 1.
4. Disease characteristics will include date of diagnosis, primary tumour type, histology, stage, etc.
5. Baseline MRI (preferred) or CT (only if MRI contraindicated or unavailable) of the brain must be performed on all patients to rule out current leptomeningeal metastases, brain metastases, or spinal cord compression secondary to metastasis. Post-baseline scans should be performed in all patients with documented metastases at baseline and as clinically indicated (e.g., symptoms suggestive of CNS progression) in all patients.
6. Lesion assessments must be done for chest, abdomen, pelvis, and any area of known disease. Lesion assessment by contrast CT (preferred) or MRI must be performed within 5 weeks prior to randomisation and at the times indicated until disease progression, death, or withdrawal of consent, whichever occurs first. (See Section 7.3.3 for instructions regarding chest X-Rays and CT assessment.) Target and non-target lesions must be identified at the time of screening and the same lesions must be re-assessed at each timepoint in a consistent manner according to RECIST, version 1.1. The same diagnostic method, including use of contrast when applicable, must be used

throughout the study to evaluate each lesion. Lesion measurements will be taken using ruler or calipers. The Week 8 assessment for patients in arms A & B should be done before starting the combination treatment. If the last assessment was > 8 weeks prior to study withdrawal and disease progression had not been documented, a disease assessment should be obtained.

7. Randomisation will occur via RAMOS on Day 1.
8. Refer to Section 7.4.6 for details regarding vital sign measurements.
9. A complete physical examination will be performed at Screening and End-of-study; brief physical examinations will be performed at all other timepoints as indicated. In females, genitourinary exam should include a visual inspection of the cervix. If the patient has had a genitourinary and rectal exam within 6 months of screening the genitourinary and rectal exam do not need to be repeated. Refer to Section 7.4.7 for details.
10. An ophthalmic examination will be performed at Screening; additional ophthalmic examinations will be performed only as symptomatically warranted. Refer to Section 7.4.5 for details.
11. Adverse events will be recorded from the time the first dose of study treatment is administered until 30 days after discontinuation of study treatment. Serious adverse events will be collected over the same time period as AEs except SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy), study treatment, or a GSK concomitant medication which must be recorded from the time a patient consents to participate in the study up to and including any follow-up contact.
12. At each timepoint listed, a single 12-lead ECG will be performed by qualified site personnel after the patient has rested in a semi-recumbent or supine position for at least 5 minutes.
13. While on treatment, patients who have an asymptomatic, absolute decrease in LVEF of > 10% compared to screening and whose ejection fraction is below the institution's LLN, must be followed according to LVEF guidelines for study drug management and requirements for subsequent ECHO.
14. All medications the patient takes during the study from the time of screening until 30 days after the last dose of study treatment will be recorded.
15. Analysis of clinical chemistry and haematology samples will be performed by the local lab. Screening labs performed within 2 weeks prior to randomisation do not need to be repeated.
16. Serum pregnancy test is required at Screening. Subsequent tests may be urine tests, and should be performed as clinically indicated.
17. A 4-week supply of study medication should be dispensed at each scheduled study visit as of Day 1. Patients should be provided with dosing instructions. Patients should start treatment as soon as possible after randomisation but no later than 72 hours post-randomisation.
18. Patients should be instructed to return study drug vials at each visit; compliance will be assessed through querying the patient and through pill count at the time of new dispensation. Dose modifications and interruptions must be recorded.
19. The date and exact time of PK sample collection and most recent dose will be recorded. Details of collection procedures, including dosing instructions for morning and afternoon visits, will be provided in the SPM.
20. End of study assessments do not need to be repeated if performed within 4 weeks
21. Biomarker-related sampling to be conducted at randomisation to avoid biomarker sample collection for ineligible patients
22. Biopsies are to be taken at the judgement of the investigator at the various time-points to ensure that any potential risk or impact to the patients are kept to a minimum, All biopsies, be they from cutaneous or sub-cutaneous lesions, are to be performed only if the lesions are easily accessible.Biopsies are to be performed by either the investigator, a dermatologist, a surgeon or a physician qualified in radiology if an ultrasound-led biopsy is necessary.
23. For Subjects enrolled in France, refer to the Appendix 6: Additional Monitoring for Patients Enrolled in France

Rationale: Change of brain MRI from 4 weeks to 5 weeks before Day 1; Amendment of the the time and events table to be in alignment with footnote 21 which states that the biopsies will be taken at the randomisation visit and not the screening visit.; Amendment and further clarification around the biopsies taken for this study as requested by the ANSM. This includes: a) That the biopsies will only be done on cutaneous and subcutaneous lesions only if they are easily accessible; b) confirmation that no deep lesion biopsies will be performed; c) clarification of who is qualified to perform the biopsies; refer to footnote 22.; The addition of footnote 23 refering to the Appendix 6, Additional Monitoring for patients enrolled in France.

Previous

No Appendix 6 - Additional Monitoring for Patients Enrolled in France

Evaluation for Cutaneous Squamous Cell Carcinoma (cuSCC), New Primary Melanoma, and Non-cutaneous Secondary/Recurrent Malignancy Following Discontinuation of Dabrafenib

Revised

Addition of Appendix 6 - Additional Monitoring for Patients Enrolled in France

Evaluation for Cutaneous Squamous Cell Carcinoma (cuSCC), New Primary Melanoma, and Non-cutaneous Secondary/Recurrent Malignancy Following Discontinuation of Dabrafenib

Rationale: New France specific Appendix 6 added to reflect the monitoring required for Cutaneous Squamous Cell Carcinoma (CuSCC), new primary melanoma and non-cutaneous secondary/recurrent malignancy as reqested by ANSM.