NOVARTIS

Clinical Development

GSK1120212 and GSK2118436

Protocol MEK116833 / NCT01750918

An Open-Label, Four-Part, Phase I/II Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of the MEK Inhibitor GSK1120212, BRAF Inhibitor GSK2118436 and the anti-EGFR Antibody Panitumumab in Combination in Subjects with BRAF-mutation V600E Positive Colorectal Cancer and in Subjects with CRC With Secondary Resistance to Prior Anti-EGFR Therapy

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Amendment 05

Amendment rationale

Subsequent to the acquisition of GlaxoSmithKline (GSK) compound GSK1120212 and GSK2118436, the purpose of this protocol Amendment 05 is to:

- Delete or replace references to GlaxoSmithKline or its staff with that of Novartis and its authorized agents to align with the change of sponsorship;
- Make administrative changes to align with Novartis processes and procedures;

As of 08 February 2017:

166 patients have received study treatment in 8 countries.

161 patients have completed or discontinued study treatment.

The changes described in this amended protocol require Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) approval prior to implementation.

A copy of this amended protocol will be sent to the IRBs/IECs and Health Authorities (HAs).

The changes herein affect the Informed Consent and all sites are required to update and submit for approval, a revised Informed Consent that takes into account the change of study sponsorship described in the protocol amendment.

Upon approval of this amendment, patients who have already been enrolled in the study will sign a new informed consent form indicating Novartis is the new study sponsor and continue the appropriate visit schedule.

Revision Chronology

GlaxoSmithKline Document Number	Date	Version
2012N139131_00	2012-OCT-10	Original
2012N139131_01	2013-JUN-07	Amendment No. 1
Restriction of enrollment to V600E mutation positive CRC; formerly allowed V600E or V600K mutations Move of pharmacodynamics from [redacted] Secondary Objective Simplification of Part 1 study schematic Revision to Cardiac DLT Definition Clarification that intra-subject dose escalation is allowed in triplet cohorts only Addition of guideline for cuSCC Text revised to allow use of MUGA to evaluate LVEF if ECHO is not available Updated visual changes stopping criteria Clarification of time and events tables Allow use of therapeutic warfarin (previously exclusionary) Addition of text on Bayesian design for Part 2 Addition of section on follow-up (PFS, OS) for subjects who discontinue study treatment Updates to prohibited medications Revision of study completion criteria Addition of Sentinel Events and Cardiovascular Events Updates to blood volume requirements in Appendix 2 For subjects enrolled at sites in France---Revised criteria for assessment of valvular toxicity, and withholding and stopping criteria for QTc prolongation per request by ANSM		
2012N139131_02	2013-OCT-28	Amendment No. 2
Revised medical monitor contact information Updated abbreviations table Changed central serous retinopathy (CSR) to retinal pigment epithelium detachment (RPED) throughout Revised headers in Table 1, and text in Section 3.4.2 for clarity Clarified opening of Part 2 cohorts in Section 3.4.2 Revised text in Section 3.7.3 to allow subjects in Part 1 and Part 2 to crossover from		

doublet to triplet dosing Updated QTc withholding and stopping criteria in Section 3.7.9 For all Time and Events tables (Section 3.8.1, Section 3.8.2 and Section 3.8.3), added cross-reference to table in inclusion/exclusion criteria defining adequate organ function at baseline; added footnote regarding dermatological toxicity monitoring for subjects enrolled in France For Part 1 and Part 2 Time and Events tables (Section 3.8.1 and Section 3.8.2), clarified collection of tumor biopsy in subjects with a response to study treatment For Part 3 Time and Events table (Section 3.8.3), added optional tumor biopsy at progression Section 4.2.1.1, Section 4.2.1.2, Section 7.1.1 and Section 7.1.2, updated text on timing of use of contraception prior to start of dosing and after last dose of study treatments Section 5.2.3, defined crossover population Section 5.3.8.7.1, clarified text regarding crossover population and efficacy analysis Added Section 6.7.2 Fresh Tumor Tissue at Progression For subjects enrolled at sites in France---Revised criteria for monitoring of dermatological toxicity per request by ANSM		
2012N139131_03	2014-MAY-01	Amendment No. 3
Revision of medical monitor information Addition of text throughout protocol describing Part 4 (study and dose rationale; objectives and endpoints; eligibility criteria; investigational plan; Part 4 study design and schematic; time and events table) Revision of eligibility criteria to allow enrolment of subjects who have been previously treated with anti-EGFR, and to reflect updated asset-specific guidances on toxicities. Revision of general guidelines for clinically significant toxicities. [redacted]		
2012N139131_04	2015-MAR-26	Amendment No. 4
Addition of text and schema for Part 2B, dose cohort expansion to enroll additional subjects to the triplet regimen at two different doses of panitumumab including updated Bayesian probabilities to accommodate increase sample size for triplet. Collection of OS overall survival data for subjects in all parts has been included to the Time and Events Tables as well as to Section 6.3.1. Revision of dose modification guidelines. Clarification of intrasubject crossover from doublet to triplet including the addition of a Time and Events Table for crossover.		

<table>
<tr><td colspan="3">Minor changes to the timing of assessment in the Time and Events Tables for Part 2 and Part 4.

Revision of medical monitor information.</td></tr>
<tr><td>2012N139131_05</td><td>2015-APR-13</td><td>Amendment No. 4
Republished</td></tr>
<tr><td colspan="3">Compound number was updated from the GSK reference to the combination of trametinib and dabrafenib to the GSK compound numbers for trametinib and dabrafenib, GSK112012 + GSK2118436.</td></tr>
<tr><td>NA</td><td>2017-FEB-08</td><td>Amendment No. 5</td></tr>
<tr><td colspan="3">Delete or replace references to GSK or its staff with that of Novartis/Novartis and its authorized agents.

Make administrative changes to align with Novartis processes and procedures.</td></tr>
</table>

SPONSOR SIGNATORY

[redacted] Date

[redacted] Novartis Pharma AG

SPONSOR INFORMATION PAGE

Novartis Pharmaceuticals Corporation

Clinical Leader and Sponsor Contact Information:

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In some countries, the clinical trial sponsor may be the local Novartis and its authorized agents. If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

If you have any questions regarding the protocol, please contact your local Novartis office.

Regulatory Agency Identifying Number(s): IND# 113557, EUDRACT# 2012-004802-81, NCT# 01750918

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number: MEK116833

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described 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 receives the appropriate information throughout the study.

Investigator Name:		
Investigator Address:		
Investigator Phone Number:		
Investigator Signature		Date

TABLE OF CONTENTS

PAGE

LIST OF ABBREVIATIONS

µg	Microgram
µL	Microliter
ADL	Activities of daily living
AE	Adverse Event
ALT	Alanine aminotransferase (SGPT)
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase (SGOT)
ATP	Adenosine triphosphate
AUC	Area under concentration-time curve
AUC(0-∞)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC(0-τ)	Area under the concentration-time curve over the dosing interval
AUC(0-8)	Area under the concentration-time curve from zero (pre-dose) 8 hours
AUC(0-t)	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a subject across all treatments
BAL	Bronchoalveolar lavage
BBB	Bundle-branch block
BID	twice daily
BLRM	Bayesian logistic regression model
BORR	Best overall response rate
BP	Blood pressure
BPM	Beat Per Minute
BQL	Below quantifiable limits
BRAT	Bananas, rice, apples, toast (diet)
[redacted]	[redacted]
BST	Bioanalytical Science & Toxicokinetic
BUN	Blood urea nitrogen
CBC	Complete blood count
[redacted]	[redacted]
CI	Confidence Interval
CL	Systemic clearance of parent drug
CL/F	Apparent clearance following oral dosing
Cmax	Maximum observed concentration
Cmin	Minimum observed concentration
CO_2	Carbon dioxide
CPK	Creatinine phosphokinase
CPK/M&S PK	Clinical Pharmacokinetics/ Modeling & Simulation Pharmacokinetic
CPMS	Clinical Pharmacology Modeling & Simulation
CR	Complete response
CRC	Colorectal cancer
CRP	C-reactive protein
Ct	Last observed quantifiable concentration

CT	Computed tomography
CuSCC	Cutaneous squamous cell carcinoma
Cτ	Pre-dose (trough) concentration at the end of the dosing interval
DBP	Diastolic blood pressure
DLT	Dose-limiting toxicity
DMPK	Drug Metabolism and Pharmacokinetics
[redacted]	[redacted]
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	Epidermal growth factor receptor
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
FTIH	First time in humans
GCP	Good Clinical Practice
GCPH	Global Clinical Program Head
GCSP	Global Clinical Safety and Pharmacovigilance
GGT	Gamma glutamyltransferase
GI	Gastrointestinal
GLP	Good Laboratory Practice
GSK	GlaxoSmithKline
h/hr	Hour(s)
HA	Health Authorities
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HFSR	Hand-foot skin reaction
HR	Heart rate
HRT	Hormone replacement therapy
IB	Investigator's Brochure
IC50	Half maximal inhibitory concentration
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
ILD	Interstitial lung disease
IND	Investigational New Drug
INR	International normalized ratio
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent to treat
IU	International Unit
IUD	Intrauterine device
IUS	Intrauterine system

IV	Intravenous
Ka	Absorption rate constant
KA	Keratoacanthoma
Kg	Kilogram
L	Liter
LDH	Lactate dehydrogenase
LFTs	Liver function tests
LLN	Lower limit of normal
LMWH	Low molecular weight heparin
LSLV	Last subject last visit
LVEF	Left ventricular ejection fraction
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
mCRC	Metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligrams
mL	Milliliter
MRI	Magnetic resonance imaging
MRT	Mean residence time
MSDS	Material Safety Data Sheet
msec	Milliseconds
MTD	Maximum tolerated dose
MUGA	Multigated acquisition scan
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NED	No evidence of disease
NSAIDs	Nonsteroidal anti-inflammatory drugs
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PD	Progressive Disease
pEGFR	phosphorylated epidermal growth factor receptor
PFS	Progression-free survival
PGx	Pharmacogenetics
PK	Pharmacokinetic
PR	Partial response
PSRI	Periodic Safety Reports for Investigators
PT	Prothrombin time
PTT	Partial thromboplastin time
Q	Every
QC	Quality control
QTcB	QT duration corrected for heart rate by Bazett's formula
QTcF	QT duration corrected for heart rate by Fridericia's formula
RAP	Reporting and Analysis Plan
RBC	Red blood cells

RECIST	Response Evaluation Criteria In Solid Tumors
REML	Restricted maximum likelihood
RNA	Ribonucleic acid
RP2R	Recommended Phase 2 Regimen
RPED	Retinal pigment epithelium detachment
RR	Response rate
RTK	Receptor tyrosine kinase
RVO	Retinal vein occlusion
SAE	Serious adverse event(s)
SMT	Safety Monitoring Team
SAS	Statistical Analysis Software
SAS Proc Mixed	SAS procedure MIXED
SBP	Systolic blood pressure
SCC	Squamous cell carcinoma
SD	Standard deviation
SD	Stable disease
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	Standard of care
SOP	Standard Operating Procedure
SPM	Study Procedures Manual
SUSAR	Suspected, Unexpected, Serious Adverse drug Reaction
T	Infusion duration
t	Time of last observed quantifiable concentration
t½	Terminal phase half-life
tmax	Time of occurrence of Cmax
[redacted]	[redacted]
ULN	Upper limit of normal
US	United States
V/F	oral volume of distribution
WBC	White blood cells
τ	Dosing interval

1. INTRODUCTION

1.1. Background

1.1.1. Colorectal Cancer: Unmet Medical Need

Colorectal cancer (CRC) is the fourth most common visceral malignancy and the second most frequent cause of cancer death. Although the incidence of CRC has increased significantly over the past 3 decades, the mortality rate has decreased. This is due, in part, to improved screening techniques but also to improved therapies. While there has been improvement, the unmet need remains very high, particularly for subjects with BRAF-mutation V600E positive CRC, which has substantially worse outcomes than both the KRAS-mutant and the KRAS/BRAF-wild type populations.

One improvement in CRC therapy has been the inclusion of anti-epidermal growth factor receptor (EGFR) therapy. Cetuximab, the first anti-EGFR therapy approved for the treatment of CRC, was demonstrated to have a benefit on progression free survival (PFS) and overall survival (OS) as a single agent in subjects with CRC that was resistant to standard chemotherapy [Jonker, 2007]. Subsequently it was demonstrated that cetuximab also demonstrated improvement in PFS when combined with standard chemotherapy (leucovorin calcium, fluorouracil, irinotecan hydrochloride; FOLFIRI) in previously untreated CRC subjects [Van Cutsem, 2009]. However, subsequent analyses of these studies, and a randomized Phase 2 evaluation of cetuximab with FOLFOX (leucovorin calcium, fluorouracil, oxaliplatin) demonstrated that the improvement in PFS was limited to cancers that harboured the wild-type version of the proto-oncogene KRAS [Karapetis, 2008; Bokemeyer, 2009; Van Cutsem, 2009]. Furthermore, a benefit in overall survival could also be demonstrated in wild-type KRAS subjects. More recently, the fully humanized anti-EGFR antibody panitumumab (Vectibix) was demonstrated to have very similar efficacy in the first line and second line settings with less frequent dosing (once every two weeks) and a lower rate of infusion reactions [VECTIBIX, 2014; Douillard, 2010; Peeters, 2010]. Again, the therapeutic benefit was limited to the KRAS wild-type population. Subsequent analyses of studies that have investigated anti-EGFR therapy (cetuximab and panitumumab) in CRC have confirmed that the clinical benefit of these therapies is limited to subjects with wild-type KRAS/NRAS [DeRoock, 2010, Schwartzberg, 2014; Douillard, 2013].

The RAS/RAF/MEK/ERK pathway is a critical proliferation pathway in many human cancers. Under normal circumstances, this pathway is activated by the stimulation of upstream signalling pathways, particularly receptor tyrosine kinases (RTKs). It is through the aberrant stimulation of this pathway that the KRAS mutation confers resistance to anti-EGFR therapy [Lievre, 2010].

The RAS/RAF/MEK/ERK pathway can also be constitutively activated by alterations in the BRAF oncogene. BRAF, which activates MEK through its phosphorylation on two regulatory serine residues, is frequently mutated in a number of cancers, including melanoma, CRC, and thyroid cancer. The most common point mutations of BRAF result in a change at valine 600, usually V600E. In melanomas that harbour mutant BRAF,

small molecule inhibitors of BRAF, or the downstream kinase MEK, result in substantial therapeutic benefit [Chapman, 2011; Flaherty, 2012; Hauschild, 2012].

Although the BRAF mutation rate varies substantially across studies, approximately 8-12% of metastatic colorectal cancer cases harbors a BRAF mutation [Maughan, 2011; Souglakos, 2009; Bokemeyer, 2012; Tveit, 2012; Richman, 2009; Tran, 2011; Yokota, 2011; Tie, 2011]. Approximately 90% of all identified BRAF mutations that occur in human cancer are a T1799A transversion mutation in exon 15, which results in a V600E amino acid substitution [Wan, 2004]. This mutation appears to mimic regulatory phosphorylation and increases BRAF activity approximately 10-fold as compared to wild-type [Davies, 2002]. Accumulating data demonstrate that the presence of a BRAF-mutation is a poor prognostic factor in CRC, with BRAF-mutation positive CRC demonstrating a more aggressive natural history than either KRAS mutant or KRAS/BRAF wild-type CRC. Although the data are derived from a series of retrospective analyses of the BRAF-mutant population that typically have relatively small sample sizes, the efficacy of current therapies can be summarized in the first line and post-first line settings. In the first line setting, current chemotherapy-based regimens (± bevacizumab or anti-EGFR therapy) tend to have a response rate in the range of 15 to 25%, median PFS of ~4 to 7 months and median OS of ~9 to 14 months in subjects with BRAF-mutant CRC[Maughan, 2011; Souglakos, 2009; Bokemeyer, 2012; Tveit, 2012; Richman, 2009; Tran, 2011; Yokota, 2011; Tie, 2011]. Beyond the first line setting, currently available therapies appear to provide very little benefit, with very few responses, median PFS of 1.5 to 3 months and median OS of 4 to 7 months [Loupakis, 2009; Di Nicolantonio, 2008; Laurent-Puig, 2009].

The utility of anti-EGFR therapy in the BRAF-mutation positive CRC patient population is an unsettled question. The literature includes a number of conflicting reports, some suggesting benefit [Bokemeyer, 2012] and others suggesting the absence of benefit [Di Nicolantonio, 2008; Loupakis, 2009; Maughan, 2011]. Since the BRAF mutation activates the same primary pathway as the KRAS mutation, the conferral of resistance to anti-EGFR therapy would not be surprising; however the available clinical data do not yet provide a clear answer. What does appear clear is that, given the poor prognosis and limited activity of currently available agents in all lines of treatment, BRAF-mutant CRC is a substantial unmet medical need.

As mentioned above, recently developed inhibitors of the BRAF and MEK kinases have demonstrated substantial clinical benefit in the treatment of subjects with BRAF-mutant melanoma [Chapman, 2011; Flaherty, 2012; Hauschild, 2012]. This benefit has come in the form of profound tumor shrinkage (confirmed response rates of >50%), prolonged progression free survival and improvements in overall survival. Preliminary studies evaluating the activity of these same targeted inhibitors of BRAF and MEK have not demonstrated similar efficacy in BRAF-mutant CRC as they have demonstrated in BRAF-mutant melanoma, with overall response rates in BRAF-mutant CRC of <10% [Falchook, 2012; Kopetz, 2010].

Recently published preclinical studies provide a potential molecular explanation for the discrepant activity of BRAF inhibitors in BRAF-mutant melanoma vs. BRAF-mutant CRC. Similar to the clinical experience to date, CRC cell lines are relatively insensitive

to BRAF inhibitors, both in vitro and in vivo. However, whereas BRAF-mutant melanoma cell lines generally lack expression of EGFR, BRAF-mutant CRC cell lines express high levels of activated EGFR protein (pEGFR). The addition of an anti-EGFR therapy (including anti-EGFR biological agents [cetuximab] and small molecule inhibitors of EGFR [e.g., erlotinib and gefitinib]) sensitized the CRC cell lines to the BRAF inhibitor, resulting in synergistic activity of the combination in in vitro and in vivo models [Prahallad, 2012; Corcoran, 2012]. Based on these data, the differential expression of EGFR in BRAF-mutant CRC, and not in BRAF-mutant melanoma, may explain the insensitivity of BRAF-mutant CRC and provides a strong rationale to evaluate the combination of anti-EGFR antibodies with a BRAF inhibitor and with the combination of a BRAF inhibitor and a MEK inhibitor.

The current study is designed to test the hypothesis that the combination of an anti-EGFR antibody with either a BRAF inhibitor (dabrafenib; GSK2118436) alone or with the combination of a BRAF inhibitor and a MEK inhibitor (trametinib; GSK1120212) will result in clinically meaningful anti-tumor activity that represents an improvement over the chemotherapy comparator (a regimen of FOLFOX, FOLFIRI or irinotecan with or without panitumumab or bevacizumab) for BRAF-mutant CRC. This will include the evaluation of the safety and tolerability of the two combinations, a preliminary assessment of clinical activity and then a randomized evaluation relative to the chemotherapy comparator therapy. In addition, the study will test the hypothesis that the combination of panitumumab and trametinib can overcome secondary resistance to an anti-EGFR therapy in patients that initially derived benefit from the anti-EGFR therapy (further rationale in Section 1.3.2).

1.1.2. Dabrafenib (GSK2118436)

Dabrafenib is a 4-(3-aminosulfonylphenyl)-5-(pyrimidin-3-yl) thiazole, is a potent and selective inhibitor of BRAF kinase activity with a mode of action consistent with adenosine triphospate (ATP)-competitive inhibition, and is currently in Phase 3 development in BRAF V600E-mutation positive metastatic melanoma.

Excluding Raf enzymes, dabrafenib demonstrated high selectivity with the half maximal inhibitory concentration (IC_{50}) values <100nM against only 7 other kinases from ~300 protein and lipid kinases tested. Dabrafenib inhibits phosphorylation of MEK and ERK in vitro, inhibits cell proliferation, and achieved tumor regression in xenograft cancer models that encode $BRAF^{V600E}$. The investigator should refer to the GSK2118436 Investigator's Brochure [GlaxoSmithKline Document Number 2012N136095_00] for detailed information regarding ongoing clinical studies, pharmacokinetics in the target disease populations, as well as observed safety and efficacy findings.

Clinical data in subjects with metastatic BRAF-mutation positive melanoma have demonstrated clear benefit of dabrafenib over chemotherapy. In a randomized Phase 3 study, dabrafenib demonstrated significant benefit in PFS (hazard ratio=0.35) and confirmed response rate (50% vs. 6%) relative to chemotherapy [Hauschild, 2012]. In addition, although the OS data were still immature, there was a trend toward improved OS (HR=0.61, not statistically significant).

A complete safety summary for all ongoing studies is provided in the dabrafenib IB [GlaxoSmithKline Document Number 2012N136095_00]. Please also reference Section 1.4.1 for additional information on the safety profile and the Summary of Risk Mitigation.

1.1.3. Trametinib (GSK1120212)

Trametinib is a pyrido-pyrimidine derivative that is a potent and highly selective allosteric non-competitive inhibitor of MEK1/MEK2 activation and kinase activity [Gilmartin, 2011]. A Phase 3 study of trametinib in BRAF V600E-mutation positive metastatic melanoma (as monotherapy and in combination with dabrafenib) has been completed; trametinib is in Phase 2 development in pancreatic cancer and RAS-mutation positive acute myeloid leukemia (AML).

Trametinib has potent anti-proliferative activity against multiple cell lines, but has minimal effect on normal, non-proliferating cells. Trametinib is a potent, reversible, highly selective, allosteric inhibitor of MEK1/MEK2 activation and kinase activity. The specificity of trametinib to MEK1 and MEK2 was confirmed against a large panel of kinases and no significant inhibitory activity was measured. The investigator should refer to the GSK1120212 IB and Supplement [GlaxoSmithKline Document Number HM2009/00151/03, GlaxoSmithKline Document Number 2013N164649_00] for detailed information regarding ongoing clinical studies, pharmacokinetics in the target disease populations, as well as observed safety and efficacy findings.

Clinical data in subjects with BRAF-mutation positive metastatic melanoma have demonstrated clear benefit of trametinib over chemotherapy. In a randomized Phase 3 study, trametinib demonstrated significant benefit in PFS (hazard ratio =0.45), confirmed response rate (22% vs. 8%), and OS (hazard ratio =0.54) relative to chemotherapy [Flaherty, 2012].

A complete safety summary for all ongoing studies is provided in the trametinib IB and Supplement [GlaxoSmithKline Document Number HM2009/00151/03, GlaxoSmithKline Document Number 2013N164649_00]. Please also reference Section 1.4.2 for additional information on the safety profile and the Summary of Risk Mitigation.

1.1.4. Panitumumab, Vectibix

Panitumumab is a high-affinity (k_d 5 x 10^{-11} M), human immunoglobulin G2 (IgG2) monoclonal antibody directed against human EGFR [Davis, 1999; Yang, 1999]. Panitumumab blocks EGFR binding of epidermal growth factor (EGF), transforming growth factor-alpha (TGFα), amphiregulin, betacellulin, epiregulin, and heparin-binding EGF. Panitumumab [VECTIBIX, 2014] is currently licensed in the United States by the Food and Drug administration (FDA) for the treatment of patients with wild-type *KRAS* mCRC as determined by an FDA-approved test for this use as first-line therapy in combination with FOLFOX and as monotherapy following disease progression after prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-containing regimens. Use of panitumumab is not indicated for the treatment of patients with *KRAS*–mutant mCRC or for whom *KRAS* mutation status is unknown. Further, panitumumab is approved in Canada and other regions for use in the treatment of chemotherapy-refractory mCRC that expresses EGFR and wild-type form of the *KRAS* gene. In Japan, panitumumab is

approved for treatment of patient with unresectable, advanced or recurrent CRC with wild-type *KRAS*. However in the European Union and Australia, panitumumab is indicated for the treatment of adult patients with wild-type *RAS* mCRC in first- and second-lines as well as monotherapy. Refer to the current regionally-approved labelling for further details.

Panitumumab is administered as an intravenous infusion. The most common adverse events of panitumumab are skin rash, hypomagnesemia, paronychia, fatigue, abdominal pain, nausea and diarrhea. Please also reference Section 1.4.3 for additional information on the safety profile and the Summary of Risk Mitigation.

1.2. Preliminary Clinical Data for Dabrafenib (GSK2118436) and Trametinib (GSK1120212)

The safety, pharmacokinetic (PK) and pharmacodynamic (PD) profiles and activity of dabrafenib and trametinib administered either as monotherapy or in combination with other anti-cancer agents are currently being evaluated in multiple clinical trials involving subjects with a variety of cancers. The investigator should refer to the GSK2118436 IB [GlaxoSmithKline Document Number 2012N136095_00], the GSK1120212 IB and Supplement [GlaxoSmithKline Document Number HM2009/00151/03, GlaxoSmithKline Document Number 2013N164649_00] and the GSK1120212 + GSK2118436 Clinical IB and Supplements [GlaxoSmithKline Document Number, 2011N126811_00, GlaxoSmithKline Document Number 2012N152310_00, GlaxoSmithKline Document Number 2012N152310_01] for detailed information regarding ongoing clinical studies, pharmacokinetics in the target disease populations, as well as observed safety and efficacy findings.

Dabrafenib and trametinib have been studied in combination, primarily in subjects with advanced BRAF-V600E or V600K mutation-positive melanoma and BRAF mutation V600E -positive CRC. The combination, in which both agents are dosed at the current maximum monotherapy doses (150mg BID for dabrafenib and 2mg once daily for trametinib), has proven to be well tolerated.

Emerging data from BRF113220, a Phase I/II study to establish the recommended dose for the combination of dabrafenib and trametinib, suggest that the safety profile of the combination is consistent with the profiles observed for single-agent therapies, except that a higher incidence of pyrexia and chills, and a lower incidence of squamous cell carcinoma and hyperkeratosis were observed for the combination compared to dabrafenib monotherapy. In addition, the incidence of skin-related toxicities appeared to be lower for the combination therapy as compared to trametinib monotherapy. A complete safety summary for all ongoing studies with the combination of dabrafenib and trametinib is provided in the dabrafenib/trametinib combination IB and Supplements [GlaxoSmithKline Document Number 2011N126811_00, GlaxoSmithKline Document Number 2012N152310_00, GlaxoSmithKline Document Number 2012N152310_01]. Please also reference Section 1.4 for additional information on the safety profile and the Summary of Risk Mitigation.

The clinical efficacy of this combination also appears to be superior to either agent when dosed as monotherapy. A single arm Phase 2 study demonstrated a PFS of 10.8 months in subjects with metastatic BRAF-V600 mutation positive melanoma, which would be a significant improvement over results obtained with monotherapy inhibition of either BRAF or MEK [Weber, 2012].

1.3. Rationale

1.3.1. Study Rationale for Parts 1, 2, 3, 4

BRAF-mutation V600E positive CRC is more aggressive than KRAS-mutation positive- or KRAS/BRAF- wild-type colorectal cancer, with a lower overall response rate (ORR), reduced progression-free (PFS) and overall survival (OS) [Di Nicolantonio, 2008; Laurent-Puig, 2009; Maughan, 2011; Souglakos, 2009; Bokemeyer, 2012; Tveit, 2012; Richman, 2009; Tran, 2011; Yokota, 2011; Tie, 2011]. Efforts to target BRAF-mutant CRC with BRAF inhibitors and MEK inhibitors as monotherapies have not been successful to date [Falchook, 2012; Kopetz, 2010]. Recently published nonclinical data suggest a role for receptor tyrosine kinase activation (particularly EGFR) in the resistance mechanism and have demonstrated synergistic activity of the combination of a BRAF inhibitor and an EGFR inhibitor in in vitro and in vivo models of BRAF-mutant CRC [Prahallad, 2012; Corcoran, 2012]. Therefore, the combination of potent inhibition of the BRAF pathway (with dabrafenib alone or dabrafenib/trametinib) with an anti-EGFR agent to prevent EGFR-mediated resistance is a rational and promising approach to treat BRAF-mutant CRC.

Thus, this study is designed to identify the recommended Phase 2 dose/regimen (RP2R) for the dabrafenib/panitumumab doublet and the dabrafenib/trametinib/panitumumab triplet in Part 1 and for the trametinib/panitumumab doublet in Part 4A. In part 2 and 4B the study will identify an initial signal of clinical activity for these combinations. In Part 3, a randomized comparison of the experimental arms to a chemotherapy comparator arm (a regimen of FOLFOX or FOLFIRI with or without panitumumab or bevacizumab) will be performed.

Extrapolating from the experience in BRAF V600E/V600K -mutation positive melanoma, it is expected that the triple combination is likely to provide the greatest benefit to subjects, in which case the inclusion of the double combination serves as a control to assess the important “contribution of components” question. However, another possible outcome is that the double combination is superior (e.g., due to poor tolerability of the triple combination), an outcome that this study design will also adequately evaluate.

1.3.2. Study Rationale for Part 4

Part 4 of the study is designed to identify the RP2R for trametinib dosed orally in combination with IV infusions of panitumumab in dose escalation and to identify an initial signal of clinical activity in two patient populations, subjects with BRAF-V600E mutation-positive CRC (described above) and subjects with CRC that developed secondary resistance to anti-EGFR therapy after initially deriving benefit.

It is also important to understand whether dabrafenib is contributing to the clinical activity that has been seen with the triplet. Therefore, patients with BRAF-mutant CRC will be included in the dose escalation of the trametinib/panitumumab doublet (Part 4A) and an expansion cohort (Part 4B) further evaluating safety and efficacy of the trametinib/panitumumab doublet.

Anti-EGFR therapies, either in combination with chemotherapy or as monotherapy, are approved therapy for KRAS wild-type (wt) colorectal cancer. Although a significant proportion of patients with KRAS wt CRC derive benefit from anti-EGFR therapy, they inevitably become resistant to this therapy. In a large proportion of cases, the mechanism of resistance to anti-EGFR therapy involves the reactivation of the RAS/MEK/ERK pathway, often through acquisition of mutations to RAS genes (KRAS or NRAS) converging on activation of the RAS/MEK/ERK pathway [Misale, 2012; Misale, 2014]. This is similar to the example of BRAF mutant melanoma in which a frequent mechanism of resistance involves the reactivation of this pathway [Flaherty, 2012].

Vertical pathway inhibition can be an effective therapeutic strategy in tumors that are highly dependent on a single signaling pathway [Flaherty, 2012]. The addition of a MEK inhibitor, trametinib, to the BRAF inhibitor dabrafenib results in a significant improvement in both the depth and durability of responses in preclinical models of or in patients with BRAF mutant melanoma [TAFINLAR prescribing information January 2014]. Using a similar rationale, the combination of an anti-EGFR agent and a MEK inhibitor demonstrated efficacy in preclinical models of CRC that had developed resistance to anti-EGFR therapy [Misale, 2014].

Based on above data, the combination of the anti-EGFR agent panitumumab with the MEK inhibitor trametinib is of great interest to study in patients who were eligible for and derived benefit from anti-EGFR therapy and have subsequently developed secondary resistance to anti-EGFR therapy.

1.3.2.1. Preliminary data from ongoing MEK116833 study

Preliminary clinical data from Parts 1 and 2A of this ongoing study suggest that the triplet combination of dabrafenib/trametinib/panitumumab is more efficacious than the dabrafenib/panitumumab doublet in the BRAF-mutant patient population (see Table 1).

Table 1 Summary of investigator-assessed best confirmed response, Part 1 and Part 2A

Best confirmed response, n (%)	Doublet Cohort[a], n=20	Triplet Cohorts			
		Cohort 2[b], n=3	Cohort 3A[c] n=4	Cohort 3B[d] n=4	Cohort 4[e] N=24
Not evaluable	0	0	0	0	1 (4%)
PD	2 (10%)	0	0	2 (50%)	3 (13%)
SD	16 (80%)	1 (33%)	2 (50%)	2 (50%)	16 (67%)
PR	1 (5%)	2 (67%)	1 (25%)	0	4 (17%)
CR	1 (5%)	0	1 (25%)	0	0
PR+CR, n (%) (95% CI)	2 (10%) (1.2%, 31.7%)	2 (66%) (9.4%, 99.2%)	2 (50%) (6.8%, 93.2%)	0 (0%) (0%, 60.2%)	4 (16.7%) (4.7%, 37.4%)

From 20 October 2014 data cut-off

a. Doublet cohort combines patients enrolled in Part 1 Cohort 1 and Part 2 doublet expansion cohort; all dosed with Dabrafenib 150mg BID + Panitumumab 6mg/kg/Q2W

b. Dabrafenib 150mg BID + Panitumumab 4.8mg/kg/Q2W + Trametinib 1.5mg QD

c. Dabrafenib 150mg BID + Panitumumab 4.8mg/kg/Q2W + Trametinib 2mg QD

d. Dabrafenib 150mg BID + Panitumumab 6mg/kg/Q2W + Trametinib 1.5mg QD

e. Dabrafenib 150mg BID + Panitumumab 6mg/kg/Q2W + Trametinib 2mg QD

1.3.3. Dose Rationale

Parts 1, 2 and 3 of this study will evaluate the safety, tolerability and efficacy of the doublet dabrafenib/panitumumab and triplet trametinib/dabrafenib/panitumumab combinations in subjects with BRAF- V600E mutation positive CRC. Part 1 includes a 3+3 dose escalation that will identify tolerable combination doses for the two combinations. The safety and tolerability of these combination doses will be confirmed in expansion cohorts in Part 2, followed by a randomized evaluation of the efficacy and safety of the combinations in Part 3.

Part 4 of the study includes a 3+3 dose escalation that will identify tolerable combination doses for trametinib dosed orally in combination with IV infusions of panitumumab. The safety and tolerability of the RP2R will be confirmed in the expansion cohorts.

1.3.3.1. Potential for Drug-Drug Interactions

Dabrafenib is metabolized via CYP2C8- and CYP3A4-mediated oxidation and is a moderate inducer of CYP3A4 and potentially CYP2B6, and CYP2C enzymes. Trametinib is metabolized by non-CYP-mediated deacetylation. Panitumumab, a recombinant human immunoglobulin, is cleared through non-CYP pathways. Administration of dabrafenib plus trametinib in the ongoing study BRF113220 indicates that dabrafenib does not have a clinically relevant effect on trametinib pharmacokinetics (see the GSK1120212 + GSK2118436 Clinical IB and Supplements [GlaxoSmithKline Document Number, 2011N126811_00, GlaxoSmithKline Document Number 2012N152310_00, GlaxoSmithKline Document Number 2012N152310_01] for additional information). Cross-study comparisons indicates that exposure to dabrafenib may be greater after repeat dose administration of dabrafenib in combination with trametinib relative to administration of dabrafenib alone, at 150mg BID. The combination was relatively well tolerated. Therefore, no clinically relevant

pharmacokinetic drug-drug interactions between dabrafenib, trametinib, and panitumumab are expected.

1.3.3.2. Potential for Overlapping Toxicities

Fatigue, diarrhea, and nausea are common adverse reactions observed after administration of dabrafenib, trametinib, or panitumumab. In addition, dermatologic toxicities are common after administration of trametinib or panitumumab. Severe (National Cancer Institute Common Terminology Criteria for Adverse Events NCI-CTCAE Grade 3 or higher) dermatologic toxicities have been reported in 16% of all subjects (and ~25% of subjects with KRAS wild-type CRC) with metastatic carcinoma of the colon or rectum after administration of panitumumab alone. In addition, there is an apparent small risk for pneumonitis/interstitial lung disease (ILD) with both trametinib and panitumumab, respectively.

1.3.3.3. Part 1

The maximum tolerated dose (MTD)/Recommended Phase 2 Regimen (RP2R) of dabrafenib plus panitumumab was defined first in Part 1. The starting dose of dabrafenib was the recommended monotherapy dose of 150mg twice daily (BID). Panitumumab was administered at the recommended dose of 6mg/kg, administered as an intravenous infusion over 60 minutes, every 14 days. Additional details regarding dose escalation are provided in Section 3.7.2. These doses are clinically active with manageable toxicity with prolonged dosing and the potential for overlapping toxicities appears relatively low. However, if unexpected toxicities were to have been observed in Cohort 1, subjects would have been enrolled in Cohort -1, in which the dose of one or both agents (depending on the toxicities observed) would be reduced.

Upon definition of a tolerable dose of dabrafenib plus panitumumab, trametinib was added to the combination in Cohort 2 (see Section 3.1). Dabrafenib was administered in the triple combination at the dose that was tolerated in combination with panitumumab in Cohort 1. Due to overlapping dermatologic toxicities, the starting doses of panitumumab and trametinib were reduced. The starting dose of trametinib was 1.5mg once daily, which is below the current recommended monotherapy dose of 2mg once daily, but is a dose that has demonstrated both pharmacodynamic and clinical activity in subjects with melanoma. The starting dose for panitumumab was one dose level below the dose that was tolerated in combination with dabrafenib in Cohort 1, administered as an intravenous infusion over 60 minutes, every 14 days. It should be noted that a recent clinical study of the combination of the MEK inhibitor selumetinib and the chimeric anti-EGFR agent cetuximab was able to achieve the full monotherapy dose for both agents in combination, although there was an increased rate of skin toxicity and an episode of Grade 4 hypomagnesemia [Deming, 2012]. Also of note, panitumumab has demonstrated pharmacodynamic and clinical activity at doses as low as 1 to 2.5 mg/kg weekly [Rowinsky, 2004; Weiner, 2008].

Dose escalation is permitted, details are provided in Section 3.7.2, and dose adjustment/ stopping criteria are described in Section 3.10. Doses in combination will not exceed the monotherapy top dose for any single agent.

1.3.3.4. Part 2

For each combination (dabrafenib/panitumumab and dabrafenib/trametinib/panitumumab), the optimal safe and tolerable dose combinations defined in Part 1 were brought forward into Part 2A. This was the maximal dose from Part 1 for each combination, although a lower dose combination could have been selected if significant delayed or prolonged toxicities required frequent dose modifications. In Part 2A, expansion cohorts of 20 and 35 subjects with BRAF-V600E mutation positive CRC (including the subjects enrolled at this dose in Part 1) were enrolled to confirm safety and tolerability, and to generate signals of activity of the doublet and triplet regimens, respectively (See Table 1 for clinical data from Parts 1 and 2A).

Preliminary data from Part 2A suggested that compliance of dabrafenib, trametinib and panitumumab was similar between dose cohorts in Weeks 1 to Week4. However, during Weeks 5 to 8, the compliance of dabrafenib, trametinib and panitumumab decreased to 70-80% of the expected dose amounts in Cohort 3B and Cohort 4 compared to Cohort 2 and Cohort 3A. Adverse events leading to dose modifications were greater in the Cohort 3B and Cohort 4 compared to Cohort 2 and Cohort 3A as shown in Table 2.

Table 2 AEs Leading to Dose Modification (Triplet Cohorts)

Preferred Term	Cohort 2 N=3	Cohort 3A N=4	Cohort 3B N=4	Cohort 4 N=24	Total Triplet N=35
AEs Leading to Investigational Product Discontinuation of any Study Treatment					
Any event	0	1 (25%)	0	0	1 (3%)
Subdural haematoma	0	1 (25%)	0	0	1 (3%)
AEs Leading to Dose Reduction of any Study Treatment					
Any event	2 (67%)	1 (25%)	2 (50%)	9 (38%)	14 (40%)
Dermatitis acneiform	0	1 (25%)	2 (50%)	2 (8%)	5 (14%)
Rash	0	1 (25%)	0	1 (4%)	2 (6%)
AEs Leading to Dose Interruption/Delay of any Study Treatment					
Any event	2 (67%)	3 (75%)	4 (100%)	20 (83%)	29 (83%)
Dermatitis acneiform	0	1 (25%)	2 (50%)	2 (8%)	5 (14%)
Vomiting	1 (33%)	0	3 (75%)	1 (4%)	5 (14%)
Dehydration	0	1 (25%)	1 (25%)	2 (8%)	4 (11%)
Dry skin	0	0	1 (25%)	3 (13%)	4 (11%)
Fatigue	0	0	0	4 (17%)	4 (11%)
Nausea	0	0	3 (75%)	1 (4%)	4 (11%)
ALT increased	0	0	0	3 (13%)	3 (9%)
AST increased	0	0	0	3 (13%)	3 (9%)
Diarrhoea	0	0	2 (50%)	1 (4%)	3 (9%)
Rash	0	1 (25%)	0	2 (8%)	3 (9%)

Based on data from 20 Oct 2014 cut-off

The dose of panitumumab in Cohort 3B and Cohort 4 was 6mg/kg every two weeks. In Part 2B, an additional 60 subjects will be enrolled into 1 of 2 dose cohorts. Subjects will be enrolled at the Cohort 3A dose (Dabrafenib 150mg BID + Panitumumab 4.8mg/kg/Q2W + Trametinib 2mg QD) and Cohort 4 dose (Dabrafenib 150mg BID +Panitumumab 6mg/kg Q2W + Trametinib 2mg QD) to further explore safety, tolerability and clinical activity at the two dose levels. In addition, subjects will be enrolled by lines of therapy in order to provide a more homogeneous patient population.

1.3.3.5. Part 3

In Part 3, the randomized Phase 2 portion of the study, subjects with second line BRAF-mutation V600E positive CRC (previously failed or were intolerant to first line fluoropyrimidine-containing chemotherapy) will be randomized to 1 of 3 cohorts:

1) dabrafenib plus panitumumab,

2) dabrafenib plus trametinib plus panitumumab, or

3) chemotherapy comparator (a regimen of FOLFOX or FOLFIRI with or without panitumumab or bevacizumab).

Dose levels for dabrafenib, trametinib, and panitumumab in Part 3 will be chosen based on emerging PK, PD, and tolerability data from Part 1 and Part 2. The chemotherapy comparator will consist of a standard chemotherapy regimen with or without the addition of a biological agent, based on local practice preferences. The available chemotherapy regimens include either a fluoropyrimidine-containing regimen including either irinotecan or oxaliplatin OR irinotecan alone. In addition to the chemotherapy regimen, a biological agent, limited to panitumumab or bevacizumab, may be included. Selection of the chemotherapy comparator may be revised based on emerging data from Part 1 and Part 2. Available data from Parts 1 and 2 of this study will be provided to ethics review boards, along with any necessary changes to the protocol, prior to starting Part 3. The addition of additional arms to assess the contribution of the trametinib, dabrafenib or panitumumab monotherapies or trametinib/dabrafenib combination was considered but available clinical data are considered sufficient to demonstrate the limited activity of these therapeutic options in this clinical setting. In the event that the benefit/risk ratio for either of the two experimental combinations is not sufficiently positive (either due to excessive toxicity or clearly inferior efficacy), one of the arms may be excluded from Part 3 of the study.

1.3.3.6. Part 4

Data from Parts 1 and 2A of this ongoing study have demonstrated that both the dabrafenib/panitumumab doublet and the dabrafenib/trametinib/panitumumab triplet are tolerated by patients (see Table 3). The triplet combination studies in Cohorts 3A and 3B, in which dabrafenib is dosed at the full marketed dose (150mg po BID) and either trametinib or panitumumab is also dosed at the full marketed dose (2mg po QD or 6 mg/kg IV Q2W, respectively), with the other agent dosed at one dose level lower (1.5mg po QD or 4.8mg/kg IV Q2W, respectively) have been well tolerated to date, with no DLTs being identified. The highest triplet combination (all three agents at full dose) also has been evaluated in Cohort 4 of the dose escalation with no DLTs and an additional 20 patients has been enrolled in the expansion cohort at the full dose of all three agents. Based on the tolerability of the triplet at full dose in Part 1, the starting dose trametinib/panitumumab combinations that is being studied in the initial dose escalation cohort of Part 4 will be full dose of both agents. If these doses are not well tolerated, there will be an option to dose reduce (see Section 3.5). The optimal safe and tolerable dose combinations defined in dose escalation will be brought forward into expansion cohorts. This will likely be the maximal dose for each combination in dose escalation, although a lower dose combination may be selected if significant delayed or prolonged toxicities require frequent dose modifications. Expansion cohorts of approximately 20 subjects with BRAF V600E mCRC or advanced CRC/mCRC who progressed on previous anti-EGFR will be enrolled to confirm safety and tolerability, and to generate signals of activity.

Table 3 DLTs, Related AEs ≥Gr 3, and Related SAEs in Part 1 and Part 2 (preliminary data)

	Doublet Cohort[a], n=20	Triplet Cohorts			
		Cohort 2[b], n=3	Cohort 3A[c] n=4	Cohort 3B[d] n=4	Cohort 4[e] N=24
DLTs	None	None	None	None	None
Related SAEs	6	1	None	1	6
Related AEs ≥Grade 3	3	2	2	2	11

From 20 October 2014 data cut-off

a. Doublet cohort combines patients enrolled in Part 1 Cohort 1 and Part 2 doublet expansion cohort; all dosed with dabrafenib 150mg BID + panitumumab 6mg/kg/Q2W.
b. Part 1 Cohort 2 dose dabrafenib 150mg BID + panitumumab 4.8mg/kg/Q2W + trametinib 1.5mg QD
c. Part 1 Cohort 3A dose dabrafenib 150mg BID + panitumumab 4.8mg/kg/Q2W + trametinib 2mg QD
d. Part 1 Cohort 3B dose dabrafenib 150mg BID + panitumumab 6mg/kg/Q2W + trametinib 1.5mg QD
e. Dabrafenib 150mg BID + Panitumumab 6mg/kg/Q2W + Trametinib 2mg QD

1.4. Summary of Risk Management

Risk of administration of dabrafenib and trametinib has been assessed in clinical trials and in nonclinical toxicology studies. Based on the available risk assessments, enrollment criteria (Section 4.2) and dose adjustment guidelines (Section 3.10.2) will be followed to minimize risk of known toxicities. Procedures to minimize or monitor potential risks are listed below.

1.4.1. GSK2118436: Dabrafenib

The assessment of the risk of dabrafenib is based on clinical data from the concluded and ongoing dabrafenib studies, as well as preclinical toxicity data from 28-day studies. As a single agent, dabrafenib has been well tolerated across a range of doses. At the recommended dose of 150mg BID, the most common adverse events have been fatigue, pyrexia, headache, nausea, hyperkeratosis, skin papilloma, diarrhea, arthralgia, pain in extremity, decreased appetite, alopecia, rash and palmar-plantar erythrodysaethesia (PPE) syndrome. The most frequent serious AEs (SAEs) include squamous cell carcinoma (SCC) and pyrexia.The potential adverse events (AEs) will be managed as follows in this study:

Gastrointestinal (GI) effects: Interim medical history, continuous assessment of AEs, physical examination, and clinical laboratory assessments will be used to identify and assess toxicity in the GI tract. Supportive therapy will be provided according to standard medical practice; guidelines for management of diarrhea are provided in Section 3.10.5. Participation will be discontinued for intolerable toxicity.

Skin effects: Primary skin findings in dabrafenib-treated subjects include benign keratotic lesions, skin papillomas, hand foot skin reactions (HFSR), skin rashes and squamous cell carcinoma (SCC) including keratoacanthomas. Interim medical history, continuous assessment of AEs, and dermatological examination will be used to identify and assess skin effects. Guidelines for management of skin effects are provided in Section 3.10.4.2.

Renal effects: Acute renal failure has been reported in subjects receiving dabrafenib, and granulomatous interstitial nephritis has been reported in a clinical trial. In some cases complicated pyrexia may be associated with renal insufficiency/renal failure, possibly secondary to dehydration or hypotension. Guidelines for management of renal insufficiency are provided in Section 3.10.6.

Pyrexia: In clinical trials pyrexia, which may be associated with hypotension, rigors, dehydration, weakness, and/or renal failure, has been identified in subjects. Although this AE is considered to be related to dabrafenib, the frequency and severity of pyrexia is greater in patients receiving the combination of dabrafenib and trametinib, as compared to patients receiving dabrafenib alone. Subjects should be evaluated for signs and symptoms of infection. Guidelines for management of pyrexia are provided in Section 3.10.4.1.

Pancreatitis: There have been reports of pancreatitis and/or increased lipase/amylase with dabrafenib, typically occurring within 14 days of starting therapy. For adverse events of abdominal pain or suspected pancreatitis, amylase and lipase laboratory samples should be monitored locally.

Ophthalmology effects: Eye effects including blurred vision (2%), uveitis/iritis (<1%), eye pain (<1%), visual impairment (<1%) and reduced visual acuity (<1%) have been observed in clinical studies to date, with all events Grade 1 or 2. An ophthalmologic consult is required for subjects developing symptoms associated with uveitis including blurry vision, eye pain or erythema.

Hypersensitivity: There has been a report of hypersensitivity (blisters), occurring on the same day as the first dose of study drug as well as upon rechallenge. Grade 1 AEs of blisters on limbs (4 subjects) and drug hypersensitivity (rash, 1 subject) have been reported in previous studies with dabrafenib. However, the precise etiology of these events is unclear.

1.4.2. GSK1120212: Trametinib

As a single agent, trametinib has been well tolerated across a range of doses. At the recommended dose of 2mg once daily, the most common AEs were rash, diarrhea, fatigue, edema peripheral, nausea, dermatitis acneiform, vomiting, constipation, anemia, pruritus, alopecia, hypertension, decreased appetite, dyspnea and dry skin. AEs of Special interest for trametinib include left ventricular dysfunction, ocular toxicities (e.g., retinal pigment epithelium detachment (RPED) and retinal vein occlusion (RVO), diarrhea, rash and transaminitis.

The potential AEs (based on pre-clinical and clinical studies and data from other compounds in the same class) include:

Ocular toxicity: Ocular toxicities in a fraction of subjects (including central serous retinopathy and retinal vein occlusion) are known class effects of MEK inhibitors and have been seen with trametinib. To reduce the risk of ocular toxicity, subjects diagnosed with glaucoma within 1 month prior to study Day 1 or with history of retinal vein occlusion (RVO), RPED, predisposing factors for RVO or RPED or predisposing retinal

pathology as determined by ophthalmologic exams are excluded. Visual disturbance has been monitorable and reversible in the ongoing study of the dabrafenib/trametinib combination (GSK study BRF113220). Ophthalmologic exams will be performed at baseline and as clinically warranted, by an ophthalmologist.

Cardiac function: A reduction in cardiac function in a fraction of subjects (specifically, left ventricular ejection fraction) is a known class effect of MEK inhibitors and have been seen with trametinib. Subjects with pre-existing heart failure will be excluded from this study. Cardiac function will be assessed prior to enrollment, and will be monitored on study. In addition, withholding criteria for left ventricular ejection fraction decreases will be implemented.

Gastrointestinal toxicity: To reduce the risk of excessive gastrointestinal (GI) toxicity (primarily diarrhea), subjects will be monitored closely and supportive care guidelines implemented. In addition, due to the potential for overlapping toxicity with panitumumab, the starting dose for each of these agents will be below its recommended monotherapy dose. It should be noted that, while trametinib and dabrafenib can both cause GI toxicity, the combination of the two agents did not result in an increase in toxicities relative the rate or severity defined for each agent when administered as monotherapy.

Cutaneous toxicity Skin rash is expected to be a common event in this study. To reduce the risk of excessive cutaneous toxicity, subjects will be monitored closely and supportive care guidelines implemented. In addition, due to the potential for overlapping toxicity with panitumumab, the starting dose for trametinib and panitumumab when they are combined will be below the recommended monotherapy dose for each agent. It should be noted that, while trametinib and dabrafenib can both cause rash, the combination of the two agents did not result in an increase in toxicities relative the rate or severity defined for each agent when administered as monotherapy.

Pneumonitis/Interstitial lung disease: Pneumonitis has been observed in subjects receiving trametinib. To reduce the risk of pneumonitis, subjects will be monitored closely for symptoms, evaluated with imaging and functional tests. Subjects with a history of interstitial lung disease or pneumonitis are excluded per criteria in Section 4.2.1.2 and Section 4.2.2.2. Dose modification and supportive care guidelines for pneumonitis are provided in Section 3.10.13.

1.4.3. Panitumumab

Please refer to the FDA approved label and/or EU SmPC for panitumumab for updated detailed information. The following text is summarized from the approved FDA label [VECTIBIX (panitumumab) Injection for Intravenous Use, Revised March 2014].

The most common adverse events of panitumumab are skin rash with variable presentations (frequently acneiform), hypomagnesemia, paronychia, fatigue, abdominal pain, nausea, and diarrhea, including diarrhea resulting in dehydration. The most serious adverse events of panitumumab are pulmonary fibrosis, pulmonary embolism, severe dermatologic toxicity complicated by infectious sequelae and septic death, infusion reactions, abdominal pain, hypomagnesemia, nausea, vomiting, and constipation.

Adverse reactions requiring discontinuation of panitumumab were infusion reactions, severe skin toxicity, paronychia, and pulmonary fibrosis.

Cutaneous toxicity: Cutaneous toxicities were reported in approximately 90% of subjects receiving the 6mg/kg every (Q) 2 weeks, and were severe (Grade 3 or higher) in 12 to 16% of subjects receiving panitumumab as monotherapy. The incidence of paronychia was 25% and was severe in 2% of subjects. Nail disorders occurred in 9% of subjects. The median time to the development of dermatologic, nail, or ocular toxicity was 14 days after the first dose of panitumumab; the median time to most severe skin/ocular toxicity was 15 days after the first dose of panitumumab; and the median time to resolution after the last dose of panitumumab was 84 days. To reduce the risk of excessive cutaneous toxicity, subjects will be monitored closely and supportive care guidelines implemented.

Infusion reactions: Severe infusion reactions occurred in approximately 1% of subjects. Infusional toxicity was defined as any event within 24 hours of an infusion during the clinical study described as allergic reaction or anaphylactoid reaction, or any event occurring on the first day of dosing described as allergic reaction, anaphylactoid reaction, fever, chills, or dyspnea. Vital signs and temperature were measured within 30 minutes prior to initiation and upon completion of the panitumumab infusion. The use of premedication was not standardized in the clinical trials. Thus, the utility of premedication in preventing the first or subsequent episodes of infusional toxicity is unknown. Across several clinical trials of panitumumab monotherapy, 3% experienced infusion reactions of which approximately 1% were severe (Grade 3 or Grade 4).

Ocular toxicities: Ocular toxicities occurred in 15% of subjects and included, but were not limited to, conjunctivitis, ocular hyperemia, increased lacrimation, and eye/eyelid irritation. Stomatitis and oral mucositis were reported. One patient experienced a Grade 3 event of mucosal inflammation. Ophthalmologic exams will be performed at baseline and as clinically warranted, by an ophthalmologist.

Pulmonary fibrosis: Pulmonary fibrosis occurred in less than 1% (2/1467) of subjects enrolled in clinical studies of panitumumab. Following an initial fatality in a patient with underlying idiopathic pulmonary fibrosis, subjects with a history of interstitial pneumonitis, pulmonary fibrosis, evidence of interstitial pneumonitis, or pulmonary fibrosis were excluded from clinical studies. Therefore, the estimated risk in a general population that may include such subjects is uncertain. Subjects with pre-existing pneumonitis, interstitial lung disease or pulmonary fibrosis will be excluded from this study (Section 4.2.1.2 and Section 4.2.2.2). Subjects developing interstitial lung disease, pneumonitis, or lung infiltrates should permanently discontinue panitumumab therapy.

Electrolyte depletion: Clinically significant hypomagnesemia and hypocalcemia have occurred in patients receiving panitumumab and may be worsened with the addition of trametinib. Subjects' electrolytes will be periodically monitored during and after the completion of panitumumab therapy. Appropriate therapy (e.g., oral or intravenous electrolyte repletion) will be administered to correct abnormalities in electrolytes that occur prior to or while on panitumumab.

2. OBJECTIVES AND ENDPOINTS

2.1. Part 1: Phase 1 Dose Escalation

	Objectives	Endpoints
Primary	To determine the safety, tolerability and range of tolerated combination doses in subjects with BRAF-V600E mutation-positive CRC in two dosing groups: • dabrafenib dosed orally in combination with panitumumab • trametinib dosed orally in combination with dabrafenib and panitumumab	Adverse events and changes in laboratory values, vital signs and dose interruptions, modifications and discontinuations
Secondary	To describe the pharmacokinetics of dabrafenib, trametinib and panitumumab after combination therapy To determine preliminary clinical activity of dabrafenib dosed orally in combination with panitumumab To determine clinical activity of trametinib dosed orally in combination with dabrafenib and panitumumab To evaluate the pharmacodynamic response in colorectal tumors following combination treatment	Maximum observed concentration (Cmax), time of occurrence of Cmax (tmax), and area under the concentration-time curve from zero (pre-dose) 8 hours (AUC(0-8)), pre-dose (trough) concentration at the end of the dosing interval ($C\tau$) of trametinib and dabrafenib. Predose ($C\tau$) and Cmax concentrations of panitumumab. Response rate (complete response [CR] + partial response [PR]) Progression free survival Duration of response Response rate (CR +PR) Progression free survival Duration of response Change in levels of proteins/RNA implicated in MAPK/PI3K/EGFR pathways in pre- and post-dose tumor tissue.
[redacted]		

	Objectives	Endpoints
[redacted]		

2.2. Part 2: Cohort Expansions

	Objectives	Endpoints
Primary	To confirm the safety and tolerability of combination doses in subjects with BRAF-V600E mutation-positive CRC in two dosing groups: • dabrafenib dosed orally in combination with panitumumab • trametinib dosed orally in combination with dabrafenib and panitumumab	Adverse events and changes in laboratory values, vital signs and dose interruptions, modifications and discontinuations
	To determine clinical activity in subjects with BRAF-V600E mutation-positive CRC in two dosing groups: • dabrafenib dosed orally in combination with panitumumab • trametinib dosed orally in combination with dabrafenib and panitumumab	Response rate (CR +PR)
Secondary	To characterize the population PK parameters of dabrafenib and trametinib dosed orally in combination with anti-EGFR antibody (panitumumab)	Population PK parameters, oral clearance (CL/F), oral volume of distribution (V/F), and absorption rate constant (Ka)
	To characterize the durability of response with dabrafenib dosed orally in combination with panitumumab	Duration of response Progression-free survival Overall survival

	Objectives	Endpoints
	To characterize the durability of response with trametinib dosed orally in combination with dabrafenib and panitumumab To evaluate the pharmacodynamic response in colorectal tumors following combination treatment	Duration of response Progression-free survival Overall Survival Change in levels of proteins/RNA implicated in MAPK/PI3K/EGFR pathways in pre- and post-dose tumor tissue

[redacted]

2.3. Part 3: Randomized Phase 2

	Objectives	Endpoints
Primary	To evaluate and compare the clinical activity of the dabrafenib/panitumumab and trametinib/dabrafenib/panitumumab combinations as compared to standard of care therapy in subjects with KRAS wild-type (WT)/BRAF-V600E mutation-positive CRC	PFS
Secondary	To characterize the durability of response to dabrafenib/ panitumumab and trametinib/ dabrafenib/panitumumab combinations as compared to standard of care therapy To evaluate and compare the clinical activity of the trametinib/dabrafenib/panitumumab combination as compared to the dabrafenib/panitumumab combination with	Response rate (CR +PR) Duration of response OS PFS

	Objectives	Endpoints
	respect to PFS To confirm the safety and tolerability of dabrafenib and trametinib dosed orally in combination with panitumumab To confirm the safety and tolerability of dabrafenib dosed orally in combination with panitumumab	Adverse events and changes in laboratory values, vital signs and dose modifications and discontinuations
[redacted]		

2.4. Part 4A: Dose Escalation

	Objectives	Endpoints
Primary	To determine the safety, tolerability and range of tolerated combination doses in of the combination of panitumumab and trametinib in subjects with advanced/metastatic CRC	Adverse events and changes in laboratory values, vital signs and dose interruptions, modifications and discontinuations

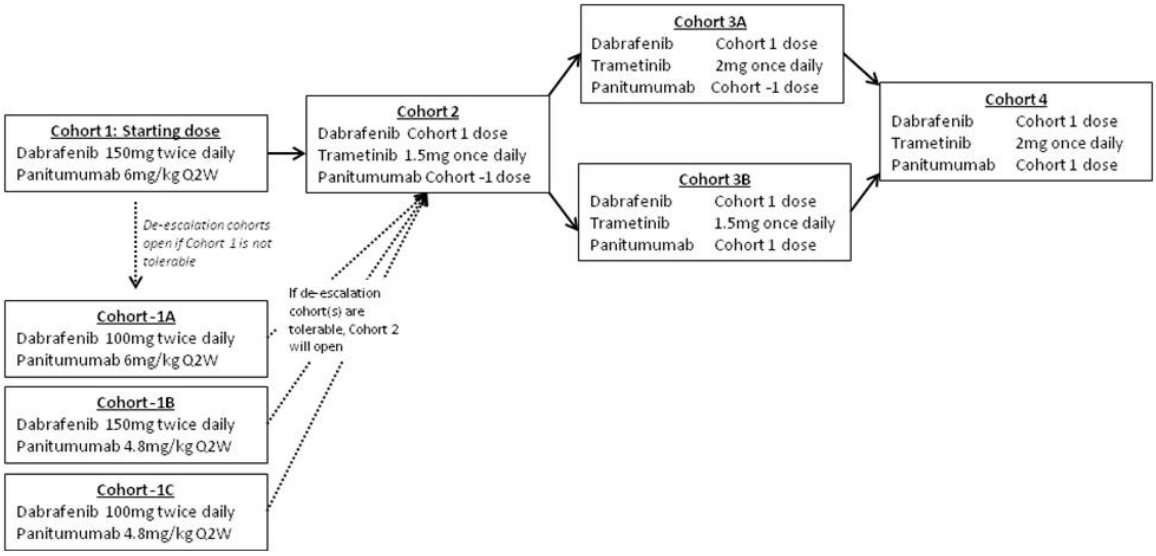
	Objectives	Endpoints
Secondary	To describe the pharmacokinetics of trametinib and panitumumab after combination therapy	Maximum observed concentration (Cmax), time of occurrence of Cmax (tmax), and area under the concentration-time curve from zero (pre-dose) the time of the last quantifiable concentration (AUC(0-t)), pre-dose (trough) concentration at the end of the dosing interval ($C\tau$) of trametinib. Predose ($C\tau$) and Cmax concentrations of panitumumab.
	To determine preliminary clinical activity of panitumumab/trametinib combination therapy in two patient populations: • subjects with BRAF-V600E mutation-positive CRC • subjects with CRC that developed secondary resistance to anti-EGFR therapy after initially deriving benefit	Response rate (complete response [CR] + partial response [PR]) Progression free survival Duration of response Change in levels of proteins/RNA implicated in MAPK/PI3K/EGFR pathways in pre- and post-dose tumor tissue.
	To evaluate the pharmacodynamic response in colorectal tumors following combination therapy	
[redacted]		

2.5. Part 4B: Cohort Expansion

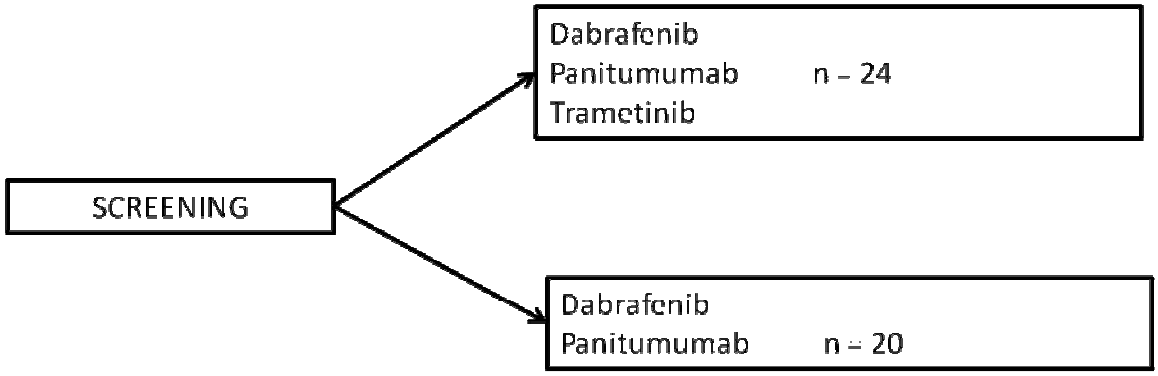
	Objectives	Endpoints
Primary	To confirm the safety and tolerability of RP2R of the panitumumab/trametinib combination in an expansion cohorts of • subjects with BRAF-V600E mutation-positive CRC • subjects with CRC that developed secondary resistance to anti-EGFR therapy after initially deriving benefit	Adverse events and changes in laboratory values, vital signs and dose interruptions, modifications and discontinuations
	To determine clinical activity of combination therapy in this patient population	Response rate (CR +PR)
Secondary	To characterize the population PK parameters of trametinib dosed orally in combination with anti-EGFR antibody (panitumumab)	Population PK parameters, oral clearance (CL/F), oral volume of distribution (V/F), and absorption rate constant (Ka)
	To characterize the durability of response with trametinib dosed in combination with panitumumab	Duration of response Progression-free survival Overall survival
	To evaluate the pharmacodynamic response in colorectal tumors following combination treatment	Change in levels of proteins/RNA implicated in MAPK/PI3K/EGFR pathways in pre- and post-dose tumor tissue
[redacted]		

3. INVESTIGATIONAL PLAN

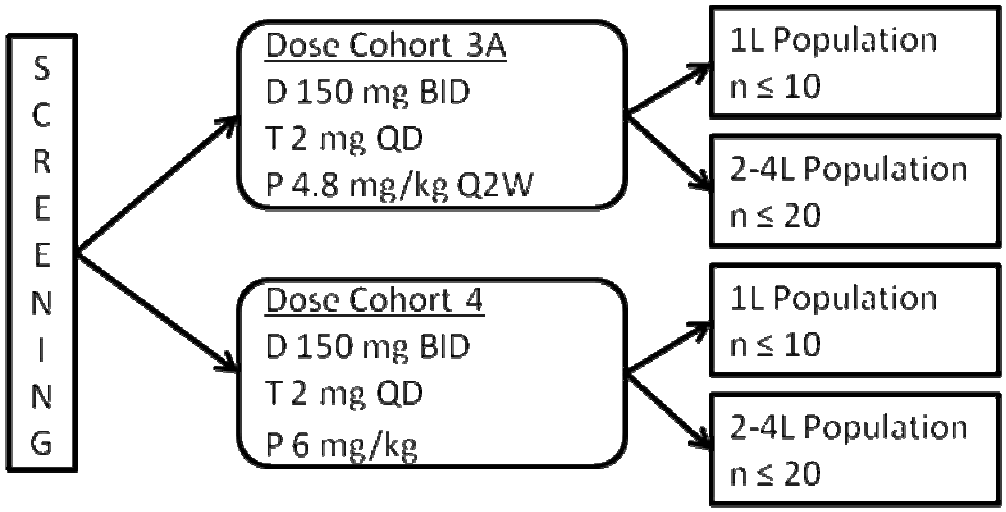
3.1. Part 1 Dose Escalation Study Design/Schematic



3.2. Part 2A: Cohort Expansions Study Design/Schematic

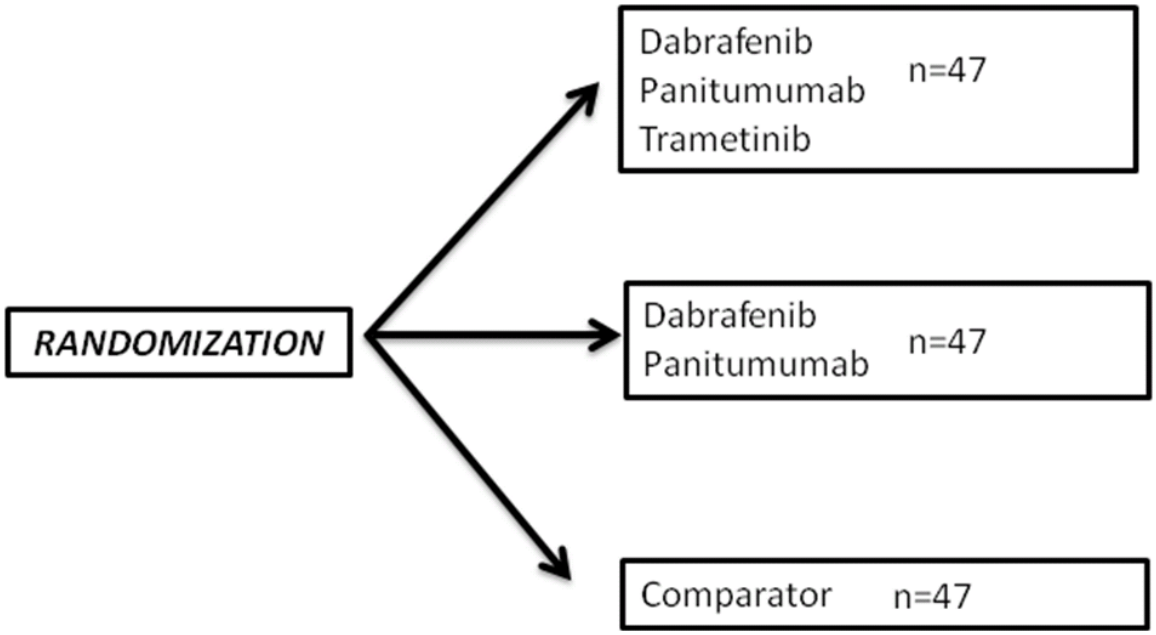


3.3. Part 2B: Cohort Expansion



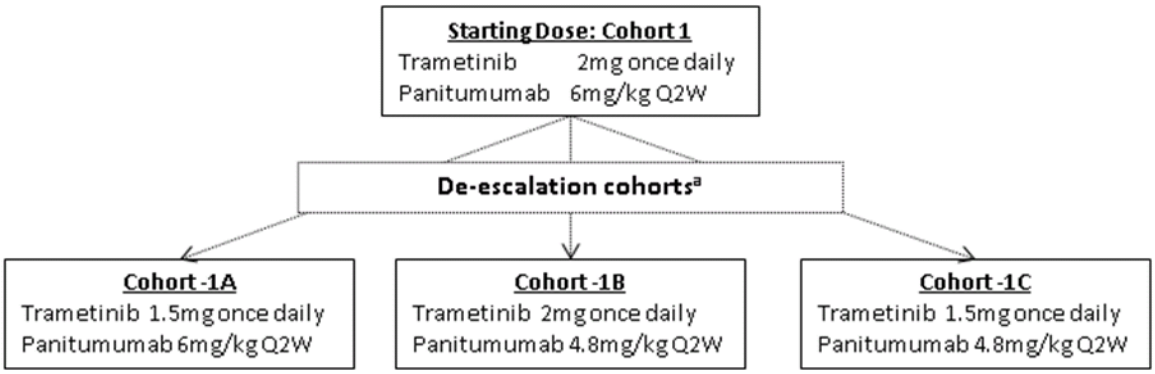
BID, twice daily dosing; D, dabrafenib; L, line of therapy; P, panitumumab; T, trametinib; Q2W, dosing every 2 weeks; QD, once daily dosing.

3.4. Part 3: Randomized Phase 2 Study Design//Schematic



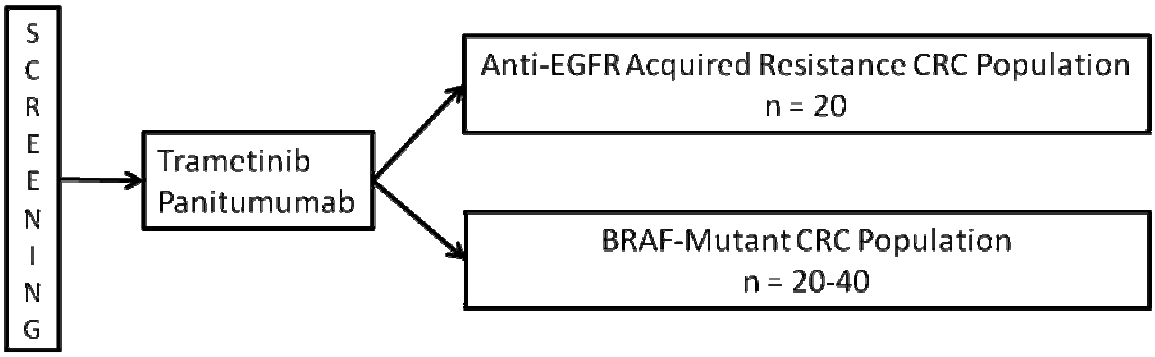
The chemotherapy comparator will consist of a standard fluoropyrimidine-containing regimen including either irinotecan or oxaliplatin. Selection of the chemotherapy comparator arm may be revised based on emerging data from Part 1, Part 2 and Part 4 through a protocol amendment.

3.5. Part 4A Dose Escalation



a. If the initial combination dose of trametinib and panitumumab in Cohort 1 (starting dose) is not tolerable, the lower dose combination defined in de-escalation cohorts (Cohort -1A, -1B and/or -1C) may be evaluated.

3.6. Part 4B Cohort Expansion



Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, is essential.

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

3.7. Discussion of Design

This four-part Phase 1/2 multi-center study allows for the phased evaluation of safety, tolerability, and activity of dabrafenib and/or trametinib in combination with panitumumab in subjects with BRAF-V600E mutation-positive CRC and in subjects with CRC with secondary resistance to prior anti-EGFR therapy. The planned number of subjects per part is described in Section 4.1. Dose adjustment and stopping criteria are described in Section 3.10. All study treatments, including investigational products, will be referred to as "study treatment(s)" for ease of presentation throughout the protocol, except for Section 3.9.

For all parts of the study, assessments throughout are calendar-based starting from the first day of dosing (Day 1) in the first treatment period. Dose interruptions should not alter the assessment schedule for any subsequent treatment period.

3.7.1. Prescreening for KRAS and BRAF Mutation Status

Note: Procedures conducted as part of the subject's routine clinical management (e.g., blood counts, imaging study) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures meet the protocol requirements.

The conduct of the KRAS- and BRAF-mutation screening prior to the baseline assessments is the responsibility of the investigator and must be performed in a CLIA-approved facility. Local testing for KRAS and BRAF mutations for enrollment in the trial can occur any time prior to dosing. If KRAS and BRAF mutation status is unknown at screening, no biopsy for assessment of mutation status in association with this protocol should be taken prior to obtaining consent. Following consent, subjects should be screened for KRAS and BRAF mutation status (if not already performed) prior to any other study-related screening procedures. For Part 1 and Part 2, a local test result for KRAS status is adequate for enrollment. Enrollment in Part 3 may only occur following confirmation of KRAS wild-type cancer, as determined by FDA-approved KRAS test for CRC (e.g., Qiagen test) and documented in source. For patients in Part 4, who have acquired secondary resistance to anti-EGFR therapy, repeat testing for RAS mutations is not required.

For subjects with known BRAFV600E mutations, confirmation of mutation must occur following registration in Parts 1, 2 and 4. Subjects will not be excluded if centralized testing is later found to be discordant or uninformative (e.g., inadequate sample), but additional subjects may be enrolled as replacement subjects at the discretion of the Sponsor and in consultation with the investigator.

Enrollment in Part 3 will only occur following centralized determination of BRAFV600E mutation. Testing must be performed in a CLIA certified central laboratory. The testing will be preferably conducted on metastatic tumor tissue or on recently obtained tumor tissue.

Archived tumor tissue sample must be collected from all subjects enrolled in this study at screening. If this has not been done and an archived tumor tissue sample is not available, the subject should undergo a biopsy prior to dosing to obtain a tumor tissue sample.

[redacted]

3.7.2. Part 1

In Part 1, a combination dose will be defined for both the dabrafenib/panitumumab combination and the dabrafenib/trametinib/panitumumab combination (Table 4). The combination dose will either be the recommended full monotherapy dose for all components of the combination or an MTD for the combination (sub-MTD dosing is also possible if the MTD is not sufficiently well tolerated with long-term dosing). Dosing for

dabrafenib and trametinib will be continuous daily dosing while panitumumab will be dosed once every two weeks, and assessments will occur in 28-day intervals. Subjects will be evaluated for dose-limiting toxicities during the first 28 days of treatment.

Table 4 Part 1 Dosing Cohorts

	COHORTS							
	De-escalation cohorts			Dose escalation cohorts				
	-1A	-1B	-1C	1 STARTING DOSE	2	3A[a]	3B[a]	4
dabrafenib[b]	100mg BID	150mg BID	100mg BID	150mg BID	RP2D* from Cohort 1 [b]	RP2D from Cohort 1 [b]	RP2D from Cohort 1 [b]	RP2D from Cohort 1 [b]
trametinib		-		-	1.5mg once daily	2mg once daily	1.5mg once daily	2mg once daily
panitumumab[c, d]	6mg/kg Q2W	4.8mg/kg Q2W	4.8mg/kg Q2W	6mg/kg Q2W	one dose level below RP2D from Cohort 1 [c]	one dose level below RP2D from Cohort 1 [c]	RP2D from Cohort 1 [d]	RP2D from Cohort 1 [d]

*RP2D= Recommended Phase 2 Dose

a. Cohorts that are designated as "A" and "B" may be opened simultaneously once the prior dosing cohort has completed the 28-day dose-limiting toxicity (DLT) window and met dose escalation criteria as specified in Table 5.

b. Cohort will dose at the dabrafenib dose level in the RP2R defined in Cohort 1 (or, -1A, -1B or -1C, depending on what combination is tolerable).

c. Cohort will dose at one dose level lower than panitumumab dose level in the RP2R defined in Cohort 1 (or, -1A, -1B or -1C, depending on what combination is tolerable).

d. Cohort will dose at the panitumumab dose level in the RP2R defined in Cohort 1 (or, -1A, -1B or -1C, depending on what combination is tolerable).

Dose escalation will follow a 3+3 dose escalation procedure as described in Table 5. Evaluation of safety data from at least 3 subjects who have completed 28 days of dosing on study is required prior to defining a new dose and starting the next cohort.

Table 5 3+3 Cohort Dose Escalation

Number of subjects in cohort with DLT	Action
0 out of 3 subjects	Escalate to next dose level according to dose escalation rules below.
1 out of 3 subjects	Accrue 3 additional evaluable subjects at current dose level for a total of 6 evaluable subjects
1 out of 6 subjects	Escalate to next dose level with an increase of ≤ 50% (this represents the sum of relative escalation for each of the drugs)
2 or more subjects in a dosing cohort (up to 6 subjects)	Maximum tolerated dose has been exceeded. Either evaluate an intermediate dose lower than current dose or expand a prior cohort up to 12 subjects.

Dose escalation decisions will take into consideration all available data, including the safety profile of prior cohorts throughout the time subjects are on study, which will be reviewed by the investigator(s), Novartis Medical Lead(s), pharmacokineticist and statistician. The dose escalation decision for the subsequent cohort and rationale will be documented in writing with copies maintained at each site and the Master Study Files.

Any cohort may be expanded beyond the initial 3 to 6 subjects enrolled during dose escalation, to a maximum of 12 subjects, to facilitate additional collection of safety data.

3.7.2.1. Dose-Limiting Toxicity Definitions

An event will be considered a dose limiting toxicity (DLT) if it occurs within the first 28 days of dosing, if it has a possible causal relationship to the study drug(s) based on investigator assessment, and if it meets at least one of the following criteria:

Toxicity	DLT Definition
Hematologic	• Grade 4 absolute neutrophil count (ANC) for ≥5 days • Febrile neutropenia (defined as concurrent Grade 4 neutropenia and fever >38.5°C and lasting >24 hrs) • Grade 4 anemia of any duration • Grade 4 thrombocytopenia (platelets <25,000/mm^3) of any duration
Non-hematologic	• Alanine aminotransferase (ALT) >5X upper limit of normal (ULN) OR, ALT >3X ULN AND bilirubin >2X ULN (after exclusion of disease progression and/or bile duct obstruction) • Grade ≥4 rash • Grade 4 Squamous Cell Carcinoma, keratoacanthoma or basal cell carcinoma • Grade 3 or greater clinically significant non-hematologic toxicity per NCI-CTCAE, v 4.0, other than those listed above, with the following exceptions: ○ Grade 3 or greater nausea, vomiting, diarrhea, or mucositis/esophagitis that responds to maximal supportive treatment(s) within 48 hours ○ Electrolyte disturbances that respond to correction within 24 hours ○ Grade 3 hypertension that is adequately controlled by the addition of up to 2 additional antihypertensive medications ○ Grade 3 pyrexia that does not result in study discontinuation
Cardiac	• Ejection fraction < lower limit of normal (LLN) with an absolute decrease of >20% from baseline
Other	• Inability to receive ≥75% of scheduled doses in treatment period due to toxicity • Grade 2 or higher toxicity that occurs beyond 28 days which in the judgment of the investigator and Novartis Medical Lead is considered to be a DLT

3.7.2.2. Maximum Tolerated Dose and Recommended Phase 2 Dose

The maximum tolerated dose (MTD) is defined as the highest dose at which one or fewer of up to 6 subjects experience a DLT during the first 28 days of treatment in Part 1. Due to the heterogeneity of the rash caused by panitumumab and/or trametinib, if any DLTs are due to rash, the cohort may be expanded to 12 subjects in order to more fully assess the true risk of intolerable rash, in which case DLTs in >3 of 12 subjects defines an intolerable dose. The recommended doses in Part 2, Part 3 and Part 4 may include doses that are less than or equal to the MTD but demonstrate biological activity and adequate tolerability.

3.7.3. Part 2

In Part 2, the primary objectives will be to further assess the safety and preliminary clinical activity of given doses and regimen(s) in subjects with BRAF-V600E mutation-positive CRC.

For Part 2A and 2B, subjects should follow the assessments in Section 3.11.2.

Part 2 will employ a Bayesian design that allows the trial to be monitored more frequently at multiple stages.

3.7.3.1. Part 2A: Cohort Expansion

Enrollment in Part 2A doublet will be initiated once dose escalation for the doublet (dabrafenib in combination with panitumumab) has been completed. Enrollment in Part 2A triplet (trametinib plus dabrafenib in combination with panitumumab) will open once dose escalation for the triplet has been completed.

Subjects will be enrolled in the expansion cohorts at a selected dose of dabrafenib in combination with panitumumab and a selected dose of trametinib plus dabrafenib in combination with panitumumab. Based on the safety data from Part 1, approximately 20 evaluable subjects with BRAF-V600E mutation-positive CRC will be enrolled at the Cohort 4 dose, the full monotherapy dose for all three component of the triplet regimen, to obtain preliminary data on the safety and efficacy of the combinations.

Subjects who participated in Part 1 of the study at the doses evaluated in Part 2A will be included in Part 2A analysis, and will contribute to the total count of the 20 subjects enrolled in Part 2A.

For Part 2A, subjects should follow the assessments in Section 3.11.2.

3.7.3.2. Part 2B: Cohort Expansion

After completion of Part 2A, additional subjects will be enrolled into the triplet combination of dabrafenib and trametinib in combination with panitumumab. Based on the efficacy (Table 1) and long term tolerability observed in Part 2A, two doses will be evaluated in Part 2B.

Up to ten subjects with no prior treatment and up to 20 subjects with at least one prior treatment will be enrolled at the Cohort 3A dose (dabrafenib 150mg BID + trametinib 2mg QD + panitumumab 4.8mg/kg IV Q2wks). Up to 10 subjects with no prior treatment and up to 20 subjects with at least one prior treatment will be enrolled at the Cohort 4 dose (dabrafenib 150mg BID + trametinib 2mg QD + panitumumab 6mg/kg IV Q2wks).

Enrolment into two patient populations will be dependent on prior therapy for their metastatic disease:

1. First Line Population (1L Population): No prior treatment is defined as subjects with no prior treatment for metastatic disease or metastatic recurrence greater than 6 months following completion of adjuvant therapy;
2. Second to Fourth Line Population (2-4L Population): At least one prior treatment is defined as subjects with progression or intolerance to at least one prior chemotherapy regimen for metastatic disease or recurrence within 6 months following completion of adjuvant therapy. Patients treated with > 4 prior lines of therapy for metastatic disease will not be eligible.

Lines of prior therapy for each subject will be agreed upon by the Meadical Lead and investigator at the time of enrolment.

This would provide safety, efficacy and tolerability data for the triplet regimen in up to 95 subjects between Part 1, Part 2A and Part 2B. .

For Part 2B subjects should follow the assessments in Section 3.11.2.

Responses will be assessed by patient population, line of therapy, dose cohort and in aggregate for a given combination to inform decisions to continue to Part 3.

Part 2 may be stopped at any time if excessive toxicities with the drug are observed. For additional details about this approach, see Section 5.

The decision to proceed to Part 3 of the study will take into consideration all available data and will be reviewed by the investigator(s), Novartis Medical Lead(s), pharmacokineticist and statistician. Data will include the safety profile [redacted] of all dosing cohorts throughout the time subjects are on study. The decision could be based on analysis of a subgroup of responders, so that a single combination arm would be carried forward into Part 3.

3.7.4. Part 3

Part 3 of the study will be conducted as a randomized Phase 2 study, enrolling subjects with BRAF-V600E mutation-positive CRC who are eligible to receive fluoropyrimidine-containing chemotherapy regimen that have experienced documented radiographic progression on one prior line of fluoropyrimidine-containing chemotherapy (previous anti-EGFR therapy is excluded), and will compare safety, tolerability and efficacy of dabrafenib in combination with panitumumab and trametinib plus dabrafenib in combination with panitumumab with standard chemotherapy. The current design reflects our current understanding of the biology and clinical management of BRAF mutation-positive CRC. However, emerging data (either from this study or others) may necessitate a change in the design of Part 3. **Available data from Parts 1 and 2 of this study will be provided to ethics review boards, along with any necessary changes to the protocol, prior to starting Part 3.** The chemotherapy comparator will be a standard fluoropyrimidine-containing regimen that includes either irinotecan or oxaliplatin. The addition of a biological therapy in the chemotherapy comparator arm will be allowed, based on local practice, and will be restricted to panitumumab or bevacizumab. Final decisions on the experimental combination dose levels and the study population for Part 3 will be chosen based on emerging PK, PD, and tolerability data from Part 1 and Part 2.

Interim analyses of Part 3 data will be reviewed for efficacy and safety, as described in Section 5.3.7.3.

Data generated during Part 3 may be reviewed by an independent data monitoring committee (IDMC) along with data from Parts 1 and 2, as described in Section 13.9.

In addition to periodic reviews of the safety and efficacy data, one planned interim analysis for PFS will be performed when 40% of the progression events are reported across either dabrafenib/panitumumab and chemotherapy comparator arms or trametinib/dabrafenib/panitumumab and chemotherapy comparator arms. The interim analysis allows a treatment arm to stop early for harm in PFS. At the interim analysis, if

the enrollment to either of dabrafenib/panitumumab arm or trametinib/dabrafenib/panitumumab arm or chemotherapy comparator arm is halted due to lack of efficacy, the subjects on the halted arm may be provided the opportunity to receive treatment on the ongoing experimental arm(s) depending on the emerging safety and efficacy profile. The details on the interim analysis, including planned stopping boundaries and decision rules in terms of hazard ratios of PFS, are described in Section 5.3.7.3.

To obtain PFS data, after study treatment is withdrawn, radiographic disease assessments (CT or MRI, as appropriate according to the method used at baseline) should continue every 8 weeks until documented disease progression, the start of new anti-cancer therapy, withdrawal of consent or death. To obtain overall survival (OS) data, the subject should be followed to the date of death due to any cause. Further details on study completion are provided in see Section 9.2.

3.7.5. Part 4A Dose Escalation

A combination dose will be defined for combination of trametinib and panitumumab as shown in Section 3.5). Once safety data has been collected for at least 3 patients in Cohort 1, preliminary data will be evaluated for dose-limiting toxicities (DLTs) during the first 28 days of treatment, per table in Section 3.7.5.1.

Table 6 3+3 Cohort Dose Escalation

Number of subjects in cohort with DLT	Action
0 out of 3 subjects	Escalate to next dose level.
1 out of 3 subjects	Accrue 3 additional evaluable subjects at current dose level for a total of 6 evaluable subjects
1 out of 6 subjects	Escalate to next dose level with an increase of ≤ 50% (this represents the sum of relative escalation for each of the drugs)
2 or more subjects in a dosing cohort (up to 6 subjects)	Maximum tolerated dose has been exceeded. Either evaluate an intermediate dose lower than current dose or expand a prior cohort up to 12 subjects.

Dose escalation decisions will take into consideration all available data, including the safety profile of prior cohorts throughout the time subjects are on study, which will be reviewed by the investigator(s), Novartis Medical Lead(s), pharmacokineticist and statistician. The dose escalation decision for the subsequent cohort and rationale will be documented in writing with copies maintained at each site and the Master Study Files.

Due to the heterogeneity of the rash caused by panitumumab and/or trametinib, if any DLTs are due to rash, the cohort may be expanded to 12 subjects in order to more fully assess the true risk of intolerable rash, in which case DLTs in >3 of 12 subjects defines an intolerable dose. If the preliminary MTD is below the full dose of both agents, re-escalation may be considered ONLY if fewer than 4 DLTs have

been reported after enrolling at least 12 patients at the preliminary MTD (including patients enrolled in the dose escalation and expansion cohorts).

3.7.5.1. Dose-Limiting Toxicity Definitions

An event will be considered a dose limiting toxicity (DLT) if it occurs within the first 28 days of dosing, has a possible causal relationship to the study drug(s) based on investigator assessment, and meets at least one of the following criteria:

Toxicity	DLT Definition
Hematologic	• Grade 4 absolute neutrophil count (ANC) for ≥5 days • Febrile neutropenia (defined as concurrent Grade 4 neutropenia and fever >38.5°C and lasting >24 hrs) • Grade 4 anemia of any duration • Grade 4 thrombocytopenia (platelets <25,000) of any duration
Non-hematologic	• Alanine aminotransferase (ALT) >5X upper limit of normal (ULN) OR, ALT >3X ULN AND bilirubin >2X ULN (after exclusion of disease progression and/or bile duct obstruction) • Grade ≥4 rash • Grade 3 or greater clinically significant non-hematologic toxicity per NCI-CTCAE, v 4.0, other than those listed above, with the following exceptions: o Grade 3 or greater nausea, vomiting, diarrhea, or mucositis/esophagitis that responds to maximal supportive treatment(s) within 48 hours o Electrolyte disturbances that respond to correction within 24 hours o Grade 3 hypertension that is adequately controlled by the addition of up to 2 additional antihypertensive medications o Grade 3 pyrexia that does not result in study discontinuation
Cardiac	• Ejection fraction < lower limit of normal (LLN) with an absolute decrease of >20% from baseline
Other	• Inability to receive ≥75% of scheduled doses in treatment period due to toxicity • Grade 2 or higher toxicity that occurs beyond 28 days which in the judgment of the investigator and Novartis Medical Lead is considered to be a DLT

3.7.6. Part 4B Cohort Expansion

In Part 4B cohort expansion, the primary objectives will be to further assess the safety and preliminary clinical activity of trametinib and panitumumab at the MTD determined in Part 4A. Clinical activity will be determined in two patient populations of subjects with advanced/metastatic CRC:

1. BRAF mutant population, subjects with BRAF-V600E mutation-positive CRC (described above)

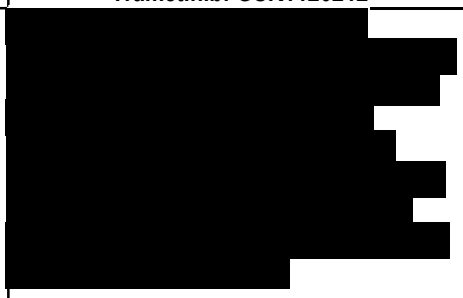
2. Anti-EGFR resistant population, subjects with CRC that developed secondary resistance to anti-EGFR therapy after initially deriving benefit.

Enrollment in expansion cohorts will be initiated once dose escalation for the trametinib and panitumumab combination has been completed. Up to 20 subjects will be enrolled into each population at the starting dose or MTD if lower dose combination is required. This will include the patients from part 4A. An additional 20 subjects with advanced/metastatic CRC with a BRAF mutation and progression or intolerance to one line of prior chemotherapy for metastatic disease or recurrence within 6 months of adjuvant therapy may be enrolled into BRAF mutant CRC population at a lower dose combination defined by the de-escalation cohorts to evaluate the tolerability and efficacy of a lower dose of one or both of the investigational products. The decision to enroll subjects at a lower dose level(s) and the lower dose(s) selected will be at the discretion of the investigators and Novartis Medical Lead. Part 4 may also be stopped at any time if excessive toxicities with the study treatment are observed.

3.8. Treatment Assignment

All subjects will be assigned to study treatment in accordance with the randomization schedule generated by Discovery Biometrics, prior to the start of the study, using validated internal software. In Part 1, subjects will be assigned to a cohort/ dose level based on evaluation of safety in subjects enrolled in prior cohorts. In Part 2, subjects will be assigned to expansion cohorts at a dose cohort from Part 1 dabrafenib in combination with panitumumab and a dose cohort from Part 1 of trametinib plus dabrafenib in combination with panitumumab. In Part 3, subjects will be randomized to study treatment. In Part 4A dose escalation, subjects will be assigned to a cohort/ dose level based on evaluation of safety in subjects enrolled in prior cohorts. In Part 4B cohort expansion, subjects will be assigned to expansion cohorts at the starting dose cohort or dose de-escalation cohort from Part 4A of trametinib in combination with panitumumab.

3.9. Investigational Products and Other Study Treatment Dosage/Administration

Product name:	Dabrafenib: GSK2118436	Trametinib: GSK1120212
Formulation description:		
Dosage form:	Capsule	Tablet
Unit dose strength(s)	50mg, 75mg	0.5mg, 2mg
Route/ Regimen	Oral/ The initial dosing regimen will be twice daily (BID) continuous oral daily dosing. • Subjects should be encouraged to take their doses at 12 hour intervals and at similar times every day with approximately 200mL of water.	Oral/ The initial dosing regimen will be once daily continuous oral daily dosing. • Subjects should be encouraged to take study medication at approximately the same time(s) of day each day with approximately 200mL of water.
Physical description:	50 mg strength capsules are Swedish orange (dark red) opaque hypromellose size 2 capsules. 75 mg strength capsules are pink opaque hypromellose size 1 capsules/	Both tablet strengths are biconvex film coated tablets with a different shape and size to facilitate the visual identification. 0.5mg: Yellow modified oval biconvex film-coated tablets;: 4.8mm X 8.9mm 2mg: Pink round biconvex film coated tablets;7.5 mm in diameter

Product name:	Panitumumab/ Vectibix
Formulation description:	Vectibix (panitumumab) is recombinant, human IgG2 kappa monoclonal antibody that binds specifically to the human epidermal growth factor receptor (EGFR). Panitumumab has an approximate molecular weight of 147kDa. Panitumumab is produced in genetically engineered mammalian (Chinese Hamster Ovary) cells.
Dosage form:	Single-use vials
Unit dose strength(s)	100mg panitumumab in 5mL (20mg/mL) single-use vial; (NDC 55513-954-01) 200mg panitumumab in 10mL (20mg/mL) single-use vial; (NDC 55513-955-01) 400mg panitumumab in 20mL (20mg/mL) single-use vial; (NDC 55513-956-01).
Route/ Dosing instructions	Intravenous The recommended dose of Vectibix is 6mg/kg, administered as an intravenous infusion over 60 minutes, every 14 days. Doses higher than

Product name:	Dabrafenib: GSK2118436	Trametinib: GSK1120212
	1000 mg should be administered over 90 minutes. • Infusion of panitumumab should be started within 30 minutes of dosing with oral medications dabrafenib and trametinib.	
Physical description:	Vectibix is a sterile, colorless, pH 5.6 to 6.0 liquid for intravenous (IV) infusion, which may contain a small amount of visible translucent-to-white, amorphous, proteinaceous, panitumumab particulates. Each single-use 5 mL vial contains 100 mg of panitumumab, 29 mg sodium chloride, 34 mg sodium acetate, and Water for Injection, USP. Each single-use 10 mL vial contains 200 mg of panitumumab, 58 mg sodium chloride, 68 mg sodium acetate, and Water for Injection, USP. Each single-use 20 mL vial contains 400 mg of panitumumab, 117 mg sodium chloride, 136 mg sodium acetate, and Water for Injection, USP.	
Manufacturer/ source of procurement:	Amgen Inc.	

Staff should refer to the prescribing information for panitumumab, as appropriate, for a detailed description of drug storage, preparation, and administration [VECTIBIX, 2014].

3.10. Dose Adjustment/Stopping Criteria

3.10.1. Continuation on Study

In the absence of unacceptable toxicity, disease progression or subject withdrawal of consent for continued treatment, subjects may continue on treatment.

Subjects who have met the criteria for disease progression (PD) according to RECIST v 1.1 may continue to receive study drug if the Investigator believes the subject is receiving clinical benefit and approval to continue is granted by the Novartis Medical Lead. In this case, all study procedures would continue per protocol. The following efficacy and safety criteria must be met during study treatment prior to disease progression in order for investigators to consider continuing study therapy beyond radiographic tumor progression:

- the subject experienced a confirmed tumor response according to RECIST v 1.1 while receiving study treatment OR disease under study had remained no worse than stable for a period of at least two consecutive scans (approximately 12 weeks) while receiving study treatment;

- absence of signs and symptoms of clinical disease progression despite radiographic disease progressive based on RECIST v 1.1 criteria outlined in Appendix 4;

- no treatment-related AEs of CTCAE Grade 4 or SAEs have occurred during the last 4 weeks of study treatment.

Prior to continuing study treatment, Investigators will be required to document that, in their opinion, the patient continues to receive clinical benefit and that the patient agreed to continue following a discussion of all available treatment options.

If the study treatment(s) is continued beyond disease progression, study procedures will be continued according to the Time and Events Table (Section 3.11).

Table 7 Categories of Dose Modification Guidelines

Adverse Event	Dabrafenib	Trametinib	Section
General Guidelines for Clinically Significant Toxicities	X	X	Section 3.10.4
Guidelines for Specific Adverse Events Cardiovascular Adverse Events[a]			
LVEF		X	Section 3.10.7.1
Hypertension	X	X	Section 3.10.8
Prolonged QTc	X	X	Section 3.10.9
Skin –Related Adverse Events (Except cuSCC)[b]			
Rash	X	X	Section 3.10.4.2
Hand-Foot Skin Reaction	X	X	Section 3.10.4.2.4
Other Adverse Events			
Pyrexia	X		Section 3.10.4.1
Diarrhea	X	X	Section 3.10.5
Renal Insufficiency	X	X	Section 3.10.6
Visual Changes	X	X	Section 3.10.11
Pneumonitis	X	X	Section 3.10.13
Liver Chemistry Stopping Criteria	X	X	Section 3.10.10

a. For subjects enrolled in France, please see Appendix 5 for additional dose modification guidelines.
b. Refer to Section 3.10.4.3 for management of cuSCC

3.10.2. Dose Adjustment

The severity of adverse events (AEs) will be graded utilizing the National Cancer Institute- Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 4.0. Guidelines for dose modifications and interruptions for management of common toxicities associated with the study treatment(s) are provided in this section:

- general guidelines for clinically significant toxicities related to study treatments

and

- specific guidelines for adverse events of special interest, which are events that have been observed with higher frequency or severity in subjects receiving dabrafenib, trametinib, or a combination of both therapies.

In the event of a DLT (for subjects enrolled in a dose escalation cohort), or other clinically significant AE in any part of the study, treatment may be withheld and supportive therapy administered as clinically indicated. If the toxicity or event resolves to baseline or Grade 1 in less than or equal to 14 days of stopping therapy, then treatment may be restarted. Dose reduction should be considered as clinically indicated. Any dose adjustment or interruption will be recorded.

If the toxicity does not resolve to at least Grade 1 in less than or equal to 14 days, withdrawal from the study drug(s) is recommended. However, if the investigator and Novartis Medical Lead agree that further treatment would benefit the subject, treatment

can continue with at least one dose level dose reduction, per Table 8. If toxicity is clearly related to one agent, a single agent in the combination may be dose-reduced.

Table 8 Dose Level Reduction Guidelines

Dose Level	Dabrafenib Dose/Schedule	Trametinib Dose/Schedule	Panitumumab Dose/Schedule
0	150mg BID	2mg once daily	6 mg/kg every 14 days
-1 (first dose reduction)	100mg BID	1.5mg once daily	4.8 mg/kg every 14 days
-2 (second dose reduction)	75mg BID	1mg once daily	3.6 mg/kg every 14 days

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 with approval from the Novartis Medical Lead.

A dose reduction below 75mg BID for dabrafenib, 1mg once daily for trametinib and 3mg/kg every 14 days for panitumumab is not allowed (per the panitumumab label [VECTIBIX, 2014]. If a dose reduction below 75mg BID for dabrafenib is required, dabrafenib will be permanently discontinued, but the subjects will be allowed to continue trametinib and panitumumab. If a dose reduction below1.0 mg once daily for trametinib is required, then trametinib will be permanently discontinued, but these subjects will be allowed to continue dabrafenib and panitumumab. If a dose reduction below 3mg/kg every 14 days for panitumumab is required, panitumumab will be permanently discontinued, but the subjects will be allowed to continue dabrafenib and trametinib.

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

3.10.3. Intra-subject Doublet to Triplet Crossover and Dose Escalation: Part 1, 2 or 4

For BRAF-mutation positive subjects enrolled in Part 1, 2 or 4 doublet dosing, intra-subject doublet to triplet crossover is allowed if a patient has not experienced intolerable toxicity that could not be managed, and has demonstrated radiographic progression on therapy by RECIST v1.1 criteria, and approval will be based on review by the Novartis Medical Lead. Subjects must crossover to triplet within 6 weeks of radiographic progression. All assessments and samples required at progression as described in Section 3.11 must be completed even though the subject crosses over to triplet. Dose administered must be from among those for which cohorts have been completed and data has been reviewed for safety.

At the time of crossover, certain safety assessments will be repeated prior to start of triplet dosing (additional information describing assessments is available in Section 6):

- brief physical examination
- vital signs
- dermatological examination

- ECG (single; repeated with 2 additional ECGs if clinically significant abnormalities are observed in the first assessment)
- ECHO/ MUGA
- disease assessment demonstrating radiographic progression on therapy by RECIST v1.1 criteria
- ophthalmic examination, repeated at Week 4 after start of dosing with trametinib

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

All crossover assessments must be completed within 14 days prior to first dose on triplet except informed consent, ophthalmology exam, ECHO/MUGA and Disease Assessment, which can occur within 35 days prior to the first dose on triplet. Assessments performed as part of the follow-up for the doublet will be acceptable if they are performed within these timeframes prior to the first dose on triplet.

The source documents for these assessments should be provided to Novartis at least 24 hours in advance to planned start of triplet dosing. The Medical Lead will review and provide approval for crossover from doublet to triplet, and site will be notified via email with a signed crossover form (refer to SPM).

Once approved, patients will follow the time and events table in Section 3.11.5, starting at the column labelled "Continuation Phase" for continued monitoring of safety and efficacy after they receive their first dose on triplet. The Initial Follow-Up and Secondary Follow-Up Assessments should be performed after last dose of triplet. Additional details are provided in the SPM.

Subjects are allowed to crossover once during the study.

Additionally, for subjects who have remained on study for ≥ 6 months in the triplet combination, their dose level for the combination may be increased up to the highest combination dose level that has previously been confirmed as not exceeding the MTD for the combination. The intra-subject dose escalation must be agreed to by the investigator and the Novartis Medical Lead.

3.10.4. 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 9 Dose Modification Algorithms

Non-hematologic and hematologic toxicity (except fever), CTCAE Grade	Dose modification algorithms [a, b, c, d]
Grade 1	• Continue dabrafenib, trametinib and panitumumab at full dose • Monitor closely • Provide supportive care according to institutional standards
Grade 2	• Consider dose de-escalation by 1 dose level or holding dabrafenib, trametinib, and/or panitumumab until resolution to Grade 1 or baseline • Provide supportive care as clinically indicated. • Monitoring of laboratory values should occur as clinically indicated. • For Grade 2 or higher respiratory symptoms (i.e., cough, dyspnea, hypoxia, etc), evaluation by CT scan is recommended.
Grade 3	• Hold dabrafenib, trametinib, and panitumumab until toxicity resolves to Grade 1 or baseline then reduce dose of dabrafenib, trametinib, and/or panitumumab by 1 dose level. • The subject may be continued at the same dose, if in the judgment of the investigator, the toxicity is considered unrelated to dabrafenib, trametinib, and/or panitumumab or clearly related to a particular agent(s). • Continue to monitor as clinically indicated.
Grade 4	• Discontinue dabrafenib, trametinib, and panitumumab. Continue to monitor as clinically indicated, and provide supportive care as needed. • If in the investigator's judgment the toxicity is unlikely to recur, hold dabrafenib, trametinib, and panitumumab until the toxicity is Grade 1 or baseline, then reduce dose of dabrafenib, trametinib, and/or panitumumab by 1 dose level. • If Grade 4 toxicity recurs after dose reduction, discuss continuation of study drug(s) with the Novartis Medical Lead.

a. The minimum dose of dabrafenib is 75mg BID; the minimum dose of trametinib is 1mg once daily; the minimum dose of panitumumab is 3.6 mg/kg. If a subject requires dose reduction below dabrafenib 75mg BID, trametinib 1mg once daily, or panitumumab 3.6 mg/kg then the subject must be discontinued from study drug(s).
b. For adverse events of abdominal pain or suspected pancreatitis, amylase and lipase laboratory samples should be collected.
c. If the subject has a Grade 3 or 4 laboratory abnormality that in the judgment of the investigator is not considered clinically significant, dose modification is not required.
d. For subjects who develop symptoms associated with uveitis, including blurry vision, eye pain or erythema, an ophthalmologic consult is required.

Table 10 Panitumumab Dose Modification and Management Guidelines for Infusion Reactions

Toxicity and Grade	Modification and Management
Infusion reaction:	
mild or moderate (Grade 1 or Grade 2) infusion reaction	• Reduce the infusion rate by 50% for the duration of that infusion • Consider premedication with antihistamines and/or corticosteroids prior to subsequent doses
severe (Grade 3 or Grade 4) infusion reaction	• Immediately discontinue panitumumab infusion • If the reaction is particularly severe and/or persistent, consider discontinuation of panitumumab. • Consider premedication with antihistamines and/or corticosteroids prior to subsequent doses.

3.10.4.1. Guidelines for Treatment of Pyrexia

Episodes of pyrexia have been observed in subjects receiving dabrafenib monotherapy and is increased in incidence and severity in subjects receiving dabrafenib in combination with trametinib (refer to the GSK2118436 IB [GlaxoSmithKline Document Number 2012N136095_00], the GSK1120212 IB [GlaxoSmithKline Document Number HM2009/00151/03] and the GSK1120212 + GSK2118436 Clinical IB [GlaxoSmithKline Document Number, 2011N126811_00]). In a minority of cases the pyrexia was accompanied by symptoms such as severe chills, dehydration, hypotension, dizziness or weakness.

Subjects should be instructed on the importance of immediately reporting febrile episodes. In the event of a fever, the subject should be instructed to take anti-pyretics (e.g., ibuprofen or acetaminophen/paracetamol) as appropriate to control fever. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient. Monitor serum creatinine and other evidence of renal function during and following severe events of pyrexia (see Section 3.10.6).

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

Table 11 Management and Dose Modification Guidelines for Pyrexia

Pyrexia[a] Management	Action and Dose Modification
All Events: • Clinical evaluation for infection and hypersensitivity[c] • Laboratory work-up[c] • Hydration as required[d]	
1st Event[b]: Administer anti-pyretic treatment if clinically indicated and continue prophylactic treatment[f] if associated with rigors, renal failure, dehydration or hypotension[e]	1st Event: • Interrupt dabrafenib • Continue trametinib and/or panitumumab • Once pyrexia resolves to baseline, restart dabrafenib at the same dose level If fever was associated with dehydration or hypotension, **reduce dabrafenib by one dose level**
2nd Event[g]: • Within 3 days of onset of pyrexia: Optimize anti-pyretic therapy Consider oral cortiocosteroids (i.e., prednisone 10mg) for at least 5 days or as clinically indicated	2nd Event: • **Interrupt dabrafenib** • Continue trametinib and/or panitumumab • Once pyrexia resolves to baseline, restart dabrafenib at the same dose level If fever was associated with rigors, renal failure, dehydration or hypotension, **reduce dabrafenib by one dose level[g]**
Subsequent Events: • Within 3 days of onset of pyrexia: Optimize oral corticosteroid dose as clinically indicated for recalcitrant pyrexia if corticosteroids have been tapered and pyrexia recurs, restart steroids if corticosteroids cannot be tapered consult the Medical Lead	**Subsequent Events:** • **Interrupt dabrafenib** • Continue trametinib and/or panitumumab Once pyrexia resolves to baseline, restart dabrafenib **reduced by one dose level[g]** If dabrafenib must be reduced to <50mg BID, permanently **discontinue dabrafenib. Trametinib may be continued.**

a. Pyrexia is defined as a body temperature equal to or above 38.5 °Celsius or 101.3° Fahrenheit.
b. For subjects experiencing pyrexia complicated by rigors, severe chills, etc., a clinical evaluation and laboratory work-up is mandatory for each event; anti-pyretic treatment should be started immediately at the first occurrence and prophylactic anti-pyretic treatment is recommended
c. Thorough clinical examination for signs and symptoms of infection or hypersensitivity is required; laboratory workup 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 subjects without evidence of dehydration. Intravenous hydration is recommended in subjects 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 subject 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.

3.10.4.2. Management of Dermatological Adverse Events Skin Toxicity

Treatment of subjects with dabrafenib, panitumumab and /or trametinib may result in skin toxicities. These skin toxicities include acneiform rash, non-acneiform rash and hand-foot-skin reaction (HFSR). Please note that the distinctions between these skin toxicities is important as it provides insight into the most likely causative agents and has implications in terms of management of the toxicity. In addition, some subjects enrolled in study BRF112680 experienced squamous cell carcinoma (SCC), keratoacanthomas (KA), and keratotic lesions. Treatment of SCC, KA and keratotic lesions should occur based upon institutional practice. Dose interruptions or modifications are usually not required for SCC/KA.

Management guidelines have been provided for acneiform rash (Section 3.10.4.2.2), non-acneiform rash (Section 3.10.4.2.3) and HFSR [Section 3.10.4.2.4]. Management can differ from the guidelines below based on the clinical judgment of the investigator. The investigator should contact the Novartis Medical Lead to discuss skin toxicity as needed. The Sponsor recommends biopsies of any new skin lesions for further study, specifically those suspicious for malignancy and pre-malignancy (SCC, actinic keratosis, and keratoacanthoma). Copies of pathology reports and slides may be collected by the sponsor for review. Photography of any lesions at baseline is recommended with photographs of any new or changing lesions recommended at subsequent visits per the Time and Events Table (Section 3.11).

3.10.4.2.1. Rash Prophylaxis and Supportive Care

In order to reduce the frequency and severity of skin toxicity (particularly rash), the following prophylactic measures are strongly suggested:

General considerations in rash management

- Encourage subjects to avoid unnecessary exposure to sunlight.
- Employ a proactive approach. Subjects should have topical steroid and/ or topical antibiotic available for prophylactic use at the start of treatment (i.e., prophylactic treatment; see below for recommendations).

If a subject develops rash, verify treatment intervention and follow-up steps outlined under “Reactive Management”.

Prophylactic treatment (during the first 6 weeks of treatment)

The exact prophylactic regimen should be based on the investigator's experience; however, the following regimen is recommended:

1. Mild strength topical steroid (e.g., hydrocortisone 1% cream), with escalation to higher strength and/or oral steroids as detailed below.

2. Offer topical antibiotics (such as clindamycin) or oral antibiotics (such as doxycycline 100mg BID or minocycline 100mg BID).

3. Topical steroids and antibiotics should be applied on a daily basis starting on Day 1 of study treatment, and more often as needed to areas such as face, chest and upper back.

4. Broad-spectrum sunscreen containing titanium dioxide or zinc oxide) with a skin protection factor (SPF) ≥15.

5. Thick, alcohol-free emollient cream (e.g., glycerine and cetomacrogol cream) on dry areas of the body.

Reactive Management for Rash

Two types of rash have been seen with the dabrafenib and trametinib combination.

Acneiform rash. The need for oral or topical antibiotics (e.g., clindamycin cream, minocycline, doxycycline, etc) and higher strength topical steroids is a clinical decision of the investigator. Prophylactic use of skin emollients, sunscreen, oral doxycycline and topical steroids was demonstrated to be more effective than reactive use of the same agents after rash developed [Lacouture, 2010]. Oral or topical retinoids are not recommended. Consider the algorithm provided in Table 12 for management of acneiform rash.

1. **Inflammatory rash**, which is often patchy, with sudden onset, and accompanied by erythema, pruritus and/ or pain. If diagnosis is unclear, a biopsy and photographs should be obtained.

    a. For Grade 2 or worse inflammatory rash, hold dabrafenib until resolution to Grade 1. Dabrafenib may be restarted at full dose while monitoring for recurrence of skin reaction. Consider holding trametinib if symptoms are troublesome. Consider treatment with systemic steroids, such as a Medrol dose pack. If the reaction occurs a second time, hold until resolution and then reduce dose by at least 25%.

It is strongly recommended that subjects who develop rash or other skin toxicities have a consultation with a dermatologist to determine appropriate management.

- For **pruritic lesions**, the use of cool compresses and oral antihistamine agents may be helpful.

- For **fissuring**, the use of Monsel's solution, silver nitrate, or zinc oxide cream is advised.

- For **desquamation**, thick emollients and mild soap are recommended.

- For **paronychia**, antiseptic bath and local potent corticosteroids, in addition to oral antibiotics, are recommended. If no improvement is seen, a dermatology or surgery consultation is recommended.

For **infected lesions**, bacterial and fungal culturing followed by the appropriate culture-driving systemic or topical antibiotics is indicated.

3.10.4.2.2. Acneiform Rash

Acneiform rash is a common adverse event associated with trametinib and panitumumab and it is expected to be a common adverse event in the current study. The management of acneiform rash is outlined in Table 12.

Table 12 Acneiform Rash Management Guidelines

Step	Rash grading	Rash severity	Management of Rash	Dose Modification for Trametinib and Panitumumab[a]
1	Mild	Localized Minimally symptomatic No impact on activities of daily living (ADL) No sign of superinfection	Initiate prophylactic regimen, including oral antibiotics, if not already started (see Section 3.10.4.2.1). Consider using moderate strength topical steroids[a]	Consider reduction of panitumumab dose by one dose level. Reassess after 2 weeks; if rash worsens or does not improve, proceed to Step 2.
2	Moderate	Generalized Mild symptoms (e.g., pruritus, tenderness) Minimal impact on ADL No sign of superinfection	Initiate prophylactic regimen, including oral antibiotics, if not already started (see Section 3.10.4.2.1), using moderate strength topical steroids[b]	Reduce panitumumab dose by one dose level or consider interrupting panitumumab until resolution of toxicity to Grade 1. Reduce trametinib by one dose level or consider interrupting trametinib until resolution of toxicity to Grade 1. If toxicity resolves, then can consider re-escalation to initial dose level. Reassess after 2 weeks; if rash worsens or does not improve, proceed to Step 3.
≥3	Severe	Generalized Severe symptoms (e.g., pruritus, tenderness) Significant impact on ADL Sign of or potential for superinfection	Initiate prophylactic regimen, including oral antibiotics, if not already started, using moderate strength topical steroids[b] plus methylprednisone dose pack (see Section 3.10.4.2.1). Consider obtaining dermatology consultation. Manage rash per dermatologist's recommendation.	Interrupt panitumumab and trametinib until rash improves (mild), or resolves. If rash worsens or does not improve after 2 weeks, permanently discontinue panitumumab and trametinib. If rash does improve/resolve, restart trametinib and panitumumab, each reduced by a single dose level. 1. If it is not tolerated, hold both agents until resolution to Gr1 and then restart both agents, each reduced by another dose level.

a. Recommendations for modification of panitumumab dosing may deviate from the package insert [VECTIBIX, 2014].
b. Hydrocortisone 2.5% cream or fluticasone proprionate 0.5% cream.

3.10.4.2.3. Non-Acneiform Rash

Non-acneiform rashes are also seen following treatment with the dabrafenib/trametinib combination and are generally thought to be related to dabrafenib. Therefore, the management guidelines for non-acneiform rash in Table 13 focuses on dabrafenib dose interruption/reduction. However, if the non-acneiform rash is not resolving, administration of trametinib and panitumumab may also be interrupted/reduced.

Table 13 Non-acneiform Rash Management Guidelines

Skin Toxicity Grade (NCI CTCAE, v4.0)	Guideline for Management	Dabrafenib Dose Reduction[a]
1	Topical corticosteroids, such as mometasone, betamethasone or fluocinonide creams	None
2	As for Grade 1, with the addition of diphenhydramine oral prednisone (short course)[b]	None: if unacceptable to subject or if medically concerning, then hold dabrafenib until recovery of toxicity to ≤ Grade 1. Restart at the same dose.
≥3		Hold dabrafenib until recovery of toxicity to ≤ Grade 1. Restart dabrafenib with a dose reduction of 1 dose level.

a. If no recovery after 2 weeks of holding dabrafenib, then subjects must be withdrawn from study drug, unless in the opinion of the investigator and the Novartis Medical Lead there is reason to believe that the subject will experience clinical benefit from future treatment.
b. For subjects with Grade 3 or Grade 4 extensive or symptomatic dermatological event, or chronic, persistent or recurring lower-grade dermatological events, a dermatology consult is recommended.

3.10.4.2.4. Hand-Foot-Skin Reaction (HFSR)

Episodes of hand-foot skin reaction (HFSR) have been observed in subjects receiving dabrafenib. Guidelines for management of HFSR are based on experience with other kinase inhibitors [Lacouture, 2008; McClellan, 2011] and are listed in Table 14.

Table 14 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 treatments at current dose level
Grade 2	Life-style changes recommended[b] Initiate symptomatic treatment[c]	Interrupt study treatment(s)[f] until recover to ≤ Grade 1[d] If there is recovery to ≤Grade 1 within 7 days, restart study treatment(s)[f] at previous dose level. If not recovered to ≤Grade 1 within 7 days, or at the 2nd occurrence, restart study treatment(s)[f] with a one dose level reduction in dabrafenib[e]
Grade ≥3	Life-style changes recommended[b] Initiate symptomatic treatment[c] • Consult dermatologist	Interrupt study treatment until recover to ≤ Grade 1[d] Restart study treatment(s)[f] with a one dose level reduction in dabrafenib[e] If 3rd occurrence, discontinue study treatments permanently

a. A full-body skin examination and a removal of pre-existing calluses and keratotic skin are recommended prior to initiation of study treatment (Section 6.2).
b. Life-style changes: (1) reduce exposure of hands and feet to hot water, (2) avoid traumatic activity including vigorous exercise especially in the first 4 weeks after start of study treatment, (3) avoid constrictive footwear, (4) avoid excessive friction on the skin, when applying topical treatments, (5) wear thick cotton socks and gloves, and shoes with padded insoles.
c. Symptomatic Treatments: (1) use moisturizing creams frequently and especially on hands and feet (2) consider topical keratolytics: urea 20-40 % cream, or salicylic acid 6%, or tazarotene 0.1% cream, or fluorouracil 5% cream; (3) erythrematous areas: clobetasol propionate 0.05% ointment; (4) Pain: topical lidocaine 2%, and / or systemic pain medication such as nonsteroidal anti-inflammatory drugs, codeine, and pregabalin.
d. Approval of the Novartis Medical Lead is required to restart study treatment after ≥21 days of interruption.
e. Escalation of study treatment to the previous dose level is allowed if no HFSR is observed in the 4 weeks subsequent to dose reduction.
f. Modification to study treatment(s) should be discussed with the Novartis Medical Lead.

3.10.4.3. Guidelines for cuSCC

Cutaneous squamous cell carcinomas have been observed in subjects treated with dabrafenib and the combination of dabrafenib and trametinib (see the GSK1120212 + GSK2118436 Clinical IB and Supplements [GlaxoSmithKline Document Number, 2011N126811_00, GlaxoSmithKline Document Number 2012N152310_00, GlaxoSmithKline Document Number 2012N152310_01]). 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. Submit cuSCC tumor tissue for analysis as directed in the SPM.

3.10.5. Guidelines for Diarrhea

Episodes of diarrhea have occurred in subjects receiving dabrafenib, panitumumab and /or trametinib. Other, frequent causes for diarrhea 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 diarrhea considered to be related to study treatment by the investigator are provided in Table 15.

Table 15 Management and Dose Modification Guidelines for Diarrhea

CTCAE Grade	Adverse Event Management	Action and Dose Modification
Uncomplicated diarrhea[a] Grade 1 or Grade 2	Diet: Stop all lactose-containing products; eat small meals, BRAT diet (bananas, rice, apples, toast) is recommended. Hydration: 8 to 10 large glasses of clear liquids per day (e.g., Gatorade or broth) Loperamide: initially 4mg, followed by 2mg every 4 hours or after every unformed stool, to a maximum of 16mg/ day. Continue until diarrhea-free for 12 hours. Diarrhea ≥ 24 hours: Loperamide 2mg every two hours to a maximum of 16mg/ day. Consider adding oral antibiotics. Diarrhea ≥48 hours: Loperamide 2mg every two hours to a maximum of 16mg/ day. Add budesonide or other 2nd line therapies (otreotide, or	Continue study treatments. Consider dose reduction of trametinib and panitumumab by one dose level. If diarrhea is Grade 2 for >48 hours, interrupt study treatments until resolution to ≤Grade 1. Restart study treatments at the current dose level.

CTCAE Grade	Adverse Event Management	Action and Dose Modification
	tincture of opium) and oral antibiotics.	
Uncomplicated diarrhea[a] Grade 3 or Grade 4 Any complicated diarrhea[b]	Clinical evaluation is mandatory. Loperamide[c]: initially 4mg, followed by 2mg every 4 hours or after every unformed stool, to a maximum of 16mg/ day. Continue until diarrhea-free for 12 hours. Oral antibiotics and 2nd line therapies should be implemented if clinically indicated. Hydration: intravenous fluids should be administered if clinically indicated. Antibiotics (oral or IV) should be administered if clinically indicated. **Interventions should be continued until the subject is diarrhea-free for ≥24 hours.** **Intervention may require hospitalization for subjects at risk of life-threatening complications.**	Interrupt study treatments until diarrhea recovers to ≤ Grade 1. Restart study treatments with a one dose level reduction. If 3 dose reductions of study treatment are clinically indicated, **permanently discontinue study treatments.**

a. Uncomplicated diarrhea is 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 IV fluid substitution.
b. Complicated diarrhea is 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 IV fluid substitution.
c. Loperamide should be made available prior to the start of study treatment so that loperamide administration can begin at the first signs of diarrhea.

3.10.6. Guidelines for Renal Insufficiency

Cases of renal insufficiency have occurred in subjects receiving dabrafenib and the combination of dabrafenib and trametinib. Prior to start of any 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 16.

Table 16 Management and Dose Modification Guidelines for Renal Insufficiency

Creatinine	Adverse Event Management	Action and Dose Modification
For subjects with serum creatinine increase >0.2 mg/dL (18 μmol/L) but ≤0.5 mg/dL (44 μmol/L) above baseline:	• Re-check serum creatinine within 1 week • If serum creatinine increases > 1 week, contact the Novartis Medical Lead • If pyrexia is present, treat pyrexia as per guidelines[a]	Continue study treatment at the same dose level.
For subjects with serum creatinine increase >0.5 mg/dL (44 μmol/L) above baseline or serum creatinine >2 mg/dL (> 177 μmol/L)	• Follow serum creatinine at least twice weekly • Consider hospitalization if serum creatinine cannot be monitored frequently • If pyrexia is present, treat pyrexia as per guidelines[a] • Consult nephrologist if clinically indicated • Perform renal biopsy if clinically indicated, for example: • Renal insufficiency persists despite volume repletion • Subject has new rash or signs of hypersensitivity (such as elevated eosinophil count)	• Interrupt study treatment(s)[c] until serum creatinine recovers to baseline. • Restart with study treatment[b] at either the same or a reduced dose level

a. Nonsteroidal anti-inflammatory drugs (NSAIDs) can induce renal insufficiency, especially in subjects with dehydration. Encourage oral fluids or consider IV fluids as clinically indicated. Refer to guidelines for pyrexia in Section 3.10.4.1.

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

c. Modification to study treatment(s) should be discussed with the Novartis Medical Lead. Since panitumumab is not associated with renal toxicity and its pharmacokinetics are not altered by renal insufficiency, the panitumumab dose should be restarted at the same dose.

3.10.7. Guidelines for Cardiovascular Adverse Events

Cardiovascular adverse events have been observed in subjects receiving either dabrafenib, trametinib, or the two drugs in combination. Additional information is available in the IBs: GSK2118436 IB [GlaxoSmithKline Document Number 2012N136095_00], the GSK1120212 IB [GlaxoSmithKline Document Number HM2009/00151/03] and the GSK1120212 + GSK2118436 Clinical IB [GlaxoSmithKline Document Number, 2011N126811_00]. Guidelines for LVEF decreases, hypertension and prolonged QTc are provided in Section 3.10.7.1, Section 3.10.8 and Section 3.10.9, respectively.

3.10.7.1. Left Ventricular Ejection Fraction (LVEF)

Decreases of the left-ventricular-ejection-fraction (LVEF) have been observed in subjects receiving trametinib monotherapy and in combination with dabrafenib. Therefore, ECHO/MUGAs must be performed to assess cardiac ejection fraction in regular intervals as outlined in the Time and Events Table (Section 3.11). All assessments for an individual patient must be performed with the same modality (*i.e.,* ECHO or MUGA) and, preferably, by the same institution/operator, in order to reduce variability. Copies of all LVEF assessments and cardiology consultations performed on subjects who experience a >10% decrease in LVEF from baseline and whose cardiac ejection fraction is <institution's LLN will be required by Novartis for review. Instructions for submitting qualifying ECHOs/ MUGAs are provided in the Study Procedures Manual (SPM).

Dose modification guidance and stopping criteria for LVEF decrease are provided in Table 17. Additional guidelines for subjects enrolled at sites in France are provided in Appendix 5.

Table 17 Dose Modification Guidelines and Stopping Criteria for LVEF Decrease

Clinic Presentation	LVEF decrease (%) or CTCAE grade	Action and Dose Modification[d]
Asymptomatic	Absolute decrease of >10% in LVEF compared to baseline and ejection fraction below the institutional LLN	Interrupt trametinib and repeat ECHO/MUGA within 2 weeks[a] IF LVEF **recovers** within 4 weeks (defined as LVEF ≥LLN and absolute decrease ≤10% compared to baseline): • Consult with the Novartis Medical Lead and request approval for restart • If approved, restart trametinib reduced by one dose level[b] • Repeat ECHO/MUGA at 2, 4, 8, and 12 weeks after re-start; continue in 12 week intervals thereafter If LVEF **does not recover** within 4 weeks: • Consult with cardiologist • **Permanently discontinue trametinib** • **Report as SAE** • Repeat ECHO/MUGA after 2, 4, 8, 12 and 16 weeks or until resolution •
Symptomatic[c]	Grade 3: resting LVEF 39-20% or >20% absolute reduction from baseline Grade 4: resting LVEF <20%	Permanently discontinue trametinib Interrupt dabrafenib[d] **Report as SAE** Consult with cardiologist Repeat ECHO/MUGA after 2, 4, 8, 12 and 16 weeks or until resolution.

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

a. If ECHO/MUGA does not show LVEF recovery after 2 weeks, repeat ECHO/MUGA 2 weeks later.
b. If recurrent episodes of LVEF reduction occur in subjects receiving dabrafenib monotherapy, consult the Medical Lead.
c. Symptoms may include: dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema.
d. Once LVEF recovers to baseline, restarting dabrafenib monotherapy may be considered in consultation with the Novartis Medical Lead.

3.10.8. Monitoring and Management of Hypertension

Increases in blood pressure have been observed in subjects receiving trametinib. Recommendations for blood pressure monitoring and management are provided in Section 3.10.8.1 and Section 3.10.8.2, respectively.

3.10.8.1. Monitoring of Hypertension

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

- subject has been seated with back support, ensuring that legs are uncrossed and both feet are flat on the floor,
- subject has relaxed comfortably for at least 5 minutes prior to measurements,
- preparatory steps, such as removal of restrictive clothing over the cuff area and selection of the appropriate cuff size has been ensured,
- the arm is supported so that the middle of the cuff is at heart level, and
- the subject remains quiet and still during the measurement.

In subjects with an initial blood pressure reading within the hypertensive range, a second reading should be taken at least 1 minute after the initial reading, with the average of the 2 readings averaged to obtain a final blood pressure measurement. The averaged value should be recorded in the electronic Case Report Form (eCRF).

Persistent hypertension is defined as an increase of systolic blood pressure (SBP) to >140mm Hg and / or diastolic blood pressure (DBP) to >90mm Hg in up to 3 consecutive visits with blood pressure assessments from 2 readings under the optimal conditions described above. Visits to monitor increased blood pressure can be scheduled independently from the per-protocol visits outlined in the Time and Events Table (Section 3.11). Ideally, subsequent blood pressure assessments should be performed within 1 week.

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

3.10.8.2. Management of Hypertension

For subjects experiencing an increase in systolic and/or diastolic blood pressure that is persistent and may be associated with study drug(s), recommendations for the clinical management of hypertension are described in Table 18:

Table 18 Guidelines for Management of Hypertension

Hypertension	Action and Dose Modification
Scenario A: Asymptomatic and persistent[a] SBP ≥140mm Hg and <160mm Hg, or DBP ≥90mm Hg and <100mm Hg, or a clinically significant increase in DBP of 20mm Hg (but DBP still <100 mmHg).	Step 1: Continue study treatments at the current dose. Step 2: Adjust current or initiate new antihypertensive medication(s). Step 3: Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled[b] blood pressure. If BP is not well-controlled within 2 weeks, consider referral to a specialist and follow steps outlined for Scenario B.
Scenario B: Asymptomatic SPB ≥160mm Hg, or DBP ≥100mm Hg, or failure to achieve well-controlled BP within 2 weeks in Scenario A	Step 1: Interrupting study treatment(s)[d], if clinically indicated. Step 2: Adjust current or initiate new antihypertensive medication(s). Step 3: Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. Step 4: Once blood pressure (BP) is well-controlled[b], restart study treatment(s)[f] with **one dose level reduction**[c].
Scenario C: Symptomatic hypertension or Persistent[e] SBP ≥160mm Hg, or DBP ≥100mm Hg, despite modification of antihypertensive medication(s) and dose reduction of trametinib	Step 1: Interrupt study treatment(s)[f] Step 2: Adjust current or initiate new antihypertensive medication(s). Step 3: Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. Referral to a specialist for further evaluation and follow-up is also recommended. Step 4: Once BP is well-controlled[b], restart study treatment(s)[f] with **one dose level reduction**[c].
Scenario D: Refractory hypertension unresponsive to above interventions, or having hypertensive crisis	Discontinue administration of study treatment(s)[f] 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 subsequent visits.
b. Blood pressure of SBP ≤140 mm Hg and DBP ≤ 90 mm Hg in two separate readings during up to three consecutive visits.
c. Escalation of trametinib to previous dose level can be considered if BPs remain well-controlled for 4 weeks after restarting of trametinib. Approval from the Novartis Medical Lead is required.
d. 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
e. Persistent asymptomatic hypertension after initially successful anti-hypertensive intervention.
f. Modification to study treatment(s) should be discussed with the Novartis Medical Lead.

3.10.9. Guidelines for Prolonged QTc

Guidelines for dose modification and stopping criteria due to QTc prolongation are provided in Table 19. For subjects enrolled in France, please refer to Appendix 5 for QTc prolongation withholding and stopping criteria.

Table 19 Withholding and Stopping Criteria for QTc Prolongation

QTc Prolongation[a]	Action and Dose Modification
QTcB≥501msec	• Interrupt study treatment until QTcB prolongation resolves to Grade 1 or baseline • Test serum potassium, calcium, phosphorus and magnesium. If abnormal, correct per routine clinical practice to within normal limits. • Review concomitant medication for usage of agents that prolonged QTc. • If event resolves, restart study treatment at current dose level[b] • **If event does not resolve, permanently discontinue study treatments. Consider evaluation with cardiologist.** • **If event recurs, permanently discontinue study treatments. Consider evalution with cardiologist.**

Abbreviations: msec = milliseconds; QTcB = QT interval on electrocardiogram

a. Based on an average QTc value of triplicate electrocardiograms (ECGs). For example, if an ECG demonstrates a prolonged QT interval, obtain 2 more ECGs over a brief period, and then use the averaged QTc values of the 3 ECGs to determine if study treatments should be interrupted or discontinued.
b. If the QTc prolongation resolves to Grade 1 or baseline, the subject may resume study treatment if the investigator and the Novartis Medical Lead agree that the subject will benefit from further treatment.

3.10.10. Liver Chemistry Stopping Criteria

Liver chemistry threshold stopping criteria have been designed to assure subject safety and evaluate liver event etiology during administration of study treatment(s) and the follow-up period. Study treatment(s) will be stopped if any of the following liver chemistry stopping criteria is/are met:

1. Alanine aminotransferase (ALT) ≥3x upper limit of normal (ULN) AND bilirubin ≥2xULN (>35% direct bilirubin) (or ALT≥3xULN and international normalized ratio [INR]>1.5, if INR measured and subject not receiving warfarin therapy).

    - NOTE: If serum bilirubin fractionation is not immediately available, study drug 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 the appearance or worsening of symptoms of hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, 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 5 liver chemistry stopping criteria is met, do the following:

- Immediately discontinue investigational product(s).
- Report the event to Novartis within 24 hours of learning its occurrence.
- Complete the liver event eCRF 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 subjects receiving anticoagulants), termed 'Potential Hy's Law', must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
- Complete the liver imaging and/or liver biopsy CRFs if these tests are performed.
- Perform liver event follow up assessments, and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below.
- Follow-up for Overall Survival (OS) is required following permanent discontinuation from investigational product.
- Do not re-challenge with investigational product.

In addition, for **criterion 1**:

- Make every reasonable attempt to have subjects return to clinic within 24 hours for repeat liver chemistries, liver event follow up assessments (refer to Section 12), and close monitoring.
- A specialist or hepatology consultation is recommended.
- Monitor subjects twice weekly until liver chemistries (ALT, aspartate aminotransferase (AST), alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

In addition, for subjects meeting any of the **criteria 2 to 5**:

- Make every reasonable attempt to have subjects return to clinic within 24 to 72 hours for repeat liver chemistries and liver event follow up assessments (refer to Section 12).

- Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

3.10.11. Guidelines for Visual Changes or Specified Ophthalmic Examination Findings

Episodes of visual changes have been observed in subjects receiving trametinib, dabrafenib, and combination therapy. An ophthalmologist should be consulted if changes in vision develop. However, if the visual changes are clearly unrelated to study treatment (e.g., allergic conjunctivitis), then monitor closely as it may be reasonable to defer ophthalmic examination.

Treatment with dabrafenib has been associated with the development of uveitis, including iritis. Monitor patients for visual signs and symptoms (such as, change in vision, photophobia and eye pain) during therapy. Special attention should be given to retinal findings (e.g., retinal pigment epithelial detachment (RPED) or retinovascular abnormalities (i.e., branch or central retinal vein occlusions (RVO).

For events of visual changes (regardless of severity) for which an ophthalmic examination is conducted, a blood sample for PK analysis must be drawn as close as possible to the time of the event.

Guidelines regarding management and dose reduction for visual changes considered to be related to study treatment are provided in Table 20.

Table 20 Management and Dose Modification Guidelines for Visual Changes and/or Ophthalmic Examination Findings

CTCAE Grade[a]	Adverse Event Management	Action and Dose Modification
Grade 1 [b] .	• Consult ophthalmologist within 7 days of onset	• If dilated fundus examination cannot be performed within 7 days of onset, interrupt study treatment until RPED and RVO can be excluded by retinal specialist / ophthalmologist • if RPED and RVO excluded, continue (or restart) trametinib at same dose level • If RPED is suspected or diagnosed: see RPED dose modification Table 21 below; **report as SAE if diagnosed.** • If RVO diagnosed, **Permanently discontinue trametinib and report as SAE.**
Grade 2 and Grade 3	• Consult ophthalmologist immediately • Interrupt trametinib. If subject is receiving trametinib/dabrafenib combination therapy, dabrafenib may be discontinued.	• If RPED and RVO excluded, restart trametinib at same dose level • If RPED diagnosed: see RPED dose modification Table 21 below; **report as SAE**. • If RVO is diagnosed: **Permanently discontinue trametinib and report as SAE**
Grade 4	• Consult ophthalmologist immediately • Interrupt trametinib. . If subject is receiving trametinib/dabrafenib combination therapy, dabrafenib may be discontinued.	• If RPED and RVO excluded, may consider restarting trametinib at same or reduced dose after discussion with study the Medical Lead • **If RVO or RPED diagnosed, permanently discontinue study treatment**

Abbreviations: RPED = Retinal pigment epithelium detachment; 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.

Table 21 Recommended dose modifications for trametinib for retinal pigment epithelial detachments (RPED)[a]

CTCAE Grade	Action and Dose Modification
Grade 1 RPED (Asymptomatic; clinical or diagnostic observations only)	• Continue treatment with retinal evaluation monthly until resolution. If RPED worsens follow instructions below
Grade 2-3 RPED (Symptomatic with mild to moderate decrease in visual acuity; limiting instrumental ADL)	• Interrupt trametinib • Retinal evaluation monthly • If improved to ≤ Grade 1, restart trametinib at lower dose (reduced by 0.5 mg) or discontinue in patients taking trametinib 1 mg daily

a. Refers to CTCAE Version 4.0 'Retinopathy'

3.10.12. Supportive Care

3.10.12.1. Supportive Measures for Respiratory Symptoms

For Grade 2 or higher respiratory symptoms (i.e., cough, dyspnea, hypoxia, etc), evaluation by a CT scan is recommended.

3.10.12.2. Supportive Measures for Abdominal Pain or Suspected Pancreatitis

For adverse events of abdominal pain or suspected pancreatitis, amylase and lipase laboratory samples should be collected.

3.10.13. Pneumonitis/ Interstitial Lung Disease Management Guidelines

Pneumonitis/ILD has been observed in subjects receiving trametinib. To reduce the risk of pneumonitis/ILD, subjects will be monitored closely for symptoms, evaluated with imaging and functional tests. Dose modification and supportive care guidelines for pneumonitis/ILD are described in Table 22.

Table 22 Management and Dose Modification Guidelines for Pneumonitis/ILD

CTCAE Grade	Adverse Event Management	Action and Dose Modification
Grade 1	CT scan (high-resolution with lung windows) is recommended. Clinical evaluation and laboratory work-up for infection should be performed. Monitoring of oxygenation via pulse-oximetry is recommended. Consultation by a pulmonologist is recommended.	Continue dabrafenib and trametinib at current dose. Permanently discontinue panitumumab.
Grade 2	CT scan (high-resolution with lung windows) is recommended. Clinical evaluation and laboratory work-up for infection should be performed. Consult a pulmonologist. Pulmonary function testing should be performed; if < normal, repeat every 8 weeks until results are normal. Bronchoscopy with biopsy and/or bronchalveolar lavage (BAL) is recommended. Symptomatic therapy including corticosteroids is recommended if clinically indicated.	Interrupt dabrafenib and trametinib until recovery to ≤Grade 1. Permanently discontinue panitumumab. Restart dabrafenib and trametinib, **reduced by one dose level**. Escalation to previous dose level after 4 weeks and after consultation with the Novartis Medical Lead If symptoms do not recover to ≤Grade 1 within 4 weeks, **permanently discontinue dabrafenib and trametinib**.
Grade 3	CT scan (high-resolution with lung windows) should be performed. Clinical evaluation and laboratory work-up for infection should be performed. Consult a pulmonologist. Pulmonary function testing should be performed; if < normal, repeat every 8 weeks until results are normal. Bronchoscopy with biopsy and/or BAL if possible. Symptomatic therapy including corticosteroids is recommended if clinically indicated.	Interrupt dabrafenib and trametinib until recovery to ≤Grade 1. Permanently discontinue panitumumab. After consultation with the Novartis Medical Lead, dabrafenib and trametinib may be restarted with a one dose level reduction. If symptoms do not recover to ≤Grade 1 within 4 weeks, **permanently discontinue dabrafenib and trametinib**
Grade 4	Same as Grade 3.	Permanently discontinue dabrafenib, panitumumab and trametinib

3.11. Time and Events Tables

3.11.1. Part 1 Dose Escalation

	Screening[1]	**First Treatment Period (Day 1 through Day 28)**			**Continuation Phase**[2] **(±7 days)**	**Initial follow-up**[3] (14 days [±7 days] from last dose of study drugs)	**Secondary follow-up**[3]	
		Day 1	**Day 15 (± 2 days)**	**Day 21 (± 2 days)**			4 weeks (±7 days) after the last dose of panitumumab	8 weeks (±7 days) after the last dose of panitumumab
Informed Consent	X							
Archival tumor tissue or fresh tumor biopsy (BRAF mutation confirmation)[14]	X							
Tumor Biopsy (mandatory)[10]	X (pre-dose)[14]		X[11] (to be collected from Day 15 to Day 18)			X[12] (at progression)		
Demographics	X							
Medical history/ Interim History	X	X[6]			At Week 4, then every 4 weeks	X		
Concurrent medications	X	X[6]	X	X	At Week 4, then every 4 weeks	X		
Serum or urine pregnancy test (β-human chorionic gonadotropin [hCG]; women)[4]	X				Every 8 to 12 weeks[4]	X		
Complete physical examination[5]	X					X		
Brief physical examination[5]		X[6]	X		At Week 4, then every 4 weeks			

	Screening[1]	**First Treatment Period (Day 1 through Day 28)**			**Continuation Phase[2] (±7 days)**	**Initial follow-up[3]** (14 days [±7 days] from last dose of study drugs)	**Secondary follow-up[3]**	
		Day 1	**Day 15 (± 2 days)**	**Day 21 (± 2 days)**			4 weeks (±7 days) after the last dose of panitumumab	8 weeks (±7 days) after the last dose of panitumumab
Dermatological examination[7]	X				At Week 4, then every 8 weeks More frequently if there are new or changing lesions	X		
Height (at screening only) and weight	X	X			Weight: At Week 4, then every 4 weeks	X		
Ophthalmic examination	X				At Week 4, then as symptomatically warranted	X		
Eastern Cooperative Oncology Group (ECOG) Performance Status	X	X[6]			At Week 4, then every 4 weeks	X		
Vital signs (BP, HR, Body Temperature)	X	X[15]	X[15]	X	X[15]	X		
12-lead ECG[8]	X	X[6]	X	X	At Week 4, then every 4 weeks until Week 24, then every 8 weeks	X		
Hematology/Clinical Chemistry	X	X[6]	X	X	At Week 4, then every 4 weeks until Week 24, then every 8 weeks	X	X[3]	X[3]
Coagulation Repeat as clinically indicated	X							
CEA	X	X[6]	X	X	At Week 4, then every 4 weeks until Week 24, then every 8 weeks	X	X[3]	X[3]
ECHO (or MUGA)[18]	X				At Week 4, then at Week 12 and every 12 weeks thereafter	X		

	Screening[1]	First Treatment Period (Day 1 through Day 28)			Continuation Phase[2] (±7 days)	Initial follow-up[3]	Secondary follow-up[3]	
		Day 1	Day 15 (± 2 days)	Day 21 (± 2 days)		(14 days [±7 days] from last dose of study drugs)	4 weeks (±7 days) after the last dose of panitumumab	8 weeks (±7 days) after the last dose of panitumumab
Collection of blood PK samples[9]		X	X	X	X[9]	X[9] (at progression)		
[redacted]								
Panitumumab dosing[15]		X	X		X Every 2 weeks			
Dabrafenib and trametinib dosing		CONTINUOUS daily dosing; Dabrafenib BID and trametinib once daily should be administered under fasting conditions, either one hour before a meal or 2 hours after a meal.						
AE assessment		CONTINUOUS						
Urinalysis	X	X[6]				X		
Disease Assessment[13]	X				Every 6 weeks until Week 24, then every 8 weeks	X[13]	X[17]	
Long-term survival follow-up								X[19]

AE, Adverse Event; BP, blood pressure; CEA, ; ECHO, echocardiogram; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; HR, heart rate; MUGA,

1. **SCREENING WINDOW**: All screening assessments must be completed within 14 days prior to first dose except informed consent, ophthalmology exam, dermatology exam. ECHO/MUGA and Disease Assessment, which can occur within 35 days prior to the first dose. Note: Procedures conducted as part of the subject's routine clinical management (e.g., blood counts, imaging study) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures meet the protocol requirements.
2. **TREATMENT PHASE**: Assessments throughout the study are calendar-based starting from the first day of dosing (Day 1) in the first treatment period. Dose interruptions should not alter the assessment schedule for any subsequent treatment period. The Continuation Phase starts with Day 29; events in the Continuation Phase are allowed ±7 days from projected date. Safety lab tests (chemistry/hematology/coag/UA) may be done the day before the visit so that results are ready on the day of the visit, but all assessments should be done within the ±7 day window.
3. **FOLLOW-UP VISIT**: Initial follow-up visit should be 14 days from last dose of study drugs (±7 days). If a subject is unable to return to the clinic due to hospitalization, site staff are encouraged to telephone the subject for assessment of AEs. Secondary follow-up visits should occur at 4 weeks and 8 weeks after the last dose of panitumumab.
4. **PREGNANCY TEST**: Serum pregnancy test should be performed at screening; all subsequent pregnancy tests may be either serum or urine, and performed every 8 to 12 weeks.
5. **PHYSICAL EXAMINATION**: Complete physical examination must include integument and genitalia. Note: pelvic exam in female subjects may be completed up to 24 weeks prior to date of first dose. Complete and brief physical examinations are defined in Section 6.2.
6. **DAY1 ASSESSMENTS**: If within 72 hours of Screening, this assessment does not need to be repeated on Day 1.
7. **DERMALOGICAL EVALUATION**: Baseline skin photography should be performed at Screening. Photographs should be taken of new skin lesions that occur, or skin lesions that change on therapy. Refer to Section 6.2. French sites will perform dermatological exams monthly while on-therapy, and monthly for 6 months following discontinuation of dabrafenib or until initiation of another anti-neoplastic therapy, whichever comes first. Refer to Appendix 7 for full information.
8. **ECG**: Single ECGs will be collected prior to dosing.
9. **PHARMACOKINETIC SAMPLES**: Blood samples (4 mL) for PK analysis of dabrafenib and metabolites (hydroxy-dabrafenib and desmethyl-dabrafenib) and trametinib will be collected on Day 1 and on Day 15 predose (within 30 minutes of dosing) and at 1, 2, 4, 6,and 8 hours after administration. Blood samples (4 mL) for PK analysis of panitumumab will be collected on Day 1 and Day 15 predose (within 30 minutes of dosing panitumumab) and at 1 hour (end of infusion of panitumumab). A single 4 mL blood sample for analysis of panitumumab will be collected pre-dose on Day 21 during the clinic visit. During the continuation phase, PK samples will be collected pre-dose at Week 8, Week 12, Week 16, and Week 20. PK blood samples for dabrafenib, trametinib, and panitumumab analysis should be collected along with the tumor biopsy taken at progression. On days when serial PK samples are collected, subjects should be instructed to hold doses of dabrafenib and trametinib, report to the clinic for the predose PK blood draw, then dose with dabrafenib and trametinib. Collect PK samples at the time indicated ± 5 minutes up to 2 hour sample, ± 20 minutes up to the 8 hour sample. On all days when a PK sample is collected, date and time of PK sample, date and time of the last doses of dabrafenib, trametinib, and panitumumab prior to the predose PK samples, and the date and time of the doses dabrafenib, trametinib, and panitumumab administered in the clinic must be recorded
10. **BIOPSY**: Pre- and post-dose tumor biopsies are mandatory. If the patient's tumors are inaccessible for biopsy, permission to enroll must be granted by the Novartis Medical Lead.
11. **BIOPSY**: Collection of on-treatment tumor biopsy for subjects with accessible tumors. On-treatment biopsy may be collected 2 to 4 hours after dosing with oral study medication'from Day 15 to Day 18 (+3 days). Biopsies should be performed on non-target lesions when possible. PK samples for dabrafenib, trametinib and panitumumab analysis will be collected at the time of the post-dose tumor biopsy (±24 hours) (unless the post-dose biopsy occurs on the same day that the Day 15 serial PK samples are collected).
12. **BIOPSY**: Tumor biopsy at tumor progression in subjects who have had a radiologic response (20% or more) or had a stable disease for 6 months is highly encouraged. .
13. **DISEASE ASSESSMENT**: CT is the preferred method to measure lesions selected for response assessment. Refer to Appendix 4 for additional information regarding Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 methodology and criteria. Follow-up disease assessment results for subjects who discontinue study medication for any other reason than progression or death. Even if study treatment is withdrawn, radiographic disease assessments (computed tomography [CT] or magnetic resonance imaging

[MRI], as appropriate according to the method used at baseline) should continue every 8 weeks until documented disease progression, the start of new anti-cancer therapy, withdrawal of consent or death.

14. **TUMOR TISSUE SAMPLE**: Collection of archived tumor tissue or fresh tumor biopsies and determination of the subject's tumor BRAF mutation status is required for enrollment; if a fresh tumor biopsy is collected during screening and up to prior to dosing on Day 1 for BRAF mutation confirmation, this tissue may be used for the day 1/ predose tumor biopsy. [redacted] The Day 1/predose tumor biopsy may be collected at any point after signing consent, after completing wash-out from prior therapies (either 5 half-lives or 14 days from last dose of prior therapy)..
15. **VITAL SIGNS**: Vital signs and temperature should be measured within 30 minutes prior to initiation and upon completion of the panitumumab infusion (up to 15 minutes after the end of infusion).
16. [redacted]
17. After study treatment is withdrawn, disease assessments (the method used at baseline) should continue every 8 weeks until documented disease progression, the start of new anti-cancer therapy, withdrawal of consent, or death.
18. **ECHO**: ECHO is preferred. MUGA may be used only if ECHO is not available. The same method must be used consistently from screening throughout the study.
19. **OVERALL SURVIVAL**: Subjects will be followed for Overall Survival every 8 weeks after last dose of study drugs. See Section 6.3.1.for additional information.

3.11.2. Part 2 Expansion Cohorts

	Screening[1]	**First Treatment Period (Day 1 through Day 28)**		**Continuation Phase[2] (±7 days)**	**Initial Follow-up[3]**	**Secondary Follow-up[3]**	
		Day 1	**Day 15 (± 2 days)**			4 weeks (±7 days) after the last dose of panitumumab	8 weeks (±7 days) after the last dose of panitumumab
Informed Consent	X						
Archival tumor tissue or fresh tumor biopsy (BRAF mutation confirmation)[12]	X						
Tumor tissue biopsy (mandatory)[9]	X (pre-dose)[12]		X (to be collected from Day 15 to Day 18)[10]		X[13] (at progression)		
Demographics	X						
Medical history/ Interim History	X	X[5]		At Week 4, then every 4 weeks	X		
Concurrent Medications	X	X[5]	X	At Week 4, then every 4 weeks	X		
Serum or urine pregnancy test (β-hCG; women)[4]	X			Every 8 to 12 weeks[4]	X		
Complete physical examination[6]	X				X		
Brief physical examination[6]		X[5]	X	At Week 4, then every 4 weeks			

	Screening[1]	**First Treatment Period (Day 1 through Day 28)**		**Continuation Phase[2] (±7 days)**	**Initial Follow-up[3]**	**Secondary Follow-up[3]**	
		Day 1	**Day 15 (± 2 days)**			4 weeks (±7 days) after the last dose of panitumumab	8 weeks (±7 days) after the last dose of panitumumab
Dermatological examination[7]	X			At Week 4, then every 8 weeks More frequently if there are new or changing lesions	X		
Height (at screening only) and weight	X			Weight: At Week 4, then every 4 weeks	X		
Ophthalmic examination	X			at Week 4, then as symptomatically warranted	X		
ECOG Performance Status	X	X[5]		At Week 4, then every 4 weeks	X		
Vital signs (BP, HR, Body Temperature)	X	X[15]	X[15]	X[15]	X		
12-lead ECG[8]	X	X[5]	X	At Week 4, then every 4 weeks until Week 24, then every 8 weeks	X		
Hematology/Clinical Chemistry)	X	X[5]	X	At Week 4, then every 4 weeks until Week 24, then every 8 weeks	X[3]	X[3]	X[3]
Coagulation Repeat as clinically indicated	X						
CEA	X			At Week 6, then every 6 weeks until Week 24, then every 8 weeks	X[3]	X[3]	X[3]

	Screening[1]	First Treatment Period (Day 1 through Day 28)		Continuation Phase[2] (±7 days)	Initial Follow-up[3]	Secondary Follow-up[3]	
		Day 1	Day 15 (± 2 days)			4 weeks (±7 days) after the last dose of panitumumab	8 weeks (±7 days) after the last dose of panitumumab
ECHO (or MUGA)[18]	X			At Week 4, then at Week 12 and every 12 weeks thereafter	X		
Pharmacokinetics collection: blood		X[11]	X[10,11]	Predose; At Week 4[11]	X[11](at progression)		
[redacted]							
Panitumumab dosing[15]		X	X	X Every 2 weeks			
Dabrafenib and trametinib dosing		CONTINUOUS daily dosing; Dabrafenib BID and trametinib once daily should be administered under fasting conditions, either one hour before or 2 hours after a meal.					
Urinalysis	X	X[5]			X		
AE assessment		CONTINUOUS					
Disease Assessment[14]	X			Every 6 weeks until Week 24, then every 8 weeks	X[14]	X[17]	
[redacted]							

	Screening[1]	First Treatment Period (Day 1 through Day 28)		Continuation Phase[2] (±7 days)	Initial Follow-up[3]	Secondary Follow-up[3]	
		Day 1	Day 15 (± 2 days)			4 weeks (±7 days) after the last dose of panitumumab	8 weeks (±7 days) after the last dose of panitumumab
Long-term survival follow-up							X[20]

AE, Adverse Event; BP, blood pressure; CEA, ; ECHO, echocardiogram; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; HR, heart rate; MUGA,

1. **SCREENING**: All screening assessments must be completed within 14 days prior to first dose except informed consent, ophthalmic exam, dermatological exam, ECHO/MUGA, and Disease Assessment, which can occur within 35 days prior to the first dose. Note: Procedures conducted as part of the subject's routine clinical management (e.g., blood counts, imaging study) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures meet the protocol requirements.
2. **TREATMENT PHASE**: Assessments throughout the study are calendar-based starting from the first day of dosing (Day 1) in the first treatment period. Dose interruptions should not alter the assessment schedule for any subsequent treatment period. The Continuation Phase starts with Day 29; events in the Continuation Phase are allowed ±7 days from projected date. Safety lab tests (chemistry/hematology/coag/UA) may be done the day before the visit so that results are ready on the day of the visit, but all assessments should be done within the ±7 day window.
3. **FOLLOW-UP VISIT**: Initial follow-up visit should be 14 days from last dose of study drugs (±7 days). If a subject is unable to return to the clinic due to hospitalization, site staff are encouraged to telephone the subject for assessment of AEs. Secondary follow-up visits should occur at 4 weeks and 8 weeks after the last dose of panitumumab. Subjects are to be followed until progression for collection of PFS data and until death for collection of overall survival (OS) data. If a subject who is eligible for crossover to the triplet combination has not crossed over by 14 days past the last dose of study treatment, the Initial Follow-Up assessments should be done. If a subject who is eligible for crossover to the triplet combination has not crossed over by 4 weeks past the last dose of panitumumab, the Secondary Follow-Up assessments should be done.
4. **PREGNANCY TEST**: Serum pregnancy test should be performed at screening; all subsequent pregnancy tests may be either serum or urine, and performed every 8 to 12 weeks.
5. **PHYSICAL EXAM**: If within 72 hours of Screening, this assessment does not need to be repeated on Day 1.
6. **PHYSICAL EXAM**: Complete physical examination must include integument and genitalia. Note: pelvic exam in female subjects may be completed up to 24 weeks prior to date of first dose. Complete and brief physical examinations are defined in Section 6.2.
7. **DERMALOGICAL EVALUATION**: Baseline skin photography should be performed at Screening. Photographs should be taken of new skin lesions that occur, or skin lesions that change on therapy. Refer to Section 6.2. French sites will perform dermatological exams monthly while on-therapy, and monthly for 6 months following discontinuation of dabrafenib or until initiation of another anti-neoplastic therapy, whichever comes first. Refer to Appendix 7 for full information
8. **ECG**: Single ECGs will be collected prior to dosing.
9. **BIOPSY**: Pre- and post-dose tumor biopsies are mandatory. If the patient's tumors are inaccessible for biopsy, permission to enroll must be granted by the Novartis Medical Lead.
10. **BIOPSY**: Collection of on-treatment tumor biopsy for subjects with accessible tumors. On-treatment biopsy may be collected 2 to 4 hours after dosing with oral study medication'from Day 15 to Day 18 (+3 days). Biopsies should be performed on non-target lesions when possible. A single PK samples for dabrafenib, trametinib, and

panitumumab will be collected at the time of the post-dose tumor biopsy (±24 hours) (unless the post-dose biopsy occurs on the same day that the Day 15 serial PK samples are collected).

11. **PHARMACOKINETIC SAMPLES**: Blood samples (4 mL) for PK analysis of dabrafenib and metabolites (hydroxy-dabrafenib and desmethyl-dabrafenib) and trametinib will be collected on Day 1 and Day 15 predose (within 30 minutes of dosing) and at 1, 2, 4, 6,and 8 hours after administration. Blood samples (4 mL) for PK analysis of panitumumab will be collected on Day 1 and Day 15 predose (within 30 minutes of dosing panitumumab) and at 1 hour (end of infusion of panitumumab). A single 4 mL blood sample for analysis of panitumumab will be collected predose at the Week 4 clinic visit. On days when serial PK samples are collected, subjects should be instructed to hold doses of dabrafenib and trametinib, report to the clinic for the predose PK blood draw, then dose with dabrafenib and trametinib. Collect PK samples at the time indicated ± 5 minutes up to 2 hour sample, ± 20 minutes up to the 8 hour sample. On all days when PK samples are collected, date and time of the PK sample(s), date and time of the last doses of dabrafenib, trametinib, and panitumumab prior to the predose PK sample, and date and time of the dose of dabrafenib, trametinib, and panitumumab in the clinic must be recorded. A single blood sample for dabrafenib, trametinib, and panitumumab analysis should be collected along with the tumor biopsy taken at progression.
12. **TUMOR TISSUE SAMPLE**: Collection of archived tumor tissue or fresh tumor biopsies and determination of the subject's tumor BRAF mutation status is required for enrollment; if a fresh tumor biopsy is collected during screening and up to prior to dosing on Day1 for BRAF mutation confirmation, this tissue may be used for the day 1/ predose tumor [redacted] The Day 1/predose tumor biopsy may be collected at any point after signing consent, after completing wash-out from prior therapies (either 5 half-lives or 14 days from last dose of prior therapy).
13. **BIOPSY AT PROGRESSION**: Optional tumor biopsy for subjects who had a radiologic response (20% or more decrease) or had a stable disease for 6 months at disease progression (if feasible). A single PK sample will be collected at the time of tumor progression Refer to Section 6.7.2.
14. **DISEASE ASSESSMENT**: CT is the preferred method to measure lesions selected for response assessment. Refer to Appendix 4 for additional information regarding RECIST 1.1 methodology and criteria. Even if study treatment is withdrawn, radiographic disease assessments (CT or MRI, as appropriate according to the method used at baseline) should continue every 8 weeks until documented disease progression, the start of new anti-cancer therapy, withdrawal of consent or death.
15. **VITAL SIGNS**: Vital signs and temperature should be measured within 30 minutes prior to initiation and upon completion of the panitumumab infusion (up to 15 minutes after the end of infusion).

[redacted]

17. **DISEASE ASSESSMENT**: After study treatment is withdrawn, disease assessments (the method used at baseline) should continue every 8 weeks until documented disease progression, the start of new anti-cancer therapy, withdrawal of consent, or death.
18. **ECHO**: ECHO is preferred. MUGA may be used only if ECHO is not available. The same method must be used consistently from screening throughout the study.

[redacted]

20. **OVERALL SURVIVAL**: Subjects will be followed for Overall Survival every 8 weeks after last dose of study drugs. See Section 6.3.1.for additional information.

3.11.3. Part 3 Randomized Phase 2

	Screening[1]	Treatment				Follow-up[3]
		Day 1	Every 4 weeks[2] (± 3 days)	Every 8 weeks[2] (± 7 days)	Every 12 weeks[2] (± 7 days)	Treatment discontinuation (± 7 days)
Informed Consent	X					
Archival tissue or fresh biopsy[9]	X					
Demographics	X					
Medical history/ Interim History	X	X[5]	X			X
Concurrent medications	X	X[5]	X			X
Serum or urine pregnancy test (β-hCG; women)[4]	X	X[5]		X[4]	X[4]	X
Complete physical examination[6]	X					X
Brief physical examination[6]		X[5]	X			
Dermatological examination[7]	X		X[7]	X[7]		X
Height (at screening only) and weight	X	X[5]	X		X	X
Ophthalmic examination[12]	X		X[12]			X
ECOG Performance Status	X	X[5]	X			X
Vital signs (BP, HR, Body Temperature)	X	X[10]	X[10]	X[10]	X[10]	X
12-lead ECG[8]	X	X[5]	X		X	X
Hematology/Clinical	X	X[5]	X[13]	X[13]	X	X[3]

	Screening[1]	Treatment				Follow-up[3]
		Day 1	Every 4 weeks[2] (± 3 days)	Every 8 weeks[2] (± 7 days)	Every 12 weeks[2] (± 7 days)	Treatment discontinuation (± 7 days)
Chemistry						
Coagulation Repeat as clinically indicated	X					
CEA	X	X[5]	X[13]	X[13]	X	X[3]
ECHO[14]	X		X[14]		X[14]	X
[redacted]						
Tumor tissue biopsy (Optional)[16]						X (at progression)
Panitumumab dosing		X	X Every two weeks	X Every two weeks	X Every two weeks	
Dabrafenib and trametinib dosing		CONTINUOUS daily dosing; Dabrafenib BID and trametinib once daily should be administered under fasting conditions, either one hour before or 2 hours after a meal.				
Urinalysis	X	X[5]	X			
AE assessment		CONTINUOUS				
Disease Assessment[11]	X				Every 6 weeks until Week 24, then every 8 weeks	X[11]
[redacted]						

AE, Adverse Event; BP, blood pressure; CEA, ; ECHO, echocardiogram; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; HR, heart rate; MUGA,

1. All screening assessments must be completed within 14 days prior to first dose except informed consent, ophthalmic exam, dermatological exam, ECHO and Disease Assessment, which can occur within 35 days prior to the first dose. Note: Procedures conducted as part of the subject's routine clinical management (e.g., blood counts, imaging study) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures meet the protocol requirements.
2. Assessments throughout the study are calendar-based starting from the first day of dosing (Day 1) in the first treatment period. Dose interruptions should not alter the assessment schedule for any subsequent treatment period. Events in the continuation phase are allowed ±7 days from projected date. Safety lab tests (chemistry/hematology/coag/UA) can be done the day before the visit so the results are available on the day of the visit.
3. Follow-up visit should be 14 days from last dose of study drugs (±7 days). If a subject is unable to return to the clinic due to hospitalization, site staff are encouraged to telephone the subject for assessment of AEs. If possible, subjects should return at 8 weeks after the last dose of panitumumab to evaluate for electrolyte disturbances.
4. Serum pregnancy test should be performed at screening; all subsequent pregnancy tests may be either serum or urine and should be performed every 8 to 12 weeks.
5. If within 72 hours of Screening, this assessment does not need to be repeated on Day 1.
6. Complete physical examination must include integument and genitalia. Note: pelvic exam in female subjects may be completed up to 24 weeks prior to date of first dose. Complete and brief physical examinations are defined in Section 6.2. A brief physical examination should be performed every 4 weeks.
7. Baseline skin photography should be performed at Screening. Photographs should be taken of new skin lesions that occur, or skin lesions that change on therapy. Refer to Section 6.2. The dermatology examination should be performed at Week 4, then every 8 weeks; the examination may be performed more frequently if there are new or changing lesions. French sites will perform dermatological exams monthly while on-therapy, and monthly for 6 months following discontinuation of dabrafenib or until initiation of another anti-neoplastic therapy, whichever comes first. Refer to Appendix 7 for full information
8. Single ECGs will be collected at Week 4 then at Week 12, Week 24, and every 12 weeks thereafter.
9. Collection of archived tumor tissue or fresh tumor biopsies and central confirmation of the subject's tumor BRAF mutation status is required prior to enrollment.
10. Vital signs and temperature should be measured within 30 minutes prior to initiation and upon completion of the panitumumab infusion (up to 15 minutes after the end of infusion).
11. CT is the preferred method to measure lesions selected for response assessment. Refer to Appendix 4 for additional information regarding RECIST 1.1 methodology and criteria. Even if study treatment is withdrawn, radiographic disease assessments (CT or MRI, as appropriate according to the method used at baseline) should continue every 8 weeks until documented disease progression, the start of new anti-cancer therapy, withdrawal of consent or death.
12. Subjects are required to have a standard ophthalmic exam (including baseline color fundus photographs) performed by an ophthalmologist at baseline, at Week 4 and as clinically warranted per protocol's guidance (refer to Section 6.2). The exam will include indirect fundoscopic examination, visual acuity (corrected), visual field examination, tonometry, and direct fundoscopy, with special attention to retinal abnormality that are predisposing factors for RVO or RPED.
13. Hematology/Clinical chemistries should be assessed at baseline, then again at Week 4, then every 8 weeks.
14. LVEF should be assessed by ECHO at Week 4 then at Week 12, Week 24, and every 12 weeks thereafter. ECHO is the preferred method; MUGA may be used only if ECHO is not available. The same method must be used consistently from screening throughout the study

[redacted]

16. Optional tumor biopsy for subjects who had a radiologic response (20% or more decrease) or had a stable disease for 6 months at disease progression. The biopsy at progression is highly encouraged.

[redacted]

3.11.4. Part 4 Dose Escalation and Cohort Expansion

Day:	**Screening[1]**	**First treatment period Day 1 thru Day 28**			**Continuation phase[2]**	**Initial follow-up[3]**	**Secondary follow-up[3]**	**Tertiary follow-up[3]**
Visit Window (relative to Day 1)	**-14 to -1 days**	**on Day 1**	**on Day 15 (± 2 days)**	**On Day 21 (± 2 days)**	**±7 days**	**14 (±7) days from last dose of trametinib**	**4 weeks (±7 days) after the last dose of panitumumab**	**8 weeks (±7 days) after the last dose of panitumumab**
Informed Consent	X[1]							
Demographics	X							
Collection of archival tissue[14]	X[1]							
Complete physical[5]	X[1]					X		
Brief physical[5]		X	X		At Week 4, then every 4 wks			
Medical/medication/ drug/alcohol history	X	X[6]			X	X		
Concurrent medications	X	X	X		At Week 4, then every 4 weeks	X	X	
12-lead ECG[7]	X	X[6]	X	X	At Week 4, then every 4 weeks until Week 24, then every 8 weeks	X		
Vital signs[13] (including weight)	X	X	X	X	X[13]	X		
Height	X							
Ophthalmic examination	X[1]				At Week 4, then as symptomatically warranted			
ECOG	X	X[6]			At Week 4, then every 4 wks	X		

Day:	**Screening[1]**	**First treatment period Day 1 thru Day 28**			**Continuation phase[2]**	**Initial follow-up[3]**	**Secondary follow-up[3]**	**Tertiary follow-up[3]**
Visit Window (relative to Day 1)	**-14 to -1 days**	**on Day 1**	**on Day 15 (± 2 days)**	**On Day 21 (± 2 days)**	**±7 days**	**14 (±7) days from last dose of trametinib**	**4 weeks (±7 days) after the last dose of panitumumab**	**8 weeks (±7 days) after the last dose of panitumumab**
ECHO/MUGA[16]	X[1]				At Week 4, then at Week 12, then every 12 weeks	X		
Serum or urine pregnancy test (β-hCG;women)[4]	X				Every 8 to 12 weeks[4]			
Hematology/Clinical Chemistry	X	X[6]			At Week 4, then every 4 weeks until Week 24, then every 8 weeks		X	X
Urinalysis	X	X[6]				X		
Coagulation Repeat as clinically indicated	X[1]							
CEA	X				At Week 6, then every 6 weeks until Week 24, then every 8 weeks		X	X
Tumor biopsy[9]	X (pre-dose)[9]		X[9] (to be collected from Day 15 to Day 18)			X[11] (at progression)		
[redacted]								

Day:	**Screening[1]**	**First treatment period Day 1 thru Day 28**			**Continuation phase[2]**	**Initial follow-up[3]**	**Secondary follow-up[3]**	**Tertiary follow-up[3]**
Visit Window (relative to Day 1)	**-14 to -1 days**	**on Day 1**	**on Day 15 (± 2 days)**	**On Day 21 (± 2 days)**	**±7 days**	**14 (±7) days from last dose of trametinib**	**4 weeks (±7 days) after the last dose of panitumumab**	**8 weeks (±7 days) after the last dose of panitumumab**
[redacted]								
AE assessment		CONTINUOUS						
PK blood sample[8]		X	X	X	X			
Panitumumab Dosing		X	X		X every 2 weeks			
Trametinib dosing		CONTINUOUS daily dosing; Trametinib once daily should be administered under fasting conditions, either one hour before or 2 hours after a meal.						
Disease assessments[12]	X[1]				Every 6 weeks until Week 24, then every 8 weeks. [15]			
[redacted]								
Long-term survival follow-up								X[18]

AE, Adverse Event; BP, blood pressure; CEA, ; ECHO, echocardiogram; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; HR, heart rate; MUGA,

1. **SCREENING ASSESSMENTS**: All screening assessments must be completed within 14 days prior to first dose except informed consent, ophthalmology exam, dermatological exam, ECHO/MUGA and Disease Assessment, which can occur within 35 days prior to the first dose. Note: Procedures conducted as part of the subject's routine clinical management (e.g., blood counts, imaging study) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures meet the protocol requirements.
2. **TREATMENT PERIOD**: Assessments throughout the study are calendar-based starting from the first day of dosing (Day 1) in the first treatment period. Dose interruptions should not alter the assessment schedule for any subsequent treatment period. The Continuation Phase starts with Day 29; events in the continuation phase are allowed ± 7 days from projected date. Safety lab tests (chemistry/hematology/UA) may be done the day before the visit so that results are available on the day of the visit, but all assessments should be done within the ±7 day window.
3. **FOLLOW-UP VISIT**: Initial follow-up visit should be 14 days (±7 days) from last dose of trametinib. If a subject is unable to return to the clinic due to hospitalization, site staff are encouraged to telephone the subject for assessment of AEs. Secondary follow-up visits should occur at 4 weeks and 8 weeks after the last dose of panitumumab. Subjects are to be followed until progression for collection of PFS data and until death for collection of overall survival (OS) data. If a subject who is eligible for crossover to the triplet combination has not crossed over by 14 days past the last dose of study treatment, the Initial Follow-Up assessments should be done. If a subject who is eligible for crossover to the triplet combination has not crossed over by 4 weeks past the last dose of panitumumab, the Secondary Follow-Up assessments should be done.
4. **PREGNANCY TEST**: Serum pregnancy test should be performed at screening; all subsequent pregnancy tests may be either serum or urine, and performed every 8 to 12 weeks.
5. **PHYSICAL EXAMINATION**: Complete physical examination must include integument. Note: pelvic exam in female subjects is not required in Part 4. Complete and brief physical examinations are defined in Section 6.2.
6. **PHYSICAL EXAMINATION**: If within 72 hours of Screening, this assessment does not need to be repeated on Day 1.
7. **ECG**: Single ECGs will be collected prior to dosing.
8. **PHARMACOKINETIC SAMPLES**: Blood samples (2 mL) for PK analysis of trametinib will be collected on Day 1 and on Day 15 predose (within 30 minutes of dosing) and at 1, 2 and 4 hours after administration. Blood samples (4 mL) for PK analysis of panitumumab will be collected on Day 1 and on Day 15 predose (within 30 minutes of dosing with panitumumab) and at 1 hour (at the end of infusion of panitumumab). A single 4 mL blood sample for analysis of panitumumab will be collected pre-dose on Day 21 during the clinic visit. During the continuation phase, PK samples (for trametinib and panitumumab) will be collected pre-dose at Week 8, Week 12, Week 16, and Week 20. PK blood samples for trametinib, and panitumumab analysis should be collected along with the tumor biopsy taken at progression. On days when serial PK samples are collected, subjects should be instructed to hold doses of trametinib, report to the clinic for the predose PK blood draw, then dose with trametinib. Collect PK samples at the time indicated ±5 minutes up to 2 hour sample, ±20 minutes up to the 4 hour sample.
9. **TUMOR TISSUE SAMPLE/DAY1**: Collection of archived tumor tissue or fresh tumor biopsies and determination of the subject's tumor BRAF mutation status is required for enrollment; if a fresh tumor biopsy is collected during screening and up to prior to dosing on Day1 for BRAF mutation confirmation, this tissue may be used for the day 1/ predose tumor biopsy. [redacted] The Day 1/predose tumor biopsy may be collected at any point after signing consent, after completing wash-out from prior therapies (either 5 half-lives or 14 days from last dose of prior therapy). Pre- and post-dose tumor biopsies are mandatory. If the patient's tumors are inaccessible for biopsy, permission to enroll must be granted by the Novartis Medical Lead.
10. **BIOPSY**: Collection of on-treatment tumor biopsy for subjects with accessible tumors. On-treatment biopsy may be collected 2 to 4 hours after dosing with oral study medication from Day 15 to Day 18. Biopsies should be performed on non-target lesions when possible. PK samples for trametinib and panitumumab analysis will be collected at the time of the post-dose tumor biopsy (±24 hours) (unless the post-dose biopsy occurs on the same day that the Day 15 serial PK samples are collected).
11. **BIOPSY**: Tumor biopsy at tumor progression in subjects who have had a response is highly encouraged. PK blood samples for trametinib and panitumumab analysis should be collected along with the tumor biopsy taken at progression.
12. **DISEASE ASSESSMENT**: CT is the preferred method to measure lesions selected for response assessment. Refer to Appendix 4 for additional information regarding Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 methodology and criteria. Even if study treatment is withdrawn, radiographic disease assessments (computed

tomography [CT] or magnetic resonance imaging [MRI], as appropriate according to the method used at baseline) should continue every 8 weeks until documented disease progression, the start of new anti-cancer therapy, withdrawal of consent or death.

13. **VITAL SIGNS**: Vital signs and temperature should be measured within 30 minutes prior to initiation and upon completion of the panitumumab infusion (up to 15 minutes after the end of infusion).

15. **DISEASE ASSESSMENT**: After study treatment is withdrawn, disease assessments (the method used at baseline) should continue every 8 weeks until documented disease progression, the start of new anti-cancer therapy, withdrawal of consent, or death.
16. **ECHO**: ECHO is preferred. MUGA may be used only if ECHO is not available. The same method must be used consistently from screening throughout the study.

18. **OVERALL SURVIVAL**: Subjects will be followed for Overall Survival every 8 weeks after last dose of study drugs. See Section 6.3.1.for additional information.

3.11.5. Intra-subject Doublet to Triplet Crossover

	Crossover Screening[1]	Crossover Day 1	Crossover Treatment Phase[2] (±7 days)	Initial Follow-up[3]	Secondary Follow-up[3]	
					4 weeks (±7 days) after the last dose of panitumumab	8 weeks (±7 days) after the last dose of panitumumab
Medical history/ Interim History	X		Every 4 weeks	X		
Concurrent Medications		X	At Week 4, then every 4 weeks	X		
Serum or urine pregnancy test (β-hCG; women)			Every 8 to 12 weeks	X		
Physical examination[4]	X		Every 4 weeks	X[4]		
Dermatological examination[5]	X		At Week 4, then every 8 weeks More frequently if there are new or changing lesions	X		
Weight	X		Every 4 weeks	X		
Ophthalmic examination	X		at Week 4, then as symptomatically warranted	X		
ECOG Performance Status	X		Every 4 weeks	X		
Vital signs (BP, HR, Body Temperature)	X	X[6]	Before and after panitumumab infusion[6]	X		
12-lead ECG	X		At Week 4, then every 4 weeks until Week 24, then every 8 weeks	X		
Hematology/Clinical Chemistry)	X		At Week 4, then every 4 weeks until Week 24, then every 8 weeks	X	X	X
Coagulation			As clinically indicated			

	Crossover Screening[1]	Crossover Day 1	Crossover Treatment Phase[2] (±7 days)	Initial Follow-up[3]	Secondary Follow-up[3]	
					4 weeks (±7 days) after the last dose of panitumumab	8 weeks (±7 days) after the last dose of panitumumab
CEA	X		At Week 6, then every 6 weeks until Week 24, then every 8 weeks	X	X	
ECHO (or MUGA)[7]	X		At Week 4, then at Week 12 and every 12 weeks thereafter	X		
[redacted]						
Panitumumab dosing[6]		X	Every 2 weeks			
Dabrafenib and trametinib dosing		CONTINUOUS daily dosing; Dabrafenib BID and trametinib once daily should be administered under fasting conditions, either one hour before or 2 hours after a meal.				
Urinalysis				X		
AE assessment		CONTINUOUS				
Disease Assessment[9]	X		Every 6 weeks until Week 24, then every 8 weeks	X[9]	X[10]	
Long-term survival follow-up						X[11]

AE, Adverse Event; BP, blood pressure; CEA, ; ECHO, echocardiogram; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; HR, heart rate; MUGA,

1. **SCREENING WINDOW**: All screening assessments must be completed within 14 days prior to first crossover dose except ophthalmic exam, dermatological exam, ECHO/MUGA, and Disease Assessment, which can occur within 35 days prior to the first dose. Note: Procedures conducted as part of the subject's initial follow-up assessments may be utilized for screening or baseline purposes provided these procedures meet the protocol requirements.
2. **TREATMENT PHASE**: Assessments throughout the study are calendar-based starting from the first day of dosing (Day 1) in the first treatment period. Dose interruptions should not alter the assessment schedule for any subsequent treatment period. Safety lab tests (chemistry/hematology/coag/UA) may be done the day before the visit so that results are ready on the day of the visit, but all assessments should be done within the ±7 day window.
3. **FOLLOW_UP VISITS**: Initial follow-up visit should be 14 days from last dose of study drugs (±7 days). If a subject is unable to return to the clinic due to hospitalization, site staff are encouraged to telephone the subject for assessment of AEs. Secondary follow-up visits should occur at 4 weeks and 8 weeks after the last dose of panitumumab.
4. **PHYSICAL EXAM**: A brief physical exam should be conducted at screening and every 4 weeks. A complete physical examination including integument and genitalia should be performed during the initial follow-up visit. Note: pelvic exam in female subjects may be completed up to 24 weeks prior to date of first dose. Complete and brief physical examinations are defined in Section 6.2.
5. **DERMATOLOGICAL EVALUATION**: Baseline skin photography should be performed at Screening. Photographs should be taken of new skin lesions that occur, or skin lesions that change on therapy. Refer to Section 6.2. French sites will perform dermatological exams monthly while on-therapy, and monthly for 6 months following discontinuation of dabrafenib or until initiation of another anti-neoplastic therapy, whichever comes first. Refer to Appendix 7 for full information.
6. **VITAL SIGNS**: Vital signs and temperature should be measured within 30 minutes prior to initiation and upon completion of the panitumumab infusion (up to 15 minutes after the end of infusion).
7. **ECHO**: ECHO is preferred. MUGA may be used only if ECHO is not available. The same method must be used consistently from screening throughout the study.
8. [redacted]
9. **DISEASE ASSESSMENT**: CT is the preferred method to measure lesions selected for response assessment. Refer to Appendix 4 for additional information regarding RECIST 1.1 methodology and criteria. Even if study treatment is withdrawn, radiographic disease assessments (CT or MRI, as appropriate according to the method used at baseline) should continue every 8 weeks until documented disease progression, the start of new anti-cancer therapy, withdrawal of consent or death.
10. **DISEASE ASSESSMENT**: After study treatment is withdrawn, disease assessments (the method used at baseline) should continue every 8 weeks until documented disease progression, the start of new anti-cancer therapy, withdrawal of consent, or death.
11. **OVERALL SURVIVAL**: Subjects will be followed for Overall Survival every 8 weeks after last dose of study drugs. See Section 6.3.1.for additional information.

4. STUDY POPULATION

4.1. Number of Subjects

The number of dose levels and the level at which the MTD will be reached cannot be determined in advance. An adequate number of subjects will be enrolled into the study to establish a recommended dose(s) and schedule(s) for the further study of dabrafenib/panitumumab and dabrafenib/trametinib/panitumumab combinations.

To complete Part 1, it is estimated that 24 evaluable subjects (~4 per cohort) will be enrolled. Part 2 will enroll approximately 100 subjects in total. In order to confirm safety in Japanese patients, up to three additional Japanese patients may be enrolled in Japan in each expansion cohort. By the end of Part 2, approximately 30 subjects will be evaluated for each dose cohort. For Part 3, approximately 47 subjects per arm will be enrolled. For Part 4A (dose escalation), it is estimated that up to 18 evaluable subjects (~6 per cohort) will be enrolled. Part 4B will enroll approximately 17 additional subjects in each of two expansion populations (n=34). This will be a total of approximately 20 patients at the MTD for each patient population, including the subjects enrolled in Part 4A. In order to confirm safety in Japanese patients, three additional Japanese patients may be enrolled in Japan in each expansion population for Part 4. Up to an additional 20 subjects with BRAF mutant CRC may be enrolled in Part 4 to further explore safety and efficacy of the trametinib plus panitumumab doublet.

If subjects discontinue the study before completing Week 4, additional subjects may be enrolled at the discretion of the Sponsor in consultation with the investigator.

4.2. Eligibility Criteria

4.2.1. Part 1, 2 and 4 Inclusion and Exclusion Criteria

The investigator should refer to the GSK2118436 IB [GlaxoSmithKline Document Number 2012N136095_00], the GSK1120212 IB [GlaxoSmithKline Document Number HM2009/00151/03] and the GSK1120212 + GSK2118436 Clinical IB [GlaxoSmithKline Document Number, 2011N126811_00] for detailed information regarding ongoing clinical studies, pharmacokinetics in the target disease populations, as well as observed safety and efficacy findings.

4.2.1.1. Part 1, 2 and 4 Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on the study treatment(s) or panitumumab that may impact subject eligibility is provided in the Investigator Brochure (IB) and product label.

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

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

1. Provided signed written informed consent, which includes compliance with the requirements and restrictions listed in the consent form.
2. Male or female ≥18 years of age and able to swallow and retain orally administered study treatment and does not have any clinically significant gastrointestinal (GI) abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach and/or bowels.
3. Part 1 and Part 2: Histologically- or cytologically-confirmed diagnosis of advanced or metastatic BRAF V600E mutation positive colorectal cancer (CRC), as determined by relevant genetic testing and documented in source. For subjects enrolled based on local mutation testing, confirmation of mutation will occur following registration in Part 1 and Part 2.

   Note: Subjects will not be excluded if centralized testing is later found to be discordant or uninformative (e.g., inadequate sample), but additional subjects may be enrolled as replacement subjects at the discretion of the Sponsor and in consultation with the investigator.

4. Part 4A and 4B ONLY: Histologically- or cytologically-confirmed diagnosis of advanced or metastatic colorectal cancer (CRC) that either:
   - harbours the BRAF V600E –mutation, as determined by relevant genetic testing and documented in source, OR
   - has developed secondary resistance to anti-EGFR therapy, defined as patients that derived benefit (disease control based on investigator assessment for > 6 months OR partial response [confirmed or unconfirmed] based on RECIST 1.1) from prior anti-EGFR-containing therapy (as defined below) and then subsequently progressed on therapy. The anti-EGFR therapy must have been the most recent therapy and the patient must have progressed based on investigator assessment within 3 months of screening. Acceptable prior anti-EGFR-containing therapies include:
     a. Monotherapy anti-EGFR, including cetuximab or panitumumab OR
     b. irinotecan/anti-EGFR combo after previously having disease progression (based on investigator assessment) on an irinotecan-containing regimen
5. Archival tissue is required; if archival tissue is not available or found to not contain tumor tissue, a fresh biopsy is required.
6. Measurable disease per RECIST version 1.1(Refer to Appendix 4).
7. ECOG Performance Status of 0 or 1.
8. Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use one of the contraception methods listed in Section 7.1.2 from 7 days prior to the first dose of study drug(s) and until 6 months after the last dose of panitumumab, or 16 weeks following the last dose of dabrafenib or trametinib, whichever is later to allow for clearance of any altered sperm.
9. Female subjects are eligible if:

- Non-childbearing potential defined as pre-menopausal females with a documented tubal ligation or hysterectomy; or post-menopausal female defined as 12 months of spontaneous amenorrhea to be verified with a follicle-stimulating hormone (FSH) level >40MIU/mL and estradiol level <40pg/mL. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the contraception methods in Section 7.1.1 if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrollment. For most forms of HRT, at least 2 to 4 weeks will elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Following confirmation of post-menopausal status, they can resume use of HRT during the study without use of a contraceptive method.
- Child-bearing potential and agrees to use one of the contraceptive methods listed in Section 7.1.1 for an appropriate period of time as determined by the product label and applicable IBs) prior to the start of dosing to sufficiently minimize risk of pregnancy at that point.

10. Female subjects must agree to use contraception from 7 days prior to the first dose of study drug(s) until 6 months after the last dose of panitumumab, until 4 months after the last dose of trametinib, or 4 weeks after the last dose of dabrafenib, whichever is longer. *Note: oral contraceptives are not reliable due to potential drug-drug interactions.* Additionally, women of childbearing potential must have had a negative serum pregnancy test within 14 days prior to the first dose of study drug(s).
11. Adequate organ system function as defined in Table 23:

Table 23 Definitions for Adequate Baseline Organ Function

System	Laboratory Values
Hematologic	
Absolute neutrophil count	≥1.2 × 10^9/L
Hemoglobin	≥9 g/dL or 5.6 mmol/L
Platelets	≥100 × 10^9/L
Coagulation parameters Prothrombin Time / International Normalized Ratio (PT/INR) and Partial Thromboplastin Time (PTT)[a]	≤1.5 x ULN
Chemistry	
Mg++	≥ LLN
Hepatic	
Albumin	≥2.5 g/dL or 25 g/L
Total bilirubin	≤1.5 x ULN
AST and ALT	≤ 2.5× ULN
Renal	
Creatinine **or**	≤ 1.5 ULN
Calculated creatinine clearance[b] **or** 24-hour urine creatinine clearance	≥ 50 mL/min
Cardiac	
Left Ventricular Ejection fraction (LVEF)	≥ LLN by ECHO or multigated acquisition scan (MUGA)[c]

a. Subjects receiving anticoagulant therapy are eligible if their INR is stable and within the recommended range for the desired level of anticoagulation
b. Calculated by the Cockcroft-Gault formula.
c. Same method as used at baseline must be use throughout the study, ECHO is the preferred method.

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

4.2.1.2. Part 1, Part 2, and Part 4 Exclusion Criteria

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

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

1. History of prior malignancy, other than colorectal cancer.

Exception: Subjects who have been disease-free for 5 years, or subjects with a history of completely resected non-melanoma skin cancer or successfully treated *in situ* carcinoma are eligible.

2. Any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions that could interfere with subject's safety, obtaining informed consent or compliance to the study procedures.
3. Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones, liver metastases or otherwise stable chronic liver disease per investigator's assessment).
4. History of sensitivity to heparin or heparin-induced thrombocytopenia.
5. Currently receiving cancer therapy (chemotherapy, radiation therapy, immunotherapy or biologic therapy), as described in Section 8.
6. Prior exposure to a MEK inhibitor.
7. Part 1, Part 2 and BRAF-mutant patients in Part 4 ONLY: Prior exposure to a BRAF inhibitor.
8. Part 1, Part 2 and BRAF-mutant patients in Part 4 ONLY: Known presence of KRAS-mutation based on previous KRAS-testing.

   Note: Prospective KRAS testing is not required. However, if the results of previous KRAS testing are known, they must be used in assessing eligibility. KRAS testing will be performed retrospectively for all patients.
9. Part 2B ONLY: Patients treated with > 4 prior lines of therapy for metastatic disease will not be eligible.
10. Received an investigational or approved anti-cancer drug within 4 weeks, or within 5 half-lives (whichever is shorter) of the first dose of study drug(s). At least 14 days must have passed between the last dose of prior investigational agent and the first dose of study drug(s).
11. Current use of a prohibited medication or requirement to dose with any of these medications during treatment with study drug(s).
12. A history of Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection (subjects with laboratory evidence of cleared HBV and/or HCV will be permitted.
13. Any major surgery, radiotherapy or immunotherapy within the 4 weeks prior to first dose of study drug(s). Limited radiotherapy with in the 2 weeks prior to first dose of study drug(s).
14. Chemotherapy regimens with delayed toxicity within the 3 weeks prior to first dose of study drug(s). Chemotherapy regimens given continuously or on a weekly basis with limited potential for delayed toxicity within 2 weeks prior to first dose of study drug(s).
15. Unresolved toxicity greater than NCI-CTCAE version 4 Grade 1 from previous anti-cancer therapy, with the exception of Grade 2 alopecia, Grade 2 neuropathy, or laboratory values that are allowed per Table 23.
16. History of retinal vein occlusion (RVO).
17. Presence of active gastrointestinal disease or other condition that will interfere significantly with the absorption, distribution, metabolism or excretion of drugs. Previous colectomy is acceptable.

18. Subjects with brain metastases are excluded, unless:
    - All known lesions must be previously treated with surgery or stereotactic radiosurgery, and
    - Brain lesion(s), if present, must be confirmed stable (i.e., no increase in lesion size) for ≥90 days prior to first dose of study drug(s). This must be documented with two consecutive MRI or CT scans using contrast, and
    - Asymptomatic with no corticosteroids requirement for ≥30 days prior to first dose of study drug(s), and
    - No enzyme-inducing anticonvulsants for ≥14 days prior to first dose of study drug(s).
    - In addition, for subjects 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 MRI or CT scans (using contrast) separated by ≥6 weeks, prior to randomization. Enrollment of a subject with brain metastases who meet the above criteria requires approval of a Novartis Medical Lead.
19. Psychological, familial, sociological or geographical conditions that do not permit compliance with the protocol.
20. History or evidence of cardiovascular risk including any of the following:
    - LVEF<LLN
    - A QT interval corrected for heart rate using the Bazett's formula (QTcB;) ≥480 msec; Appendix 6.
    - History or evidence of current clinically significant uncontrolled arrhythmias.

      Exception: Subjects with controlled atrial fibrillation for >30 days prior to randomization are eligible.
    - History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within 6 months prior to randomization.
    - History or evidence of current ≥ Class II congestive heart failure as defined by New York Heart Association (NYHA).
    - 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;
    - Subjects with intra-cardiac defibrillators or permanent pacemakers;
    - Known cardiac metastases;
21. Unstable pulmonary embolism, deep vein thrombosis, or other significant arterial/venous thromboembolic event ≤ 30 days before randomization. If on anticoagulation, subject must be on stable therapeutic dose prior to randomization.

22. Subjects with a history of pneumonitis or interstitial lung disease (ILD).
23. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to the study drug(s) or their excipients.
24. Pregnant or lactating female.
25. Unwillingness or inability to follow the procedures outlined in the protocol.
26. Uncontrolled diabetes or other medical condition that may interfere with assessment of toxicity.

4.2.2. Part 3 Inclusion and Exclusion Criteria

The investigator should refer to the GSK2118436 IB [GlaxoSmithKline Document Number 2012N136095_00], the GSK1120212 IB [GlaxoSmithKline Document Number HM2009/00151/03] and the GSK1120212 + GSK2118436 Clinical IB [GlaxoSmithKline Document Number, 2011N126811_00] for detailed information regarding ongoing clinical studies, pharmacokinetics in the target disease populations, as well as observed safety and efficacy findings.

4.2.2.1. Part 3 Inclusion Criteria

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

A subject will be eligible for inclusion in Part 3 of this study only if all of the following criteria apply:

1. Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form.
2. Male or female ≥18 years of age and able to swallow and retain oral medication.
3. Histologically- or cytologically-confirmed diagnosis of BRAFV600E mutation positive advanced or metastatic colorectal cancer (CRC who are eligible to receive fluoropyrimidine-containing chemotherapy regimen that have experienced documented radiographic progression on one prior line of fluoropyrimidine-containing chemotherapy (previous anti-EGFR therapy is excluded),
4. Second-line for advanced/metastatic disease, having failed or been intolerant to at least one regimen of fluoropyrimidine-containing chemotherapy including irinotecan or oxaliplatin in the advanced/metastatic setting.
5. Tumor type criteria:
    - BRAF V600E mutation-positive colorectal cancer, as determined by relevant genetic testing and documented in source. Enrollment in Part 3 will require prospective testing for BRAF mutation V600E using a CLIA certified BRAF mutation assay that will be performed in a central laboratory.

- KRAS wild-type colorectal cancer as determined by relevant genetic testing (Codon 12 and 13) and documented in source. Enrollment in Part 3 may only occur following confirmation of KRAS wild-type cancer.

6. Archival tissue is required; if archival tissue is not available or found to not contain tumor tissue, a fresh biopsy is required for prospective central confirmation of BRAF mutation status.
7. Measurable disease per RECIST version 1.1.
8. ECOG Performance Status of 0 or 1.
9. Male subjects must agree to use one of the contraception methods listed in Section 7.1.2. This criterion must be followed from 7 days prior to the e first dose of study drug(s) until 6 months after the last dose of panitumumab, or 16 weeks following the last dose of dabrafenib or trametinib, whichever is later.
10. Female subjects are eligible if of:
    - Non-childbearing potential defined as pre-menopausal females with a documented tubal ligation or hysterectomy; or post-menopausal female defined as 12 months of spontaneous amenorrhea to be verified with a follicle-stimulating hormone (FSH) level >40MIU/mL and estradiol level <40pg/mL. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the contraception methods in Section 7.1.1 if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrollment. For most forms of HRT, at least 2 to 4 weeks will elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Following confirmation of post-menopausal status, they can resume use of HRT during the study without use of a contraceptive method.
    - Child-bearing potential and agrees to use one of the contraceptive methods listed in Section 7.1.1 for an appropriate period of time as determined by the product label and applicable IBs) prior to the start of dosing to sufficiently minimize risk of pregnancy at that point.
11. Female subjects must agree to use contraception from 7 days prior to the first dose of study drug(s) until 6 months after the last dose of panitumumab, until 4 months after the last dose of trametinib, or 4 weeks after the last dose of dabrafenib, whichever is longer. *Note: oral contraceptives are not reliable due to potential drug-drug interactions.* Additionally, women of childbearing potential must have had a negative serum pregnancy test within 7 days prior to the first dose of study drug(s).
12. Adequate organ system function as defined in Table 24:

Table 24 Definitions for Adequate Baseline Organ Function

System	Laboratory Values
Hematologic	
Absolute neutrophil count	≥1.5 × 10^9/L
Hemoglobin	≥9 g/dL or 5.6 mmol/L
Platelets	≥75 × 10^9/L
PT/INR and PTT	≤1.5 x ULN
Chemistry	
Mg++	≥ LLN
Hepatic	
Albumin	≥2.5 g/dL or 25 g/L
Total bilirubin	≤1.5 x ULN
AST and ALT	≤ 2.5× ULN
Renal	
Creatinine **or**	≤ ULN
Calculated creatinine clearance[a] **or**	≥ 50 mL/min
24-hour urine creatinine clearance	≥ 50 mL/min
Cardiac	
Left Ventricular Ejection fraction (LVEF)	≥ LLN by ECHO or MUGA[b]

a. Calculated by the Cockcroft-Gault formula.
b. Same method as used at baseline must be use throughout the study, ECHO is the preferred method

13. Subjects enrolled in France: In France, a subject will be eligible for inclusion in this study only if either affiliated to, or a beneficiary of, a social security category

4.2.2.2. Part 3 Exclusion Criteria

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

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. History of prior malignancy, other than colorectal cancer.

Exception: Subjects who have been disease-free for 5 years, or subjects with a history of completely resected non-melanoma skin cancer or successfully treated *in situ* carcinoma are eligible.

2. Any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions that could interfere with subject's safety, obtaining informed consent or compliance to the study procedures.
3. Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones, liver metastases or otherwise stable chronic liver disease per investigator's assessment).

4. History of sensitivity to heparin or heparin-induced thrombocytopenia
5. Currently receiving cancer therapy (chemotherapy, radiation therapy, immunotherapy or biologic therapy), as described in Section 8.
6. Prior exposure to BRAF or MEK inhibitors.
7. Prior exposure to EGFR inhibitors or an anti-EGFR antibody.
8. Received an investigational or approved anti-cancer drug within 4 weeks, or within 5 half-lives (whichever is shorter) of the first dose of study drug(s). At least 14 days must have passed between the last dose of prior investigational agent and the first dose of study drug(s).
9. Received more than one prior anti-cancer therapy in the metastatic setting, exclusive of previous adjuvant regimens. Previous investigational anti-cancer therapy in the metastatic setting is prohibited.
10. Current use of a prohibited medication or requirement to dose with any of these medications during treatment with study drug(s).
11. Known Hepatitis B, or Hepatitis C infection.
12. Any major surgery, radiotherapy or immunotherapy within the 4 weeks prior to first dose of study drug(s). Limited radiotherapy with in the 2 weeks prior to first dose of study drug(s).
13. Unresolved toxicity greater than NCI-CTCAE version 4 Grade 1 from previous anti-cancer therapy, with the exception of alopecia.
14. History of retinal vein occlusion (RVO).
15. Presence of active gastrointestinal disease or other condition that will interfere significantly with the absorption, distribution, metabolism or excretion of drugs. Previous colectomy is acceptable.
16. Subjects with brain metastases are excluded, unless:
    - All known lesions must be previously treated with surgery or stereotactic radiosurgery, and
    - Brain lesion(s), if present, must be confirmed stable (i.e., no increase in lesion size) for ≥90 days prior to first dose of study drug(s). This must be documented with two consecutive MRI or CT scans using contrast, and
    - Asymptomatic with no corticosteroids requirement for ≥30 days prior to first dose of study drug(s), and
    - No enzyme-inducing anticonvulsants for ≥14 days prior to first dose of study drug(s).
    - In addition, for subjects 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 MRI or CT scans (using contrast) separated by ≥6 weeks, prior to randomization. Enrollment of a subject with brain metastases who meet the above criteria requires approval of a Novartis Medical Lead.

17. Subjects with a history of pneumonitis or interstitial lung disease (ILD).
18. History or evidence of cardiovascular risk including any of the following:
    - LVEF<LLN
    - A QT interval corrected for heart rate using the Bazett's formula (QTcB; Appendix 6) ≥480 msec;
    - History or evidence of current clinically significant uncontrolled arrhythmias.

      Exception: Subjects with controlled atrial fibrillation for >30 days prior to randomization are eligible.
    - History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within 6 months prior to randomization.
    - History or evidence of current ≥ Class II congestive heart failure as defined by New York Heart Association (NYHA).
    - 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;
    - Subjects with intra-cardiac defibrillators or permanent pacemakers;
    - Known cardiac metastases;
19. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to the study drug(s) or their excipients.
20. Pregnant or lactating female.
21. Unwillingness or inability to follow the procedures outlined in the protocol.
22. Uncontrolled diabetes, hypertension or other medical condition that may interfere with assessment of toxicity.

5. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

5.1. Hypotheses and Treatment Comparisons

5.1.1. Part 1 and Part 4 Dose Escalation

The primary goals in Part 1 of this study are to determine safety and the recommended dose(s) for Part 2 and Part 4 based on available safety, PK and any clinical activity data of trametinib when administered in combination with dabrafenib and panitumumab; thus, no formal statistical hypotheses will be tested. Analysis will be descriptive [redacted]

5.1.2. Part 2 and Part 4 Cohort Expansion

For Part 2 and Part 4 cohort expansion, efficacy will be evaluated for each cohort to decide whether to proceed with further development based on the clinical activity seen in Part 1 and Part 4A. Analyses will be descriptive [redacted]. Subjects treated with the same starting dose will be analyzed together.

The Part 2 and Part 4B portion of the study will employ a Bayesian predictive adaptive design [Lee, 2008] that allows the trial to be monitored more frequently at multiple stages. The criteria will be based on a historically unimportant response rate of 15% versus a response rate of interest of 30%. Bayesian statistics will be employed to calculate the predictive probability that the response rate ≥30% and ≥15% at interim assuming a Beta prior for the Binomial distributed data. Predictive probability calculates the probability that the response rate ≥30% or ≥15% at the end of Part 2 or Part 4 given the responses have already been observed. It predicts what is likely to happen at the end of Part 2 or Part 4 so is more meaningful and straightforward than posterior probability. A weak prior Beta (0.003, 0.007) is used, which is equivalent to the information present in 0.01 subject. The first interim analysis may be conducted when at least 10 subjects are recruited for each analysis cohort specified in Table 25. Futility interim analysis decision rules for the 10^{th} to 54^{th} evaluable subjects, specifying the number of subjects with a confirmed response needed for continuing enrolment or stopping for futility when total sample size is up to 54 is presented in Table 26. These rules are intended as a guideline. Actual decisions will depend on the totality of the data.

Table 25 Sample sizes for different analysis cohorts using Bayesian predictive adaptive design.

Part	Cohorts/Population	Target sample size	Minimum sample size needed for first interim analysis
Part 1 and Part 2	D 150mg BID+P 6mg/kg	20	10
Part 1 and Part 2	D 150mg BID+ T 2mg QD +P 6mg/kg	54	10
Part 1 and Part 2	D 150mg BID+T 2mg QD+P 6mg/kg 1L	10-15	10
Part 1 and Part 2	D 150mg BID+T 2mg QD+P 6mg/kg 2L-4L	40-44	10
Part 1 and Part 2	D 150mg BID+T 2mg QD+P 4.8mg/kg	34	10
Part 1 and Part 2	D 150mg BID+T 2mg QD+P 4.8mg/kg 1L	10-14	10
Part 1 and Part 2	D 150mg BID+T 2mg QD+P 4.8mg/kg 2L-4L	20-24	10
Part 4	T+P Anti-EGFR CRC population	20	10
Part 4	T+ P BRAF+ CRC population	20-40	10

Table 26 Decision Making Criteria for Futility

Number of Evaluable Subjects	≤ This Number of Confirmed Responses to Stop Early for Futility	Probability of continuing enrolling when ORR=0.15	Probability of continuing enrolling when ORR=0.3
10	0	0.8031	0.9718
11	0	0.8031	0.9718
12	0	0.8031	0.9718
13	0	0.8031	0.9718
14	0	0.8031	0.9718
15	0	0.8031	0.9718
16	1	0.6721	0.9575
17	1	0.6721	0.9575
18	1	0.6721	0.9575
19	1	0.6721	0.9575
20	1	0.6721	0.9575
24	2	0.5805	0.9500
25	2	0.5805	0.9500
30	3	0.5126	0.9457
34	4	0.4506	0.9422
35	4	0.4506	0.9422
40	5	0.3875	0.9381
45	7	0.2785	0.9299
50	8	0.2268	0.9243
53	10	0.1345	0.9063
54	11	0	0

For the separate interim looks in each cohort, the enrollment for that cohort may be stopped due to futility if the predictive probability that the confirmed response rate ≥15%

(historical control) is small (e.g., less than 10% chance for a total sample size of 20 subjects or less than a 2% chance for a total sample size of 54 subjects). Enrollment may also be stopped due to futility if the equivalent of no confirmed response is observed in the first 10-15 enrolled evaluable subjects in that cohort or less than 1 confirmed response is observed in the first 16-19 evaluable subjects. For example, if all (10-15) or all but one (16-19) of the subjects have either progressed, withdrew from the study, were lost to follow-up, or are ongoing and have completed at least one post treatment disease assessment without a confirmed response then the cohort may be stopped for futility. Otherwise, the enrolment of the respective cohort will continue to the target sample size. If the predictive probability that the response rate of ≥30% is large (i.e., greater than 80% chance) is observed during the interim looks, strong statistical evidence has been provided in favor of further development of the treatment for the target population.

When the total sample size in a treatment arm/cohort is 20 and at least 2 confirmed responders out of 20 subjects are observed, further development of the corresponding treatment in Part 3 may follow.

When the total sample size in a cohort is 54 and at least 12 confirmed responders out of 54 subjects are observed, further development of the corresponding treatment in Part 3 may follow.

5.1.3. Part 3

The primary objective of Part 3 is to compare progression free survival (PFS) and of the combinations of trametinib plus dabrafenib plus panitumumab and/or dabrafenib plus panitumumab versus standard of care in subjects with BRAF-V600E mutation positive CRC. There will be two primary comparisons of interest in this study based on comparing each of the panitumumab combination arms with chemotherapy comparator.

Specifically, the study is designed to provide evidence with regard to PFS to support the null hypothesis:

$$H01: \lambda_1 = 1$$

or to reject it in favor of the alternative hypothesis:

$$HA1: \lambda_1 \neq 1,$$

where λ_1 is the hazard ratio: dabrafenib plus panitumumab / chemotherapy comparator and further to support the null hypothesis:

$$H02: \lambda_2 = 1$$

or to reject it in favor of the alternative hypothesis

$$HA2: \lambda_2 \neq 1,$$

where λ_2 is the hazard ratio: trametinib plus dabrafenib plus panitumumab/ chemotherapy comparator.

The study will have 80% power to detect a hazard ratio (HR) of 0.5 with a two-sided 0.05 level test. Under the assumption of exponential PFS, this HR is equivalent to 100% increase in median progression-free survival for dabrafenib/panitumumab versus chemotherapy comparator or dabrafenib/trametinib/panitumumab versus the chemotherapy comparator (6 months vs. 3 months). An additional secondary comparison of interest for PFS may be between the dabrafenib/panitumumab and the dabrafenib/trametinib/panitumumab arm.

5.2. Sample Size Considerations

5.2.1. Sample Size Assumptions

5.2.1.1. Part 1 and Part 4 Dose Escalation

The total number of subjects in Part 1 and Part 4 dose escalation will depend on the number of dose escalations needed. However, the maximum anticipated number of subjects will be approximately 24 in Part 1 and approximately 22 in Part 4 dose escalation.

Table 27 Statistical Basis for Phase 1 Dose Escalation

True incidence of dose-limiting toxicity	10%	20%	30%	40%	50%	60%
Probability of escalating the dose	0.91	0.71	0.49	0.31	0.17	0.08

5.2.1.2. Part 2 and Part 4 Cohort Expansions

Part 2 will enroll up to 90 subjects in total. Part 4 cohort expansion will enroll 40-60 subjects in total (20 subjects in the anti-EGFR acquired resistance CRC population and 20-40 subjects in the BRAF mutant CRC population). Subjects will be evaluated separately by dose cohort and population at the end of Part 2 and Part 4.

To determine the sample size for dabrafenib in combination with panitumumab expansion cohort, and trametinib in combination with panitumumab expansion cohort, a traditional, 2-stage Green-Dahlberg design [Green, 1992] was evaluated and the sample size for the first stage will be used for the futility analysis. To test the hypotheses (RR=30% vs. RR=15%), using a Green-Dahlberg design, 20 subjects per arm would be needed for Stage 1 (assuming a type 1 error of 10% and power of 80%). The chance to effectively terminate the trial after 20 subjects due to futility (true RR=15%) is 33%; the risk to incorrectly stop the trial after 20 subjects if the treatment is effective (true RR =40%) is less than 2% (Table 28). To determine the maximum sample size for any cohort or patient population in trametinib plus dabrafenib in combination with panitumumab, Bayesian predictive adaptive design will be used for testing hypotheses:

H_0: RR≤15%

H_A:RR≥30%

When maximum sample size is 54, the design will have a Type I error (α) of 0.089 and 88% power with the probability of termination is 0.911 when the treatment is futile and probability of early termination 0.116 when the treatment is effective (true RR=0.3).

Table 28 Futility Analysis Design Performance

True RR	Probability of Termination, after 20 pts	Probability of Termination, after 34 pts	Probability of Termination, after 40 pts	Probability of Termination, after 54 pts
15%	0.329	0.548	0.603	0.911
20%	0.180	0.288	0.324	0.641
30%	0.044	0.054	0.057	0.116
40%	0.007	0.011	0.011	0.013

A Bayesian posterior probability will also be calculated to further inform decision making. Since neither dabrafenib in combination with panitumumab, trametinib in combination with panitumumab, nor trametinib in combination with dabrafenib and panitumumab has been tested previously in the clinic in CRC subjects, a Beta (0.003, 0.007) prior is assumed. This prior is equivalent to the information from 0.01 subject. The posterior probabilities of ORR exceeding 20%, 30% and 40% based on 20 subjects and the posterior probabilities of ORR exceeding 20%, 30% and 40% based on 54 subjects are shown in Table 29.

Table 29 Bayesian Posterior Probabilities of Response Rate for Given Number of Observed Responses

# of Responses Observed out of 20 Subjects	Posterior Probability RR ≥20%	Posterior Probability RR ≥30%	Posterior Probability RR ≥40%
4	0.45	0.14	0.024
5	0.69	0.29	0.075
6	0.83	0.48	0.17
7	0.93	0.66	0.31
8	0.97	0.81	0.49
# of Responses Observed out of 34 Subjects	**Posterior Probability RR ≥20%**	**Posterior Probability RR ≥30%**	**Posterior Probability RR ≥40%**
5	0.18	0.01	0.000
6	0.33	0.04	0.002
7	0.50	0.09	0.007
8	0.67	0.18	0.019
9	0.80	0.30	0.044
10	0.89	0.45	0.092
11	0.95	0.60	0.169
12	0.98	0.73	0.276
# of Responses Observed out of 40 Subjects	**Posterior Probability RR ≥20%**	**Posterior Probability RR ≥30%**	**Posterior Probability RR ≥40%**
6	0.18	0.01	0.000
7	0.31	0.03	0.001
8	0.47	0.07	0.003
9	0.62	0.13	0.008
10	0.76	0.22	0.020
11	0.86	0.35	0.045
12	0.93	0.48	0.088
13	0.96	0.62	0.155
# of Responses Observed out of 54 Subjects	**Posterior Probability RR ≥20%**	**Posterior Probability RR ≥30%**	**Posterior Probability RR ≥40%**
11	0.50	0.05	0.001
12	0.63	0.09	0.002
13	0.75	0.15	0.006
14	0.84	0.24	0.014
15	0.91	0.34	0.028
16	0.95	0.46	0.053
17	0.97	0.58	0.092

Using these sample sizes, a Bayesian design that allows the trial to be monitored more frequently at multiple stages was evaluated. A Bayesian analysis expresses uncertainty about a parameter in terms of probability. A prior is defined to characterize the level of

knowledge about a parameter before the data are collected. Once the data are collected, a posterior distribution is formed using the prior and the likelihood (i.e., the data). Since none of the treatment has been tested previously in the clinic in the target population, a weak prior Beta (0.003, 0.007) is assumed. Thus, the posterior distribution for the response rate will be primarily driven by the data and can be derived as follows: Let p denote the response rate for the treatment, the number of responses in the current n patients, x, follows a binomial distribution, Binomial (n, p). Taking the Bayesian method and combining the weak prior and the likelihood of the observed data x, the posterior distribution of the response rate follows a beta distribution, *i.e.,* p ~ Beta (0.003 + x, 0.007 + n-x) with the posterior mean (0.003 + x)/(0.01 + n).

Based on this posterior distribution of the response rate, the predictive probability that the response rate >15% or ≥30% after 19 or 53 subjects will be calculated for decision-making as described in the Section 5.1.2 (Hypotheses). The decision rule and a minimal required sample size of 10 patients for the first interim look are determined to generate the design that leads to a reasonable chance of early termination due to futility.

The design property, by utilizing the decision rule specified in Section 5.1.2, and sample size of 20 subjects or 54 subjects are shown (Table 30). The probability of early termination of the trial is calculated by simulations. The probability of early termination after the first 19 evaluable subjects is 33% under the null hypothesized response rate, and the risk to incorrectly stop the trial early if the drug is effective is approximately 5%. Thus, the study will employ the Bayesian design that allows the trial to be monitored more frequently at multiple stages with the constraint of satisfactory stop for futility rate

Table 30 Bayesian Design Performance by Response Rate

If True Response Rate to the Treatment is: (%)	Probability (early stop for futility) after 19 subjects	Probability (early stop for futility) after 53 subjects
0.15	0.326	0.853
0.2	0.180	0.483
0.3	0.043	0.086

5.2.1.3. Part 3

Based on available published data and input from experts in treatment of BRAF-mutant colorectal cancer, the median PFS assumed for the SOC is approximately 3 months [Loupakis, 2009; Di Nicolantonio, 2008; Laurent-Puig, 2009; unpublished data].

The following assumptions were made in the estimation of sample size and the required number of events for PFS for each of the two primary comparisons:

- Exponential distributions
- Constant accrual rate of 12 subjects per month
- 20% loss-to-follow-up rate

- A 1:1:1 randomization scheme
- Power for each comparison of 80%

An overall of 5% two-sided risk of erroneously claiming difference between the experimental arms and the control arm (chemotherapy comparator) in the case of no underlying difference between the two arms (overall type I error for each comparison).

Forty-seven (47) subjects per arm will be enrolled, leading to approximately 12 months of accrual. The first interim analysis for PFS and OS will be performed (at the same time, for all three arms) when at least 29 PFS events (per RECIST v1.1) have occurred across either dabrafenib/panitumumab and chemotherapy comparator arms or trametinib/dabrafenib/panitumumab and chemotherapy comparator arms (around 9 months after the first subject enrolled). The final analysis on PFS will be conducted when at least 72 PFS events (per RECIST) have been reported in dabrafenib/panitumumab and chemotherapy comparator arms and at least 72 PFS events have been reported in trametinib/dabrafenib/panitumumab and chemotherapy comparator arms.

5.2.2. Sample Size Sensitivity

Table 31 shows the sensitivity of PFS events to smaller median PFS in the dabrafenib plus panitumumab or trametinib plus dabrafenib plus panitumumab treatment arms.

Table 31 PFS Sample Size Sensitivity

Median Progression-Free Survival (months)		Percent of Improvement	Statistical Power[a]
comparator	Dabrafenib plus panitumumab / Trametinib plus dabrafenib plus panitumumab		
3	5.4	80	69%
3	5.6	90	75%
3	6	100	80%

a. Overall power is defined as to detect a 100% increase in median progression free survival in subjects who receive dabrafenib plus panitumumab vs. chemotherapy comparator or in subjects who receive trametinib plus dabrafenib plus panitumumab compared vs. chemotherapy comparator.

5.2.3. Analysis Populations

The **Intent-to-Treat (ITT) population** will comprise all randomized subjects regardless of whether or not treatment was administered. This population will be based on the treatment to which the subject was randomized and will be the primary population for the analysis of efficacy data in Part 3.

The **All Treated Population** will consist of all subjects that received at least one dose of investigational product. Safety and clinical activity data for Parts 1, 2 and 4 will be evaluated based on this population.

The **PK Population** will consist of those subjects in All Treated Population and for whom a PK sample is obtained and analyzed.

The **Crossover Population** will comprise the subset of subjects in Part 1, Part 2 and Part 4 who had intra-subject dose escalation or intra-subject doublet to triplet crossover. It will be the primary population when summarizing data in Part 1, Part 2 and Part 4 crossover phase.

5.2.4. Analysis Data Sets

The construction of analysis data sets will be performed in accordance with all applicable Novartis standards and procedures.

5.2.5. Sample Size Re-estimation

No sample size re-estimation will be performed.

5.3. Data Analysis Considerations

Data will be listed and summarized according to the Novartis reporting standards, where applicable. Complete details will be documented in the Reporting and Analysis Plan (RAP).

5.3.1. Withdrawal

Reason for subject withdrawal will be listed.

5.3.2. Missing Data

Missing data will not be imputed. Where appropriate, available data will be summarized over specified intervals (e.g., from start of treatment until withdrawal from study) using suitable summary statistics.

5.3.3. Protocol Violations

A summary and listing of protocol violations will be provided.

5.3.4. Derived and Transformed Data

The PK parameters, AUC, Cmax, and terminal half-life will be log-transformed prior to analysis when needed.

5.3.5. Assessment Windows

Safety assessments that occur prior to the administration of study drug will be considered screening assessments. Safety assessments that occur after dosing has begun will be considered as having occurred while on treatment.

Disease assessments will be distinguished as belonging to either screening, continued therapy or post-study phases of the study.

5.3.6. Other Issues

Data from participating centers will be pooled prior to analysis. It is anticipated that subject accrual may be limited across centers and summaries of data by center would likely not be informative. Therefore, these summaries will not be provided.

Demographic and baseline characteristics will be summarized.

For pharmacokinetics analyses, assay values below quantifiable limits (BQL) will be handled according to Novartis procedures.

5.3.7. Interim Analysis

5.3.7.1. Part 1 and Part 4 Dose Escalation

No formal interim analysis will be performed. Review of all available safety and pharmacokinetic data will be performed after completion of each dosing cohort.

[redacted]

In Part 1, to further facilitate dose escalation/de-escalation decisions, an adaptive Bayesian logistic regression model (BLRM) may be utilized to predict the probability of DLT at the dose levels yet to be tested. Specifically, an 8-parameter BLRM for combination treatment [Bailey, 2009] will be fitted on the dose limiting toxicity data (i.e., absence or presence of DLT) accumulated throughout the dose-escalation to model the dose-toxicity relationship of trametinib and dabrafenib and panitumumab when given in combination.

Prior distributions of two parameters for trametinib will be calculated based on the toxicity data observed in the first time in human (FTIH) study MEK111054 where trametinib is administered alone; similarly, prior distributions of two parameters for dabrafenib will be determined based on data observed in the FTIH study BRF112680 where dabrafenib is administered alone; prior distributions of the parameter for trametinib- dabrafenib interaction based on the data observed in study BRF113220 where trametinib and dabrafenib are administered in combination; a non-informative prior will be assumed for the other parameters which accounts for the combination of the two or three compounds. The model will be used only as a guide for what further doses to study in the presence of DLTs. The primary considerations for dose escalation/de-escalation will be based on the rules described in Section 3.7.2. Further details on the model as well as prior distributions will be included in the Reporting and Analysis Plan (RAP).

5.3.7.2. Part 2 and Part 4 Cohort Expansion

No formal interim analysis will be performed. Review of all available safety and pharmacokinetic data will be performed after completion of each dosing cohort.

[redacted]

In the expansion cohorts in Part 2, if an increased incidence of clinically significant toxicity *i.e.*, ≥4 subjects of the first 10 subjects enrolled) is observed, the dosing regimen may be adjusted for all future subjects in a specific cohort or for the whole study population.

5.3.7.3. Part 3

An IDMC will be utilized in this study to ensure external objective medical and statistical review of efficacy and safety data in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. The schedule of IDMC data reviews and the scope of the IDMC reviews are described in the IDMC charter, which is available upon request.

Planned Interim Analyses for Progression Free Survival

In addition to periodic reviews of the safety and efficacy data, one planned interim analysis for PFS will be performed. The interim analysis will be performed when 29 PFS events (per RECIST v1.1 criteria; 40% of required number of events for the final PFS analysis for each comparison) are reported across either dabrafenib/panitumumab and chemotherapy comparator arms or trametinib/dabrafenib/panitumumab and chemotherapy comparator arms.

The interim analyses for PFS will be performed for the purpose of evaluating whether to stop the trial early for “harm” in PFS.

"Harm" would correspond to declaring the dabrafenib plus panitumumab arm or trametinib plus dabrafenib plus panitumumab arm to be worse than the chemotherapy comparator arm in PFS.

For the purpose of evaluating whether to stop the trial due to harm/futility, a Gamma family beta spending function with a parameter of -0.5 will be utilized. The boundary does not represent a binding decision to stop the trial should this boundary be crossed. The boundaries are defined in East to preserve Type I error at 5% under the assumption of a non-binding futility rule.

The EAST software package will be used to calculate the appropriate bounds at the time of the analyses, given the fraction of information available. Assuming an accrual time of 12 months and a follow-up time of 6 months and the accrual rate is constant, the time point of interim analyses is around 9 months. An example of the nominal significance levels corresponding to the error spending functions as well as planned stopping boundaries and decision rules in terms of hazard ratios for the analysis time points of progression free survival, are as follows:

- 40% of expected events:, stop for harm if HR>3.537

- 100% of expected events: α=0.05, claim superiority of the experimental arm if HR<0.630 or claim harm if HR>1.587.

At the interim analysis, if either the trametinib/dabrafenib/panitumumab arm or dabrafenib/panitumumab arm demonstrates harm, enrollment to that arm may be halted. The IDMC may also recommend halting the trial or arms within the trial based on accruing safety information. If one of the experimental arms is halted due to either harm or safety, subjects on that arm may be provided the opportunity to receive treatment on the other experimental arm depending in the emerging safety and efficacy profile.

5.3.8. Final Analyses

Analyses of the data captured in Part 1 and Part 2 will be undertaken after each subject has been followed at least 12 weeks. Data from the two parts may be combined for some analyses at the end of the trial, as appropriate.

For Part 3, final analyses may be conducted when sufficient PFS events (72) have accrued for each pairwise comparison of the combination arms with the chemotherapy comparator. Analysis of OS will be conducted when 99 deaths have been reported across all three arms.

5.3.8.1. Safety Analyses

Safety data for Parts 1, 2 and 3 will be presented in tabular and/or graphical format and summarized descriptively according to Novartis standards.

5.3.8.2. Extent of Exposure

Extent of exposure of trametinib, dabrafenib and panitumumab will depend on tolerability of the subjects to the doses administered and the course of their disease. The number of subjects exposed to the combination of trametinib and dabrafenib and panitumumab will be summarized for each dose level administered.

5.3.8.3. Adverse Events

Adverse events (AEs) will be coded using the standard Medical Dictionary for Regulatory Activities (MedDRA) and grouped by system organ class. Adverse events (AEs) will be graded by the investigator according to the NCI CTCAE, version 4.0.

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

If the AE is listed in the NCI CTCAE (version 4.0) table, the maximum Grade will be summarized.

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

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

5.3.8.4. Clinical Laboratory Evaluations

Hematology and clinical chemistry data will be summarized at each scheduled assessment according to NCI CTCAE (version 4.0) Grade. The proportion of values lying outside the reference range will also be presented for laboratory tests that are not graded because there are no associated NCI CTCAE criteria. Summaries by visit will include data from scheduled assessments only, and all data will be reported according to the nominal visit date for which it was recorded (i.e., no visit windows will be applied). Unscheduled data will be included in 'worse case post baseline' summaries which will capture a worst case across all scheduled and unscheduled visits after the first dose of study treatment. Further details will be provided in the RAP.

5.3.8.5. Other Safety Measures

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

5.3.8.6. Pharmacokinetic Analyses

Pharmacokinetic analysis will be the responsibility of Novartis. Plasma dabrafenib and metabolites including hydroxy- and desmethyl-dabrafenib and trametinib concentration-time data from subjects enrolled in the dose escalation phase of the study will be analyzed by non-compartmental methods with WinNonlin Version 5.2 or higher. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following pharmacokinetic parameters will be determined for trametinib and dabrafenib and metabolites, as data permit: pre-dose concentration ($C\tau$), maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve [AUC(0-t) and AUC(0-8)], and apparent terminal phase half-life (t1/2). The metabolite to parent ratio for AUC(0-t) will be calculated for each metabolite of dabrafenib. $C\tau$ (predose concentration) and Cmax (end of infusion) for panitumumab will be determined.

Mixed-effects pharmacokinetic models developed previously for trametinib, dabrafenib, and dabrafenib metabolites will be fit to the dabrafenib and trametinib concentration-time data observed after administration with panitumumab in the expanded cohort using NONMEM VII. Post-hoc estimates of population pharmacokinetic parameters CL/F, V/F, and Ka will be determined for trametinib and dabrafenib metabolites after administration with panitumumab.

Descriptive statistics for panitumumab predose concentration and Cmax (end of infusion concentration) by visit will generated.

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively. All pharmacokinetic data will be stored by Novartis.

Statistical analyses of the pharmacokinetic parameter data will be the responsibility of Novartis.

If more than two dose cohorts are required to reach MTD (or recommended dose based on available safety, PK and response data), dose proportionality of dabrafenib, trametinib and panitumumab AUC(0-τ), Cmax and Cτ following repeat dose administration will be evaluated graphically and using the power model as described below:

log(PK parameter) = a + b * log(dose)

where a is the intercept and b is the slope.

The power model will be fitted by restricted maximum likelihood (REML) using SAS procedure MIXED (SAS Proc Mixed). Both the intercept and slope will be fitted as fixed effects. If there is sufficient data, then the model may also be fit with the intercept and/or slope as random effects. The mean slope will be estimated from the power model and the corresponding 90% confidence interval (CI) calculated.

5.3.8.7. Efficacy Analyses

5.3.8.7.1. Part 1, Part 2 and Part 4

The ORR endpoint will be tabulated based on number and percentage of subjects attaining either a confirmed or unconfirmed overall best response of CR or PR in the all treated population. Per RECIST, version 1.1, confirmation of response is not required. Subjects 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.

All responses are investigator-assessed. Independent central review may be performed.

PFS will be estimated using the Kaplan Meier method. PFS will be defined as the time from study treatment start until the first date of either disease progression or death due to any cause. The date of objective disease progression will be defined as the earliest date of disease progression as assessed by the investigator using RECIST, version 1.1. For subjects who have not progressed or died at the time of the PFS analysis, censoring will be performed using the date of the last adequate disease assessment. In addition, subjects with an extended loss to follow-up or who start a new anti-cancer therapy prior to a PFS event will be censored at the date of the last adequate disease assessment prior to the extended loss to follow-up or start of new anti-cancer therapy, respectively. Further details on censoring rules will be outlined in the RAP.

For Part 1 and Part 2, anti-tumor activities will be evaluated based on clinical evidence and response criteria. If the data warrant, the response data from both parts will be combined and summarized by dose level. The efficacy data collected after crossover for those subjects who crossover from dabrafenib/panitumumab combination or trametinib/panitumumab to dabrafenib/trametinib/panitumumab combination will not be included in the main efficacy analysis for dabrafenib/trametinib/panitumumab combinations. The crossover efficacy data for these subjects will be summarized separately.

5.3.8.7.2. Part 3

PFS along with 95% confidence interval for each treatment will be estimated using the Kaplan Meier method and treatment comparisons will be made using a log-rank test (defined in Section 5.1.3). The median PFS for each treatment, the hazard ratio for each comparison along with 95% confidence intervals will be reported.

PFS will be defined as the time from randomization until the first date of either disease progression or death due to any cause and will be evaluated for the combination versus the chemotherapy comparator. The date of objective disease progression will be defined as the earliest date of disease progression as assessed by the investigator using RECIST, version 1.1. For subjects who have not progressed or died at the time of the PFS analysis, censoring will be performed using the date of the last adequate disease assessment. In addition, subjects with an extended loss to follow-up or who start a new anti-cancer therapy prior to a PFS event will be censored at the date of the last adequate disease assessment prior to the extended loss to follow-up or start of new anti-cancer therapy, respectively. Further details on censoring rules will be outlined in the RAP.

Additional sensitivity and/or subgroup analyses for PFS may be pre-specified in the RAP, if appropriate.

The ORR endpoint will be tabulated based on number and percentage of subjects attaining either a confirmed or unconfirmed overall best response of CR or PR in the ITT population. Per RECIST, version 1.1, confirmation of response is not required. Subjects 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.

OS along with 95% confidence interval for each treatment will be estimated using the Kaplan Meier method and treatment comparisons will be made using a log-rank test. All cause mortality will be used and censoring will be performed using the date of last known contact for those who are alive or lost to follow-up at the time of analysis. The hazard ratio along with 95% confidence intervals will be provided for each of the pairwise comparisons described in Section 5.3.8. Sensitivity analyses to ascertain the effect of baseline prognostic factors may be performed. Details will be provided in the RAP.

Overall response rates (ORR) for each treatment group as well as for differences between each of the three arms will be provided along with corresponding 95% CI. A chi-square

test will be used for each pairwise comparison to test for differences between treatment arms.

Duration of response will include subjects from the ITT population who achieve a confirmed best response of CR or PR and will only be analyzed provided a sufficient number of subjects 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.

6. STUDY ASSESSMENTS AND PROCEDURES

This section lists the parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table (Section 3.11). Detailed procedures for obtaining each assessment are provided in the Study Procedures Manual (SPM). Whenever vital signs, 12-lead ECGs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, blood draws. The timing of the assessments should allow the blood draw to occur at the exact nominal time.

In Part 1 and Part 2, the timing and number of planned study assessments, including: safety, pharmacokinetic, pharmacodynamic [redacted] r other assessments may be altered during the course of the study based on newly available data (e.g. to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring. The change in timing or addition of time points for any planned study assessments must be approved and documented by Novartis, but this will not constitute a protocol amendment. The Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme; and an updated informed consent form will be presented to ongoing subjects. No more than 500 mL of blood will be collected over the duration of the study, including any extra assessments that may be required.

6.1. Demographic/Medical History Assessments

The following demographic parameters will be captured: date of birth, gender, race and ethnicity.

Medical, surgical, and treatment history including date (month and year) of first diagnosis and histology, as well as cardiovascular medical history and risk factors, alcohol and tobacco history, plus family history will be taken as part of the medical history and disease status. Additional information may be requested to evaluate eligibility per Section 4.2.

6.2. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 3.11). Additional time points for safety tests such as vital signs, physical exams and laboratory safety tests may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

Physical Exams/ Dermatological Exams

A complete physical examination will be performed by a qualified physician according to local practices. At minimum, the examination should include assessments of the head and neck, skin, neurological, lungs, cardiovascular, abdomen (liver and spleen), thyroid, lymph nodes and extremities. For subjects treated with dabrafenib in Part 1, 2, and 3, 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 for subjects in Parts 1, 2 and 3. (Pap smear and colposcopy are not required unless clinically indicated.) Rectal exam must include digital rectal exam and visual inspection of the anus and perianal area. Height (at baseline only) and weight will also be measured and recorded.

A brief physical examination will include assessments of the skin, lungs, cardiovascular system and abdomen (liver and spleen); these may be performed at time points indicated in the Time and Events tables (Section 3.11).

The baseline skin examination must be performed by a dermatologist, and removal of pre-existing calluses and keratotic skin is recommended. Baseline skin photographs should be submitted electronically as described in the SPM.

Referral to a dermatologist for follow-up skin exam should be done as clinically indicated. Skin lesions that emerge during therapy or change on therapy should be photographed. Photographs should be forwarded electronically for central review as described in the SPM. Any pathology samples collected must be sent for central review.

Assessment of Skin Changes

Biopsy of skin lesions related to treatment may be performed as clinically indicated.

[redacted]

Vital Signs

Vital sign measurements will include systolic and diastolic blood pressure, pulse rate and temperature. Vital signs should be assessed under optimal conditions as described in Section 3.10.8.1.

Vital signs should be measured within 30 minutes prior to initiation and upon completion of panitumumab infusion (up to 15 minutes after the end of infusion). On other study days where vital signs are measured multiple times, temperature does not need to be repeated, unless clinically indicated.

Ophthalmic Exam

At certain time points in the trial and if visual changes develop, an eye exam is indicated (refer to Visual Changes Stopping Criteria, Section 3.10.11). The exam will include best corrected visual acuity, tonometry, slit lamp biomicroscopic examination, visual field examination, and dilated indirect fundoscopy with special attention to retinal abnormalities. Optical coherence tomography is strongly recommended at scheduled

visits, and if retinal abnormalities are suspected. Other types of ancillary testing including color fundus photography and fluorescein angiography are also recommended if clinically indicated.

In addition, it is recommended that subjects have baseline color fundus photographs taken at screening to document baseline appearance.

Electrocardiogram (ECG)

Twelve-lead ECGs will be obtained as indicated in the Time and Events table (Section 3.11) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Results of the ECG will be transmitted to a central storage facility. At each assessment, a 12-lead ECG will be performed by qualified personnel at the site after the subject has rested at least 5 minutes in a semi-recumbent or supine position. Those QTc values greater than 480msec as calculated by the machine must be confirmed manually using Bazett's formula [Bazett, 1920] given below:

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

If there are any clinically significant abnormalities including but not limited to a QTcF>500msec, confirm with 2 additional ECGs taken at least 5 minutes apart.

Refer to Section 3.10.9 for QTc withdrawal criteria and additional QTc readings that may be necessary.

Echocardiogram (ECHO) or Multiple Gated Acquisition (MUGA)

ECHO is the preferred method to assess cardiac ejection fraction and cardiac valve abnormalities; MUGA is acceptable only if ECHO is not available. Assessments should be performed as indicated in the Time and Events table (Section 3.11). Results will be transmitted to a central storage facility. Echocardiography should include an evaluation for left ventricular ejection fraction (LVEF) and both right- and left-sided valvular lesions. For each subject the same procedure should be performed at screening and any following visit to allow direct comparison. Additional ECHO/ MUGA assessments may be performed as clinically indicated.

Clinical Laboratory Assessments

Hematology, clinical chemistry, urinalysis and additional parameters to be tested are listed below:

Hematology

Platelet Count	*RBC Indices*:	*Automated WBC Differential:*
Red blood cell (RBC) Count	Mean corpuscular volume (MCV)	Neutrophils
White blood cell (WBC) Count (absolute)	Mean corpuscular hemoglobin (MCH)	Lymphocytes
Hemoglobin	Mean corpuscular hemoglobin concentration (MCHC)	Monocytes
Hematocrit		Eosinophils
		Basophils

Clinical Chemistry

Albumin	Sodium	AST (SGOT)	Magnesium
BUN	Potassium	ALT (SGPT)	Total and direct bilirubin[1]
Creatinine	Chloride	Gamma glutamyl transferase (GGT)	Uric Acid
Glucose fasting glucose at screening only; all other glucose measurements may be non-fasting	Total carbon dioxide (CO_2)	Alkaline phosphatase	Inorganic phosphorus
Lactacte dehydrogenase (LDH)	Calcium		Total Protein

[1.] Direct bilirubin is only required when total bilirubin is above the upper limit of normal.

Routine Urinalysis

Color, appearance, pH, specific gravity, glucose, protein, blood, ketones, WBC esterase, urobiligen
Microscopic examination (if blood or protein is abnormal)

Other screening tests

FSH and estradiol (as needed in women of non-child bearing potential only)
Coagulation (at screening, repeated only if clinically indicated)

Progressively decreasing serum magnesium levels leading to severe (grade 3-4) hypomagnesemia occurred in up to 7% (in Study 2) of patients across clinical trials. Monitor patients for hypomagnesemia and hypocalcemia prior to initiating panitumumab treatment, periodically during panitumumab treatment, and for up to 8 weeks after the completion of treatment. Other electrolyte disturbances, including hypokalemia, have also been observed. Replete magnesium and other electrolytes as appropriate.

Eastern Cooperative Oncology Group (ECOG) Performance Status

The performance status assessment is based on the ECOG scale [Oken, 1982]:

0. Fully active, able to carry on all pre-disease performance without restriction.

1. Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work).

2. Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.

3. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

4. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

6.3. Disease Assessments

Disease assessment will include imaging of the chest, abdomen and pelvis (e.g., computed tomography [CT], magnetic resonance imaging, bone scan, plain radiograph) and physical examination (as indicated for palpable or superficial lesions). CT is the preferred method to measure lesions selected for response assessment. To ensure comparability between baseline and subsequent assessments, the same method of assessment and the same technique will be used when assessing response [Eisenhauer, 2009]. Refer to Appendix 4 for additional information regarding RECIST 1.1 methodology and criteria. The screening disease assessment will be completed within 35 days prior to the first dose of study drug(s); for subjects with known brain metastases, MRI of the head is required to determine stability of lesions as part of screening. Subsequent timings of disease assessments are detailed in the time and event tables for Part 1 (Section 3.11.1), Part 2 (Section 3.11.2) and Part 3 (Section 3.11.3). Disease assessments throughout the study are calendar-based, starting from the first day of dosing (Day 1) in the first treatment period, and irrespective of dose interruptions or delays. More frequent disease assessments may be performed at the discretion of the investigator. Subjects who discontinue study drug(s) for any reason other than progression or death should have a disease assessment performed at the follow-up visit, and results recorded in the eCRF.

Disease response will be recorded on the electronic case report form (eCRF) as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD), according to RECIST v 1.1 criteria (Appendix 4). Subjects whose disease responds (either CR or PR), should have a confirmatory disease assessment performed at least 4 weeks after the date of the assessment during which the response was demonstrated. Response will be characterized by best overall response rate (BORR), duration of response, progression-free survival (PFS) and overall survival (OS) [Eisenhauer, 2009].

- BORR: Defined as the best response recorded from the start of study treatment until the end of treatment.

- Duration of response: Defined as the interval between the time criteria are first met for CR/ PR (whichever is first recorded) until the first date that recurrence of progressive disease is objectively documented.

- PFS: Defined as the interval between the randomization date (Part 3) or the start of study treatment (Parts 1, 2 and 4) until progressive disease is objectively documented.

- OS: Defined as the interval between the randomization date (Part 3) or the start of study treatment (Parts 1, 2 and 4) until date of death due to any cause.

Even if study treatment is withdrawn, radiographic disease assessments (CT or MRI, as appropriate according to the method used at baseline) should continue every 8 weeks until documented disease progression, the start of new anti-cancer therapy, withdrawal of consent or death.

6.3.1. Follow-up Assessments for Subjects Permanently Discontinued from Study Treatment

Subjects will be followed for progression, survival and new anti-cancer therapy (including radiotherapy) every 8 weeks. If subjects are unable or unwilling to attend clinic visits during follow-up, contact to assess survival may be made via another form of communication (e.g., phone, email, etc.).

Subjects who permanently discontinue study treatment without disease progression will have radiographic disease assessments performed as indicated in the Time and Events Table (Section 3.11) until disease progression, new anti-cancer therapy start, or death is documented.

Subjects are to be followed until progression for collection of PFS data and until death for collection of overall survival (OS) data.

6.4. Blood Requirements

The approximate amount of blood collected from subjects completing screening, a 4 week treatment period and follow-up assessments is listed for each part of the study in Appendix 2.

6.5. Pregnancy

6.5.1. Time period for collecting pregnancy information

All pregnancies in female subjects and/or female partners of male subjects will be collected after the start of dosing and until 6 months after the last dose of panitumumab, or 16 weeks following the last dose of dabrafenib or trametinib, whichever is later.

6.5.2. Action to be taken if pregnancy occurs

The investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. The investigator will record pregnancy information on the appropriate form and submit it to Novartis within 24 hours of learning of a subject's pregnancy. The subject will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to Novartis. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE.

A spontaneous abortion is always considered to be an SAE and will be reported as such. Furthermore, any SAE occurring as a result of a post-study pregnancy and that is considered reasonably related to the study treatment by the investigator, will be reported to Novartis as described in Section 11. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating will discontinue study medication or be withdrawn from the study.

6.5.3. Action to be taken if pregnancy occurs in a female partner of a male study subject

The investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. The investigator will record pregnancy information on the appropriate form and submit it to Novartis within 24 hours of learning of the partner's pregnancy. The partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to Novartis. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

6.6. Pharmacokinetics

6.6.1. Blood Sample Collection

Blood samples for pharmacokinetic analysis of dabrafenib and metabolites (hydroxy- and desmethyl-dabrafenib), trametinib, and panitumumab will be collected at the time points indicated in the Time and Events table (Section 3.11). The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

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

6.6.2. Sample Analysis

Plasma analysis will be performed under the management of Novartis. Concentrations of dabrafenib and its metabolites (hydroxy- and desmethyl -dabrafenib) and trametinib will be determined in plasma samples using the currently approved analytical methodology. Concentrations of panitumumab will be determined in serum samples using a validated method. Raw data will be stored by Novartis.

6.7. Pharmacodynamic [redacted]

6.7.1. Fresh Pre-and Post-dose Tumor Tissues

Tumor specimens that are accessible and can be sampled easily will be requested in Part 1, Part 2 and Part 4. These biopsies will be taken during the screening period, e.g., within 14 days before treatment, and within 2 to 4 hrs after dosing on Day 15 (+3 days) in those subjects who have signed the corresponding section of the informed consent. Details of the tumor biopsy collection including processing, storage and shipping procedures will be provided in the SPM.

6.7.2. Fresh Tumor Tissue at Progression

Tumor specimens that are accessible and can be sampled easily will be requested from subjects at time of demonstrated progression on therapy from all parts of the study, as determined by RECIST v1.1 criteria. Subjects of interest will be those who have had meaningful clinical response in target lesions (≥20% reduction, or stable disease for ≥6 months) and then progressed on existing target lesions or if a new lesion emerged. The guidance on the lesion selection for the progression biopsy are:

- if subject has new lesions only, preferably biopsy a new lesion if feasible
- if a subject has growth of existing lesions only, biopsy a growing lesion if feasible if a subject has both emergence of new lesions and growth of existing lesions, then biopsy both a new lesion and existing lesions, if feasible.
- If above criteria based lesions are not feasible to be biopsied, selection of lesion will be at the discretion of the interventional radiologist.

[redacted]

[redacted]

6.7.4. Archival tumor tissue

Collection of archival primary tumor tissue is required. These samples will be used to confirm or determine the BRAF or KRAS mutation status of subjects.[redacted]

Samples will be collected as indicated in the Time and Events table (Section 3.11). The timing of the collections may be adjusted on the basis of emerging pharmacokinetic or pharmacodynamic data from this study or other new information in order to ensure optimal evaluation of the pharmacodynamic endpoints.

All samples will be retained for a maximum of 15 years after the last subject completes the trial.

[redacted]

7. LIFESTYLE AND/OR DIETARY RESTRICTIONS

7.1. Contraception Requirements

7.1.1. Female Subjects

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

A female of non-childbearing potential (i.e., physiologically incapable of becoming pregnant) is defined as any female who has had a hysterectomy, bilateral oophorectomy (ovariectomy) 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 subject must have a follicular stimulating hormone (FSH) value >40 mIU/mL and an estradiol value < 40pg/mL (<140 pmol/L).

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

Female subjects of childbearing potential must not become pregnant and so must be sexually inactive by abstinence or use contraceptive methods with a failure rate of < 1% from start of dosing and.

- for 6 months after the last dose of panitumumab (Vectibix)
- for 4 months after the last dose of trametinib in combination with dabrafenib
- for 4 weeks after the last dose of dabrafenib

- for 4 months after the last dose of trametinib.

Abstinence

Sexual inactivity by abstinence must be consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Complete abstinence from sexual intercourse for 14 days prior to first dose of study treatment, through the dosing period, and from the first dose of study drug(s) until 60 days after the last dose of any study drug.

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

Contraceptive Methods with a Failure Rate of ≤ 1%

- Intrauterine device (IUD) or intrauterine system (IUS) that meets the <1% failure rate as stated in the product label
- Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into the study, and this male is the sole partner for that subject. For this definition, "documented" refers to the outcome of the investigator's/designee's medical examination of the subject or review of the subject's medical history for study eligibility, as obtained via a verbal interview with the subject or from the subject's medical records.
- Double-barrier method: condom and occlusive cap (diaphragm or cervical/vault caps) plus vaginal spermicidal agent (foam/gel/film/cream/suppository)

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

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring subjects understand how to properly use these methods of contraception.

7.1.2. Male Subjects

To prevent pregnancy in a female partner or to prevent exposure of any partner to the study treatment from a male subject's semen, male subjects must use one of the following contraceptive methods from 7 days prior to the first dose and until 6 months after the last dose of panitumumab, or 16 weeks following the last dose of dabrafenib or trametinib, whichever is later to allow for clearance of any altered sperm:

- Condom *(during non-vaginal intercourse with any partner - male or female)* plus partner use of a highly effective contraceptive (see list in Section 7.1.1).

- Abstinence, defined as sexual inactivity consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception

7.2. Meals and Dietary Restrictions

Dabrafenib and trametinib should be administered **in the morning** at approximately the same time every day. The second dose of dabrafenib (150 mg) should be administered approximately 12 hours after the morning dose. 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.

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

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

8. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

8.1. Permitted Medications

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. 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, and the dates of administration are to be recorded. Additionally, a complete list of all prior cancer therapies will be recorded in the eCRF.

Subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines. Growth factors and bisphosphonates are allowed but must not be initiated during the first 4 weeks of treatment. Use of anticoagulants such as warfarin is permitted however, caution should be exercised and additional International Normalized Ratio (INR) monitoring is recommended when dabrafenib is used concomitantly with warfarin.

While patients are on study treatment, palliative radiation therapy is permitted for non-target lesions that are either new or present at baseline.

Radiation skin injury has been reported with concurrent use of dabrafenib and radiation. It is recommended that dabrafenib be held for seven days before and two days after XRT

in subjects receiving dabrafenib monotherapy or in combination with trametinib. These recommendations can be modified based on the physician's assessment of the risk of radiation skin injury.

8.2. Prohibited Medications

The use of certain medications, and illicit drugs within 5 half-lives or 28 days, whichever is shorter prior to the first dose of study drug and for the duration of the trial will not be allowed. If a prohibited medication is required for single use (such as for a procedure) while study drug is held, the Novartis Medical Lead can approve such use.

The following medications or non-drug therapies are prohibited:

- Other anti-cancer therapy while on treatment in this study.
- Antiretroviral drugs.
- Herbal remedies (e.g., St. John's wort).
- Dabrafenib is metabolized primarily by Cytochrome P450 (CYP) 2C8 and CYP3A4. Co-administration of dabrafenib with ketoconazole, a CYP3A4 inhibition, or with gemfibrozil, a CYP2C8 inhibitor, resulted in increases in dabrafenib AUC of 71% and 47%, respectively. Drugs that are strong inhibitors or inducers of CYP3A and CYP2C8 (see list in Table 32) may only be used under special circumstances (e.g. as a single use for a procedure) while treatment with study drug is interrupted as they may alter dabrafenib concentrations; consider therapeutic substitutions for these medications. Approval of the Novartis Medical Lead is required in these situations. The list may be modified based on emerging data.
- Oral contraceptives (either combined or progesterone only), estrogenic vaginal ring/percutaneous contraceptive patches, or implants of levonorgestrel/Injectable progesterone is prohibited in this study as it is not known if there is the potential of inhibition/induction of enzymes that affect the metabolism of estrogens and/or progestins. HRT is permitted.

Table 32 Prohibited Medications

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

a. Topical formulations of these drugs/agents can be used.

8.3. Cautionary Medications

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

- Drugs that are moderate inhibitors or inducers of CYP3A, CYP2C8, or Pgp or Bcrp transporter because they may alter dabrafenib concentrations.
- Dabrafenib has been shown to induce CYP3A4 and CYP2C9 in vivo using midazolam (CYP3A4 substrate) and S-warfarin (CYP2C9 substrate). Dabrafenib is an in vitro inducer of CYP2B6 and other enzymes such as CYP2C8, CYP2C19, UDP-glucuronyl transferases, and transporters may also be affected. Co-administration of dabrafenib and medications which are affected by the induction of these enzymes (including warfarin) may result in loss of efficacy. If co-administration of these medications is necessary, investigators should monitor subjects for loss of efficacy or consider substitutions of these medications.
- Therapeutic level dosing of warfarin can be used with approval by the Novartis Medical Lead and close monitoring of PT/INR by the site. Exposure decreased by 37% due to enzyme induction when on treatment, thus warfarin dosing may need to be adjusted based upon PT/INR. Consequently, when discontinuing dabrafenib, warfarin exposure may be increased and thus close monitoring via PT/INR and warfarin dose adjustments must be made as clinically appropriate. Prophylactic low dose warfarin may be given to maintain central catheter patency.
- Dabrafenib solubility is pH-dependent with decreased solubility at higher pH. Drugs such as proton pump inhibitors that inhibit gastric acid secretion to elevate gastric pH may decrease the solubility of dabrafenib and reduce its bioavailability. No clinical study has been conducted to evaluate the effect of

pH on dabrafenib pharmacokinetics. In an ad-hoc analysis, no differences in C_{max} and AUC were noted between subjects who reported taking pH-elevating products relative to other subjects. Due to the theoretical risk that pH-elevating agents may decrease oral bioavailability and exposure to dabrafenib, these medicinal products that increase gastric pH should be used with caution when administered with dabrafenib.

These include but are not limited to those listed in Table 33.

Table 33 Cautionary Medications

USE WITH CAUTION: Moderate inhibitors of CYP3A, or CYP2C8 since concentrations of dabrafenib may be increased	
Class/Therapeutic Area	**Moderate CYP3A and CYP2C8 Inhibitors**
Antiarrhythmics	Diltiazem, verapamil
Oral Antibiotic	Erythromycin
Oral Antifungal	Fluconazole
Miscellaneous	Aprepitant,
USE WITH CAUTION: Co-administration of these drugs with study treatment may result in loss of efficacy. Monitor subjects for loss of efficacy or substitute with another medication.	
Class/Therapeutic Area	**CYP3A4, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or Transporter Substrates that May be Affected by Induction**
Analgesics	Alfentanil, buprenorphine, celecoxib, codeine, fentanyl, methadone, oxycodone
Antiarrhythmics	Disopyramide, dronedarone, mexiletine, propafenone, quinidine

USE WITH CAUTION: Co-administration of these drugs with study treatment may result in loss of efficacy. Monitor subjects for loss of efficacy or substitute with another medication.	
Class/Therapeutic Area	**CYP3A4, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or Transporter Substrates that May be Affected by Induction**
Oral 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
Oral Antifungals	Caspofungin, fluconazole, terbinafine

USE WITH CAUTION: Co-administration of these drugs with study treatment may result in loss of efficacy. Monitor subjects for loss of efficacy or substitute with another medication.	
Class/Therapeutic Area	**CYP3A4, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or Transporter Substrates that May be Affected by Induction**
Antihistamines	Astemizole, chlorpheniramine, ebastine
Antihypertensives	Amlodipine, diltiazem, felodipine, nifedipine, nilvadipine, nisoldipine, verapamil
Antimigraine Agents	Diergotamine, eletriptan, ergotamine
Corticosteroids	Dexamethasone, methylprednisolone, oral budesonide
Erectile Dysfunction Agents	Sildenafil, tadalafil, vardenafil
HMG-CoA Reductase Inhibitors	Atorvastatin, lovastatin, simvastatin, rosuvastatin, pravastatin
Hypnotics and Sedatives	Alprazolam, brotizolam, diazepam, estazolam, midazolam, triazolam, zolpidem, zopiclone
Immunosuppressants	Everolimus, sirolimus, tacrolimus
Miscellaneous	Aprepitant, cisapride, darifenacin, disopyramide, leflunomide, methohexital, oral contraceptives, quinine, ranitidine, solifenacin, sulfasalazine, tramadol, tolvaptan, chloroquine, zopiclone
Selective Aldosterone Blockers	Eplerenone
USE WITH CAUTION: Co-administration of drugs that increase gastric pH should be used with caution when administered with dabrafenib.	
pH altering agents	dexlansoprazole. esomeprazole, famotidine, ilaprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, ranitidine
Abbreviations: CYP = cytochrome P450; HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A	

Questions regarding concomitant medications should be directed to the Novartis Medical Lead for clarification.

8.4. Non-Drug Therapies

Subjects must abstain from taking any vitamins, herbal and dietary supplements within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication until completion of the follow-up visit, unless in the opinion of the investigator and sponsor the medication will not interfere with the study.

9. COMPLETION OR EARLY WITHDRAWAL OF SUBJECTS

9.1. Screen and Baseline Failures

Data for screen and baseline failures will be collected in source documentation at the site but will not be transmitted to Novartis.

9.2. Subject Completion Criteria

A completed subject is one who has discontinued study treatment for reasons listed in Section 3.10 and was followed to death or has died while receiving study treatment.

Subjects will be considered to have completed the study if they died or were ongoing at the time the study has completed. Subjects who have not died, and are no longer being followed for survival are considered to have discontinued the study. The End of Study eCRF should only be completed when a subject is no longer being followed. The study will be considered completed for purposes of a final analysis when a total of 99 deaths have occurred (70% of subjects enrolled have died). If available, subjects continuing on treatment at the time 70% of deaths have been observed may be offered the option to continue in a rollover trial.

9.3. Permanent Discontinuation from Study Treatment

Subjects will receive study treatment until disease progression, death or unacceptable toxicity, including meeting stopping criteria for liver chemistry defined in Section 3.10. In addition, study treatment may be permanently discontinued for any of the following reasons:

- deviation(s) from the protocol
- investigator's discretion
- intercurrent illness that prevents further administration of study treatment(s)
- subject is lost to follow-up study is closed or terminated.
- Disease progression. Note: Continuation of study treatment beyond radiographic disease progression (as defined by RECIST 1.1) may be possible if the investigator determines that subject has clear evidence of clinical benefit from study treatment, continuing study drug(s) may be in the best interest for the subject and the subject is willing to continue on study drug(s). In this case, consultation between the investigator and the Novartis Medical Lead is mandatory. If continuing the subject on study treatment is agreed then all study procedures, including tumor assessments, must be followed as scheduled (Section 3.11). In addition, after each tumor assessment, the investigators must confirm with the Novartis Medical Lead that the subject is still benefitting from study treatment and therefore can continue receiving study treatment.
- Female subject becomes pregnant;
- Adverse event that is considered by the investigator or a Novartis Medical Lead to warrant permanent discontinuation of the study drug;

- A clinically significant AE leading to an interruption of treatment for >14 consecutive days. If the investigator and the Novartis Medical Lead conclude that continued treatment will benefit a subject who has had a >14 day treatment delay, then the subject may continue therapy with the approval of the Novartis Medical Lead.
- Subject withdraws consent for further treatment or data collection:
  - If the subject withdraws consent for further treatment, follow-up visit assessments should be completed (as indicated in the Time and Events table (Section 3.11).
  - If the subject withdraws consent for further treatment and data collection, then no additional study visits or data collection should occur.
- Subject is withdrawn at the discretion of the investigator for safety, behavioral, or administrative reasons.

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

9.4. Subject Withdrawal Procedures

9.4.1. Subject Withdrawal from Study

Following permanent discontinuation of study treatment, every effort should be made for subjects to complete the follow-up visit as described in the Time and Events Table (Section 3.11). The follow-up visit should occur approximately 14 days from last dose of study drugs (±7 days) and prior to initiating further anti-cancer therapy or dosing of a different investigational agent. The reason for discontinuing treatment with study drug will be clearly documented in the subject's medical record and on the Study Conclusion eCRF page. If the subject withdraws from treatment due to toxicity, 'Adverse Event' will be recorded as the primary reason for withdrawal.

9.4.2. Subject Withdrawal from Study Treatment

If the subject withdraws consent for further treatment, final study visit should be completed (see Time and Events Tables in Section 3.11). If the subject withdraws consent for further treatment and data collection, then no additional study visits or data collection should occur. The investigator may also, at his or her discretion, discontinue a subject from participating in this study at any time.

In the event that a subject is prematurely discontinued from the study at any time due to an AE (as defined in Section 0, "Definition of an AE") or SAE (as defined in Section 11.1 "Definition of a SAE"), the procedures stated in Section 11.4, ("AEs and SAEs") must be followed. All subjects who have a Grade 3 or 4 clinical or laboratory abnormality at the time of withdrawal from the study must be followed until resolution to Grade 2 or less, unless it is unlikely to improve because of underlying disease.

9.5. Treatment After the End of the Study

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

Subjects will receive standard of care treatment as determined by their health care provider after discontinuation from the study.

10. STUDY TREATMENT

Study treatment dosage and administration details are listed in Section 3.9.

Supplies of the investigational products will be provided to sites by Novartis, with the exception of sites in China (if applicable) where GSK will continue to provide supplies.

10.1. Blinding

This will be an open-label study.

10.2. Packaging and Labeling

The contents of the label will be in accordance with all applicable regulatory requirements.

10.3. Preparation/Handling/Storage/Accountability

Investigational products (dabrafenib and trametinib) must be dispensed or administered according to procedures described herein. Only subjects enrolled in the study may receive investigational product. Only authorized site staff may supply or administer investigational product.

10.3.1. Preparation

No special preparation of dabrafenib and trametinib is required. Refer to the GSK2118436 IB [GlaxoSmithKline Document Number 2012N136095_00], the GSK1120212 IB [GlaxoSmithKline Document Number HM2009/00151/03] and the GSK1120212 + GSK2118436 Clinical IB [GlaxoSmithKline Document Number, 2011N126811_00] for detailed information regarding dabrafenib and trametinib.

Please refer to the FDA approved label and/or EU SmPC for panitumumab for updated detailed information. The following text is summarized from the approved FDA label [VECTIBIX, 2014].

Prepare the solution for infusion, using aseptic technique, as follows:

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Although panitumumab should be colorless, the solution may contain a small amount of visible translucent-to-white,

amorphous, proteinaceous, panitumumab particulates (which will be removed by filtration; see below). Do not shake. Do not administer if discoloration is observed.

- Withdraw the necessary amount of panitumumab for the study- prescribed dose.
- Dilute to a total volume of 100 mL with 0.9% sodium chloride injection, USP. Doses higher than 1000 mg should be diluted to 150 mL with 0.9% sodium chloride injection, USP. Do not exceed a final concentration of 10 mg/mL.
- Mix diluted solution by gentle inversion. Do not shake.
- Administer using a low-protein-binding 0.2μm or 0.22μm in-line filter.
- Vectibix must be administered via infusion pump.
    - Flush line before and after Vectibix administration with 0.9% sodium chloride injection, USP, to avoid mixing with other drug products or intravenous solutions. Do not mix Vectibix with, or administer as an infusion with, other medicinal products. Do not add other medications to solutions containing panitumumab.
    - Infuse over 60 minutes through a peripheral intravenous line or indwelling intravenous catheter. Doses higher than 1000mg should be infused over 90 minutes.

10.3.2. Handling and Storage of Study Treatments

Precaution will be taken to avoid direct contact with the investigational product. Material Safety Data Sheets (MSDS) for dabrafenib and trametinib describing occupational hazards and recommended handling precautions will be provided to the investigator.

Please refer to the FDA approved label and/or EU SmPC for panitumumab for updated detailed information [VECTIBIX, 2014].

However, precautions are to be taken to avoid direct skin contact, eye contact, and generating aerosols or mists. In the case of unintentional occupational exposure notify the Medical Lead and/or study manager.

Precaution will be taken to avoid direct contact with the investigational product. A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions will be provided to the investigator.

Dabrafenib and trametinib must be dispensed and administered in accordance with the protocol, and only to subjects 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.

Please refer to the FDA approved label and/or EU SmPC for panitumumab for updated detailed information. The following text is summarized from the approved FDA label [VECTIBIX, 2014]. Store vials in the original carton under refrigeration at 2° to 8°C (36° to 46°F) until time of use. Protect from direct sunlight. DO NOT FREEZE. Since panitumumab does not contain preservatives, any unused portion remaining in the vial must be discarded.

Procedures for final disposition of unused study treatments will be provided in the Study Procedures Manual (SPM).

10.3.3. 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 (IP) dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to Novartis, when applicable. Product accountability records must be maintained throughout the course of the study.

The required accountability unit for this study will be tablet (trametinib), capsule (dabrafenib) and vial (panitumumab). Discrepancies are to be reconciled or resolved.

Refer to the SPM for further detailed instructions on product accountability. Procedures for final disposition of unused investigational product are listed in the SPM.

10.4. Assessment of Compliance

When subjects are dosed at the study site, they will receive study treatment(s) directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents, including a supplied subject dosing diary. When subjects are dosed at the study site, the dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

When subjects self-administer study treatment(s) at home, compliance with dabrafenib and/or trametinib dosing will be assessed through querying the subject during the site visits, review of the subject dosing diary and documented in the source documents and electronic case report form (eCRF). A record of the number of dabrafenib capsules and/or trametinib tablets dispensed to and taken by each subject 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 eCRF.

Panitumumab will be intravenously administered to subjects at the study site. Administration will be documented in the source documents and reported in the electric case report form (eCRF).

10.5. Treatment of Study Treatment Overdose

In the event of a dabrafenib overdose, defined as administration of more than 300mg as a single dose or 600mg daily (the highest dose tested in clinical studies to date), or in the event of 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 Novartis Medical Lead immediately and closely monitor the subject for AEs/SAEs and laboratory abnormalities. Novartis does not recommend specific treatment. The investigator will use clinical judgment to treat any overdose. Haemodialysis is not expected to enhance the elimination of either dabrafenib or trametinib as both are highly bound to plasma proteins.

In the event of an overdose of panitumumab, refer to the package insert [VECTIBIX, 2014].

Decisions regarding dose interruptions or modifications should be made by the investigator in consultation with the Novartis Medical Lead based on the clinical evaluation of the subject.

A plasma sample for PK analysis may be requested by the Novartis Medical Lead on a case-by-case basis. This plasma sample should be collected as soon as possible, but within 10 days from the date of the last dose of on-study dosing.

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

11. ADVERSE EVENTS (AE) AND SERIOUS ADVERSE EVENTS (SAE)

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE. The severity of adverse events (AEs) will be graded utilizing the National Cancer Institute- Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 4.0.

AEs will be collected from the time a subject consents to participate in and completes the study (See Section 9.2), all SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy), will be reported promptly to Novartis, as indicated in Section 11.5 from the start of Study Treatment and until the follow-up contact.

SAEs will be collected over the same time period as stated above for AEs. In addition, any SAEs assessed **as related** to study participation (e.g. protocol-mandated procedures, invasive tests, or change in existing therapy, study treatment[s]) will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact. All SAEs will be recorded. Only SAEs relating to study procedures should be reported to Novartis within 24 hours, as indicated in Section 11.4.

After discontinuation of study treatment, the investigator will monitor all AEs/SAEs that are ongoing until resolution or stabilization of the event or until the subject is lost to follow-up. At any time after at least 5 terminal half lives or 30 days the investigator may report any AE that they believe possibly related to study treatment.

Definition of Adverse Events

An AE is any untoward medical occurrence in a subject or clinical investigation subject, 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 unfavorable 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
- 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/serious adverse event [SAE]).
- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment of the investigator.

"Lack of efficacy" or "failure of expected pharmacological action" *per se* is not to be reported as an AE or SAE. However, any signs and symptoms and/or clinical sequelae resulting from "lack of efficacy" will be reported as an AE or SAE, if they fulfill the definition of an AE or SAE.

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

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (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.

- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

11.1. Definition of Serious Adverse Events

If an event is not an AE per Section 0, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

An 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 subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

   NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

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

d. Results in disability/incapacity, 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, diarrhea, influenza, and 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

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

g. Is associated with liver injury **and** impaired liver function defined as:

- ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or**
- ALT ≥ 3xULN and INR** > 1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

- Refer to Section 12 for the required liver chemistry follow-up instructions.

h. All grade 4 laboratory abnormalities.

i. 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 subjects receiving anticoagulants).

  Note: Bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥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 tumor, including cutaneous squamous cell carcinoma, basal cell carcinoma, and secondary melanoma

- Symptomatic LVEF decrease that meets stopping criteria or asymptomatic LVEF decrease that does not recover, as outlined as LVEF guidance Section 3.10.7.1.

- RPED or RVO.

11.2.1. Sentinel Events

A Sentinel Event is a Novartis -defined SAE that is not necessarily drug-related but has been associated historically with adverse reactions for other drugs and is therefore worthy of heightened pharmacovigilance. The Novartis Medical Lead is accountable for reviewing all SAEs for possible Sentinel Events which is mandated at Novartis. The Novartis Medical Lead may request additional clinical information on an urgent basis if a possible Sentinel Event is identified on SAE review. The current Novartis -defined Sentinel Events are listed below:

- Acquired Long QT Syndrome
- Agranulocytosis/Severe Neutropenia
- Anaphylaxis & Anaphylactoid Reactions
- Hepatotoxicity
- Acute Renal Failure
- Seizure
- Stevens Johnson syndrome/Toxic epidermal necrosis

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

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis), or other safety assessments (e.g., electrocardiogram [ECGs], radiological scans, vital signs measurements) 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 an adverse event (AE) or serious adverse event (SAE), 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, dose reduction, and/or dose interruption/delay.

Any new primary cancer must be reported as a SAE.

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

11.3.1. Cardiovascular Events

Investigators will be required to fill out event specific data collection tools for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularisation

This information should be recorded in the specific cardiovascular eCRF within one week of when the AE/SAE(s) are first reported.

11.3. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

11.4.1. Assessment of Causality

The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE. A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated. The investigator will also consult the Investigator Brochure (IB), IB Supplement(s) and/or Product Information, for marketed products, in the determination of his/her assessment.

For each AE/SAE the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to Novartis. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to Novartis.** The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

11.4. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by Novartis to elucidate as fully as possible the nature and/or causality of the AE or SAE. The

investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals. If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide Novartis with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded in the originally completed data collection tool. The investigator will submit any updated SAE data to Novartis within the designated reporting time frames.

11.5. Prompt Reporting of SAEs to Novartis

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

	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"	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	"CV events" and/or "death" data collection tool(s) if applicable	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	Updated "CV events" and/or "death" data collection tool(s) if applicable
Pregnancy	24 hours	Pregnancy Notification Form	2 Weeks	Pregnancy Follow-up Form
Liver chemistry abnormalities:				
ALT ≥3 times ULN and bilirubin ≥2 times ULN (>35% direct) (or ALT ≥3 times ULN and INR >1.5, if INR is measured)[c]	24 hours[a]	SAE data collection tool; Liver Event eCRF and liver imaging and/or biopsy eCRFs if applicable[b]	24 hours	Updated SAE data collection tool. Updated Liver Event eCRF[b]
ALT ≥5 times ULN; ALT ≥3 times ULN with hepatitis or rash **or** 3 times ULN ≥4 weeks	24 hours[a]	Liver Event eCRF[b]	24 hours	Updated Liver Event eCRF[b]
ALT ≥3 times ULN and <5 times ULN and bilirubin <2 times ULN	24 hours[a]	Liver Event eCRF does not need to be completed unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks[b]		

a. Novartis to be notified at onset of liver chemistry elevations to discuss subject safety.
b. Liver event documents should be completed as soon as possible
c. INR measurement is not required; if measured, the threshold value stated will not apply to subjects receiving anticoagulants.

Methods for detecting, recording, evaluating, and following up on adverse events (AEs) and serious adverse events (SAEs) are provided in the Study Procedures Manual (SPM).

11.6. Regulatory Reporting Requirements for SAEs

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

Novartis have a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Novartis will comply with country specific regulatory requirements relating to safety reporting to regulatory authorities, IRBs/IECs and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Novartis policy and are 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 Novartis will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

12. LIVER CHEMISTRY FOLLOW-UP PROCEDURES

12.1. Liver Chemistry Testing Procedures

For subjects meeting any of the liver chemistry stopping criteria in Section 3.10.10, 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, then obtain heterophile antibody or monospot testing)
- Blood sample for pharmacokinetic (PK) analysis, obtained within 10 days of the last dose of study drug(s). Record the date and time of the PK blood sample draw and the date and time of the last dose of study drug(s) prior the blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date or time of the last dose cannot be approximated, or if a PK sample cannot be collected within the 10-day period following the last dose, do not obtain a PK sample. Instructions for sample handling and shipping are found in the Study Procedures Manual (SPM).
- Serum creatinine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin ≥2 X upper limit of normal (ULN).
- Obtain a complete blood count (CBC) with differential to assess eosinophilia.

- Record the appearance or worsening of clinical symptoms indicative of hepatitis or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia as relevant on the AE eCRF.
- Record the use of concomitant medications, including acetaminophen, herbal remedies or any other over the counter (OTC) medications, or any putative hepatotoxins, on the concomitant medication eCRF.
- Record alcohol use on the liver event alcohol intake eCRF.

The following assessments are required for subjects with ALT ≥3 X ULN and bilirubin ≥2X ULN (>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.
- Liver imaging (ultrasound, magnetic resonance imaging [MRI] or computed tomography [CT]) to evaluate liver disease.

12.2. Liver Chemistry Monitoring Criteria

For subjects with ALT ≥3 X ULN **but** <5X ULN **and** bilirubin <2 X ULN, without symptoms indicative of hepatitis or rash, and who can be monitored safety for 4 weeks, the following actions should be taken:

- Notify the Novartis Medical Lead within 24 hours of learning of the abnormality to discuss subject safety.
- Continue administration of study drug(s).
- Evaluate liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) weekly until they resolve, stabilize or return to within baseline levels.
- If at any time the subject meets any of the liver chemistry stopping criteria 1 to 5 (Section 3.10.10), then proceed as described in Section 12).
- If, after 4 weeks of monitoring, ALT <3X ULN and bilirubin <2 X ULN, then monitor subjects twice monthly until liver chemistries normalize or return to within baseline values.

12.3. Drug Restart/Rechallenge Following Liver Events that are Possibly Related to Study Drug(s)

Approval by the Novartis Medical Lead to restart/rechallenge study drug(s) may be considered where:

- The subject is receiving compelling benefit, the benefit exceeds the risk, and no effective alternative therapy is available. Approval of restart/rechallenge by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) must be obtained, as required.
- If the restart/rechallenge is approved by Novartis in writing, then the subject must be provided with a clear description of the possible benefits and risks of

administration of study drug(s), including the possibility of a recurrence, a more severe liver injury or death.

- The subject must also provide signed informed consent specifically for the study drug(s) restart/rechallenge. Documentation of the informed consent must be recorded in the subject's study chart.
- Study drug(s) must be administered at the dose specified by the Novartis Medical Lead.
- Subjects approved by Novartis for restart/rechallenge of study drug(s) must return to the clinic twice a week for evaluation of liver chemistry tests until stable liver chemistries have been demonstrated and laboratory monitoring may resume per protocol.

12.4. Drug Restart Following Transient, Resolving Liver Events Not Related to Study Drug(s)

Approval by the Novartis Medical Lead to restart study drug(s) may be considered where:

- Liver chemistry abnormalities 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 <3X ULN. Approval of restart by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) may be required.
- If the restart/rechallenge is approved by Novartis in writing, then the subject must be provided with a clear description of the possible benefits and risks of administration of study drug(s), including the possibility of a recurrence, a more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the study drug(s) restart/rechallenge. Documentation of the informed consent must be recorded in the subject's study chart.
- Study drug(s) must be administered at the dose specified by the Novartis Medical Lead.
- Subjects approved by Novartis for restart/rechallenge of study drug(s) must return to the clinic once a week for evaluation of liver chemistry tests until stable liver chemistries have been demonstrated and laboratory monitoring may resume per protocol.
- If protocol-defined stopping criteria for liver chemistry abnormalities are met, study drug(s) administration must stop.

13. STUDY CONDUCT CONSIDERATIONS

13.1. Posting of Information on Publicly Available Clinical Trial Registers

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

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

Novartis will obtain favorable opinion/approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements prior to a site initiating the study in that country.

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

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and, the guiding principles of the 2008 Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval to conduct the study and of any subsequent relevant amended documents
- Written informed consent (and any amendments) to be obtained for each subject before participation in the study
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)

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

In approving the clinical protocol the IEC/IRB and, where required, the applicable regulatory agency are also approving the optional assessments, [redacted], unless otherwise indicated. Where permitted by regulatory authorities, approval of the optional assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the optional assessments is being deferred and the study, except for the optional assessments, can be initiated. When the optional assessments are not approved, then the approval for the rest of the study will clearly indicate this and therefore, the optional assessments will not be conducted.

13.2.1. Urgent Safety Measures

If an event occurs that is related to the conduct of the study or the development of the study treatment, and this new event is likely to affect the safety of subjects, the sponsor and the investigator will take appropriate urgent safety measures to protect subjects against any immediate hazard.

The sponsor will work with the investigator to ensure the IEC/IRB is notified.

13.3. Quality Control (Study Monitoring)

In accordance with applicable regulations including GCP, and Novartis procedures, Novartis personnel (or designated Clinical Research Organization [CRO]) will contact the site 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 Novartis requirements. When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the CRF will serve as the source document.

Novartis (or designated CRO) personnel will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the Medical Lead direct access to all relevant documents

13.4. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, Novartis 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.

13.5. Study and Site Closure

Upon completion or premature discontinuation of the study, Novartis personnel (or designated CRO)will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and Novartis procedures.

In addition, Novartis reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites. If Novartis determines such action is needed, Novartis will discuss this with the investigator or the head of the medical institution (where applicable), including the reasons for taking such action. When feasible, Novartis will provide advance notification

to the investigator or the head of the medical institution, where applicable, of the impending action prior to it taking effect.

If the study is suspended or prematurely discontinued for safety reasons, Novartis will promptly inform investigators or the head of the medical institution (where applicable) and the regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action. If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

13.6. Records Retention

Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records, except for those required by local regulations to be maintained by someone else, in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible and are a true and accurate copy of the original, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless the Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.The investigator must notify Novartis of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator leaves the site.

13.7. Provision of Study Results to Investigators, Posting of Information on Publically 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. Investigators 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 Novartis site or other mutually-agreeable location.

Novartis will also provide investigators with the full summary of the study results. Investigators are encouraged to share the summary results with the study subjects, as appropriate.

Novartis will provide the investigator with the randomization codes for their site after completion of the full statistical analysis and finalization of the clinical study report (CSR).

Novartis aims to post a results summary to the Novartis Clinical Trial Results website (www.novartisclinicaltrials.com) and other publicly available registers no later than 12 months after the last subject's last visit (LSLV). In addition, upon study completion and finalization of study report, Novartis aims to submit results of the study for publication.

When publication is not feasible, please refer to the Novartis Clinical Trial Results website (www.novartisclinicaltrials.com) for a summary of the trial results.

13.8. Data Management

For this study subject data will be entered into the electronic case report forms (eCRFs), transmitted electronically to the sponsor (or designee) and be combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable Novartis standards and data cleaning procedures to ensure the integrity of the data, e.g., resolving errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and a custom drug dictionary. eCRFs (including queries and audit trails) will be retained by Novartis, and copies will be sent to the investigator to maintain as the investigator copy.

13.9. Independent Data Monitoring Committee (IDMC)

An IDMC will be utilized during the conduct of this study to review all available data in Part 3. An IDMC is generally assembled when there are significant safety or efficacy issues that warrant external objective medical and/or statistical review in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. The schedule of any planned interim analysis and the analysis plan for IDMC review is described in the charter. A copy of the IDMC charter will be available from Novartis, prior to start of Part 3, upon request.

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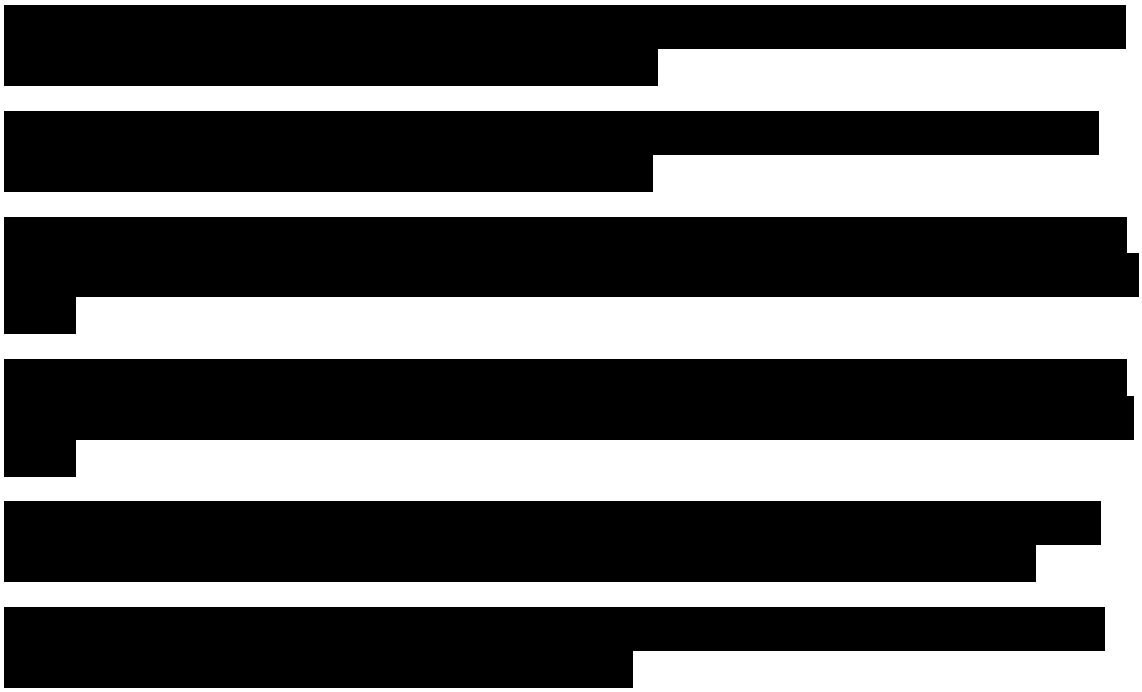

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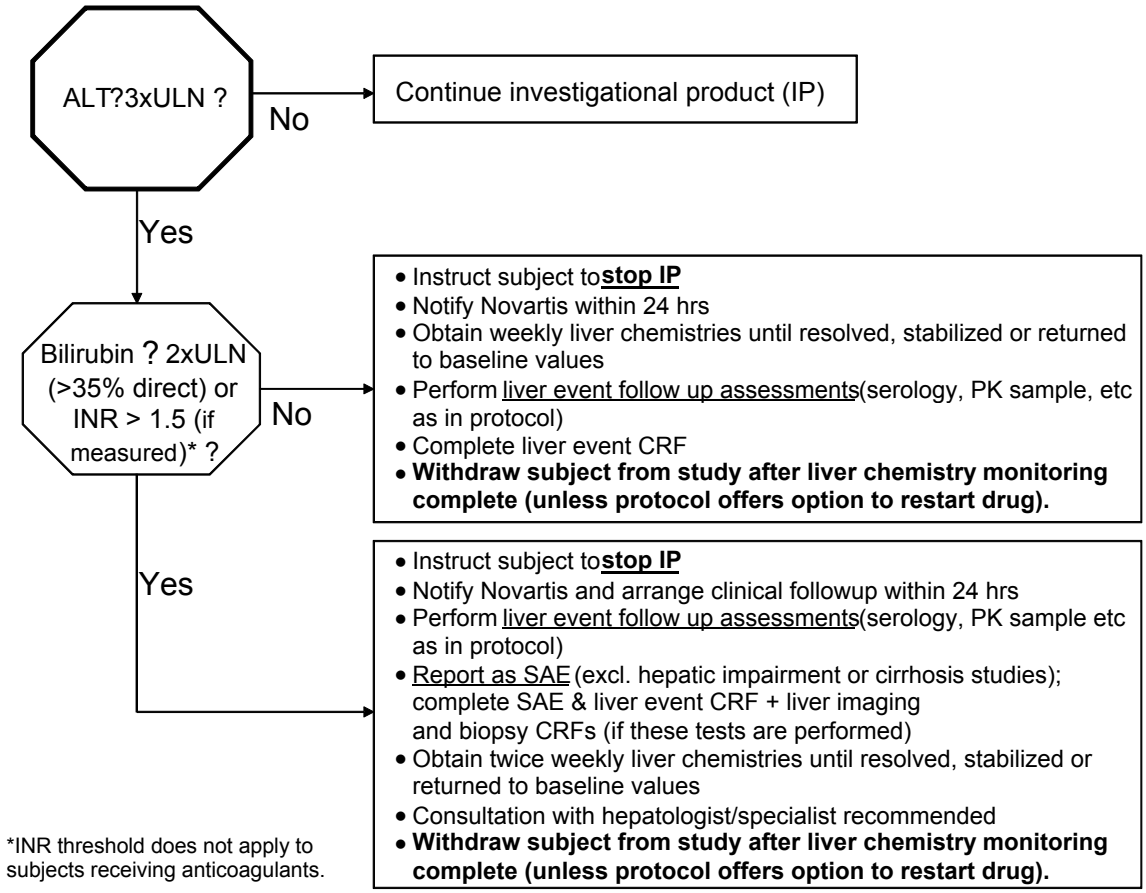
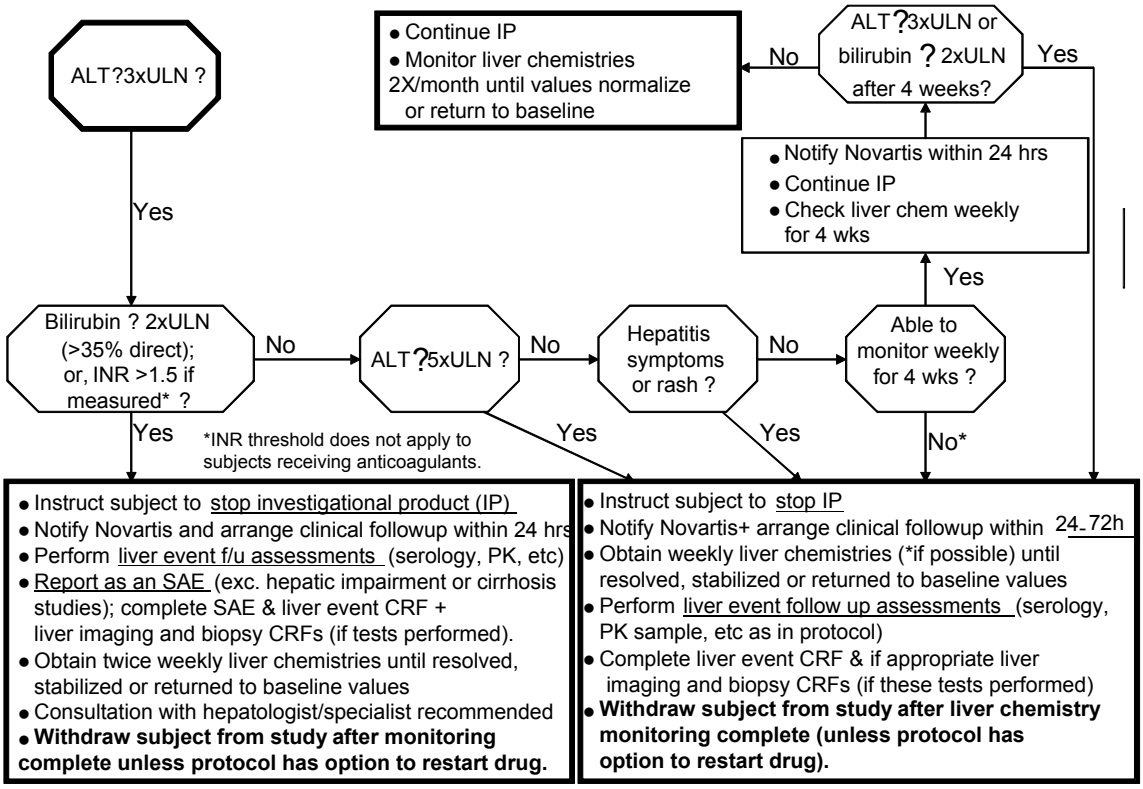
Appendices

Appendix 1: Liver Safety Algorithms

Part 1, Part 2 and Part 4



Part 3


ALT?3xULN ?
Yes
Bilirubin ? 2xULN (>35% direct); or, INR >1.5 if measured* ?
No
ALT?5xULN ?
No
Hepatitis symptoms or rash ?
No
Able to monitor weekly for 4 wks ?
Yes
No*
Yes
Yes
Yes
*INR threshold does not apply to subjects receiving anticoagulants.
● Instruct subject to stop investigational product (IP)
● Notify Novartis and arrange clinical followup within 24 hrs
● Perform liver event f/u assessments (serology, PK, etc)
● Report as an SAE (exc. hepatic impairment or cirrhosis studies); complete SAE & liver event CRF + liver imaging and biopsy CRFs (if tests performed).
● Obtain twice weekly liver chemistries until resolved, stabilized or returned to baseline values
● Consultation with hepatologist/specialist recommended
● Withdraw subject from study after monitoring complete unless protocol has option to restart drug.
● Instruct subject to stop IP
● Notify Novartis+ arrange clinical followup within 24-72h
● Obtain weekly liver chemistries (*if possible) until resolved, stabilized or returned to baseline values
● Perform liver event follow up assessments (serology, PK sample, etc as in protocol)
● Complete liver event CRF & if appropriate liver imaging and biopsy CRFs (if these tests performed)
● Withdraw subject from study after liver chemistry monitoring complete (unless protocol has option to restart drug).
ALT?3xULN or bilirubin ? 2xULN after 4 weeks?
No
Yes
● Continue IP
● Monitor liver chemistries 2X/month until values normalize or return to baseline
● Notify Novartis within 24 hrs
● Continue IP
● Check liver chem weekly for 4 wks
Yes

Appendix 2: Blood Requirements

Part 1: Dose Escalation Cohorts

Test	Sample Volume	Total Volume for Screening, One 4-wk treatment period and Follow-up
Hematology/Clin Chem	5 mL	30
Coagulation	5 mL	5
PK Analysis (panitumumab)	4 mL	20
PK & Metabolite Analysis (dabrafenib, trametinib)	4 mL	48
[redacted]		
Serum Pregnancy Test	1 mL	1
CEA	2 mL	12
Total		**167mL/subject plus any wasteage associated with collection**

Part 2: Expansion Cohorts

Test	Sample Volume	Total Volume for Screening, One 4-wk treatment period and Follow-up
Hematology/Clin Chem	5 mL	25
Coagulation	5 mL	5
PK Analysis (panitumumab)	4 mL	16
PK & Metabolite Analysis (dabrafenib, trametinib)	4 mL	48
[redacted]		
Serum Pregnancy Test	1 mL	1
[redacted]		
CEA	2	10
Total		**187mL/subject plus any wasteage associated with collection**

Part 3: Randomized Phase II Study

Test	Sample Volume	Total Volume for Screening, One 4-wk treatment period and Follow-up
Hematology/Clin Chem	5 mL	20
Coagulation	5 mL	5
[redacted]		
Serum Pregnancy Test	1 mL	1
Total		**82/subject plus any wasteage associated with collection**

Part 4A and 4B: Dose Escalation and Expansion Cohorts

Test	Sample Volume	Total Volume for Screening, One 4-wk treatment period and Follow-up
Hematology/Clin Chem	5 mL	20
Coagulation	5 mL	5
PK Analysis (panitumumab)	4 mL	16
PK & Metabolite Analysis (dabrafenib, trametinib)	4 mL	48
[redacted]		
Serum Pregnancy Test	1 mL	1
[redacted]		
CEA	2	10
Total		**182mL/subject plus any wasteage associated with collection**

Appendix 3: Liver Safety Drug Restart Guidelines

Drug restart may be considered for a subject exhibiting compelling benefit for a critical medicine following drug-induced liver injury, if there is favorable benefit: risk ratio and no alternative medicine available.

Background Information on Drug Restart/Rechallenge

Following drug-induced liver injury, **drug restart or rechallenge is associated with a 13% mortality across all drugs in prospective studies.**[1] Clinical outcomes vary by drug, with nearly 50% fatality with halothane readministered in one month of initial injury. However, some drugs seldom result in recurrent liver injury or fatality. Risk factors for a fatal drug restart/rechallenge outcome include: hypersensitivity[1] with initial liver injury (e.g. fever, rash, eosinophilia), jaundice or bilirubin ≥2xULN or INR>1.5 suggesting severe liver injury, prior IP-related severe or fatal drug restart/rechallenge[2,3] or evidence of drug-related preclinical liability / mitochondrial impairment[3].

Drug Restart/Rechallenge Process (also see Figure 1)

1. Principal Investigator (PI) requests consideration of drug restart for a subject receiving compelling benefit from a critical or life-saving drug, who exhibits liver chemistry elevation meeting subject stopping criteria, with no alternative treatment.
2. Novartis Safety Monitoring Team (SMT) to review the subject's restart/rechallenge risk factors and complete checklist (Table 34).

Table 34 Checklist for drug restart/rechallenge for critical medicine

(Following drug-induced liver injury, drug rechallenge is associated with 13% mortality across all drugs in prospective studies)		
	Yes	**No**
Compelling benefit of the investigational product (IP) **for this subject and no alternative therapy**. **Provide brief explanation**:		
Relative benefit-risk favorable for drug restart/rechallenge, after considering the **following high risk factors**:		
• Initial liver injury event included:		
– fever, rash, eosinophilia, or hypersensitivity		
– or bilirubin ≥2xULN (direct bilirubin >35% of total)		
• Subject currently exhibits ALT ≥3xULN, bilirubin ≥2xULN (direct bilirubin >35% of total, if available), or INR ≥1.5		
• Severe or fatal restart/rechallenge has earlier been observed with IP **If yes, please provide brief explanation**:		
• IP associated with known preclinical hepatic liability/ injury		

3. If Novartis provides written approval for restart/rechallenge following the above review, the Principal Investigator (PI) must ensure the following:

   - The PI is to obtain Ethics Committee or Institutional Review Board review of drug re-initiation, as required.

   - PI must discuss the possible benefits and risks of drug re-initiation with the subject.

   - The subject must sign informed consent with a clear description of possible benefits and risks of drug administration, including recurrent liver injury or death. Consent specifically for the IP restart must be recorded in the study chart.

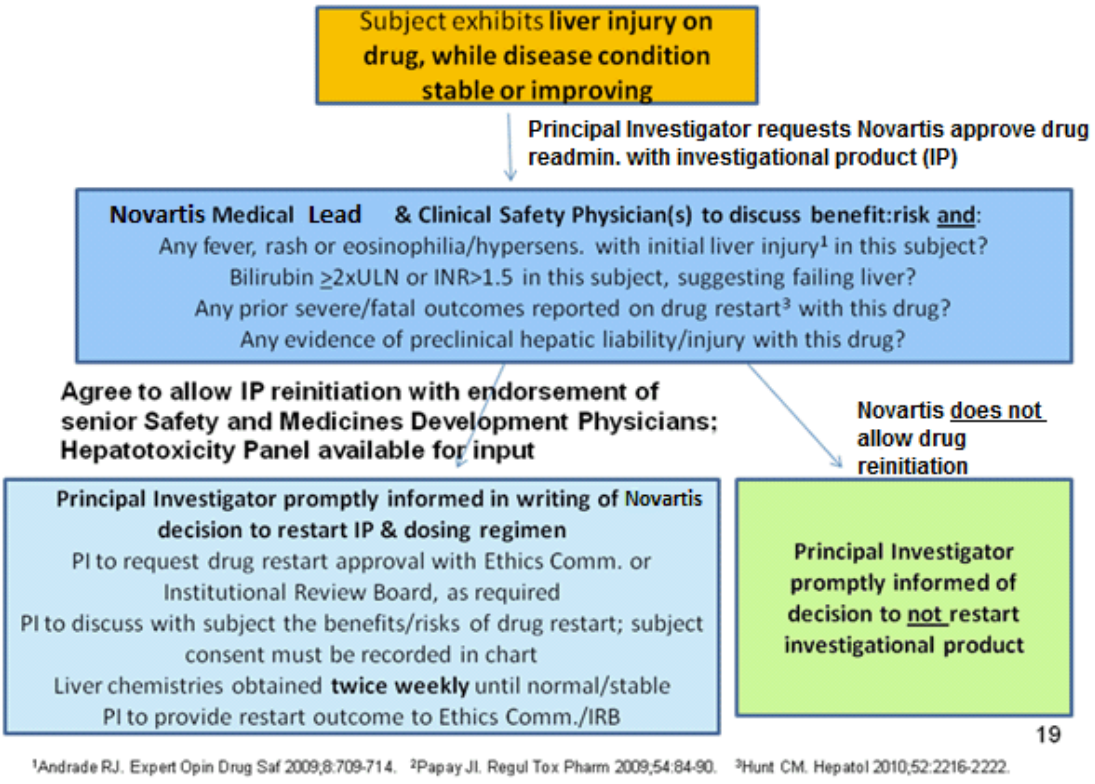
   - The drug must be reinitiated at Novartis approved dose(s).

   - Subjects approved by Novartis for restart of IP 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. If protocol defined stopping criteria for liver chemistry elevations are met, study drug must be stopped.

   - The Ethics Committee or Institutional Review Board is to be informed of the subject's outcome, as required.

   - Novartis is to be notified of any adverse events, as per Section 11.

Figure 1 Novartis process for drug restart after possible drug-induced liver injury



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Appendix 4: RECIST 1.1 Criteria

[Eisenhauer, 2009]

Measurability of tumor lesions at baseline

Measurable lesion:

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

- ≥10 mm with MRI or CT when the scan slice thickness is no greater than 5mm. If the slice thickness is greater than 5mm, 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 calliper/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

- ≥15mm in the short axis when assessed by CT or MRI (slice thickness recommended to be no more than 5mm). At baseline and follow-up, only the short axis will be measured [Eisenhauer, 2009].

Non-measurable lesion:

All other lesions including lesions too small to be considered measurable (longest diameter <10 mm or pathological lymph nodes with ≥ 10 mm and <15 mm short axis) 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, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques [Eisenhauer, 2009].

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

Non-Measurable only disease: The presence of only non-measurable lesions.

Specifications by methods of measurements

- The same diagnostic method, including use of contrast when applicable, must be used throughout the study to evaluate a lesion.
- 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 (FDG)-PET is generally not suitable for ongoing assessments of disease. However FDG-PET can be useful in confirming new sites of disease where a positive FDG-PET scans 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. 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 on the CRF.

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

CT and MRI: <u>Contrast enhanced CT with 5mm contiguous slices is recommended.</u> 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. 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. [Eisenhauer, 2009].

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].

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 be <10mm in the short axis.
- 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 (e.g. percent change from baseline).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease.

- 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 (e.g. 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 5mm.
- Not Applicable (NA): No target lesions at baseline.
- Not Evaluable (NE): Cannot be classified by one of the five preceding definitions.

Note:

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

Evaluation of non-target lesions

Definitions for assessment of response for non-target lesions 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 (e.g. <10 mm short axis).
- 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 ≥ 10 mm short axis.

- 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 four 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.
- In the presence of non-measurable only disease consideration should be given to whether or not the increase in overall disease burden is comparable in magnitude to the increase that would be required to declare PD for measurable disease.
- 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 (e.g. non-target response does not have to be "Not Evaluable").

Frequency of tumor re-evaluation

Target and non-target lesions will be re-evaluated every 6 weeks for the first 24 weeks and every 8 weeks thereafter, or more frequently, based on clinical judgment.

Confirmation of response

To be assigned a status of PR or CR, a confirmatory disease assessment should be performed no less than 4 weeks (28 days) after the criteria for response are first met.

Overall response criteria

Table 35 presents the overall response at an individual time point for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions for subjects with measurable disease at baseline.

Table 35 Evaluation of Overall Response for Subjects with Measurable Disease at Baseline

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

1. CR=complete response, PR = partial response, SD=stable disease, PD=progressive disease, NA= Not applicable, and
2. NE=Not Evaluable

Note:

- Subjects with a global deterioration of health status requiring discontinuation of treatment 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 discontinuation of treatment.
- 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 (fine needle aspirate/biopsy) to confirm the CR.

Appendix 5: Withholding and Stopping Criteria for QTc Prolongation for Subjects Enrolled in France

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 [Bazett, 1920]

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

b. If the QTc prolongation resolves to grade 1 or baseline, the subject may resume study treatment if the investigator and Novartis Medical Lead agree that the subject will benefit from further treatment.

Guidelines for Valvular Toxicity for Subjects Enrolled in France

- Subjects who have an asymptomatic, moderate regurgitation or stenosis by ECHO (Grade 2 mitral/tricuspid/aortic valvular toxicity per CTCAE v4.0) should temporarily discontinue dabrafenib 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.
    - If the valve recovers to baseline any time during the next 4 weeks, after consultation and approval of the Novartis Medical Lead, the subject may be restarted on dabrafenib at a reduced dose(s). For such subjects, 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.
    - If repeat ECHO does not reveal valve recovery to baseline within 4 weeks, then the subject should permanently discontinue dabrafenib. The valve should continue to be monitored via ECHO every 4 weeks for 16 weeks or until resolution.
- Subjects with a Grade 3 or 4 (symptomatic, severe regurgitation/stenosis by imaging, with symptoms controlled by medical intervention) valvular toxicity must discontinue dabrafenib. 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 subject may restart dabrafenib at a reduced dose after consultation and approval of the Novartis Medical Lead. For such subjects, 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 subjects who experience a valvular toxicity will be required by Novartis and its authorized agents for review.

Appendix 6: Bazett's Correction

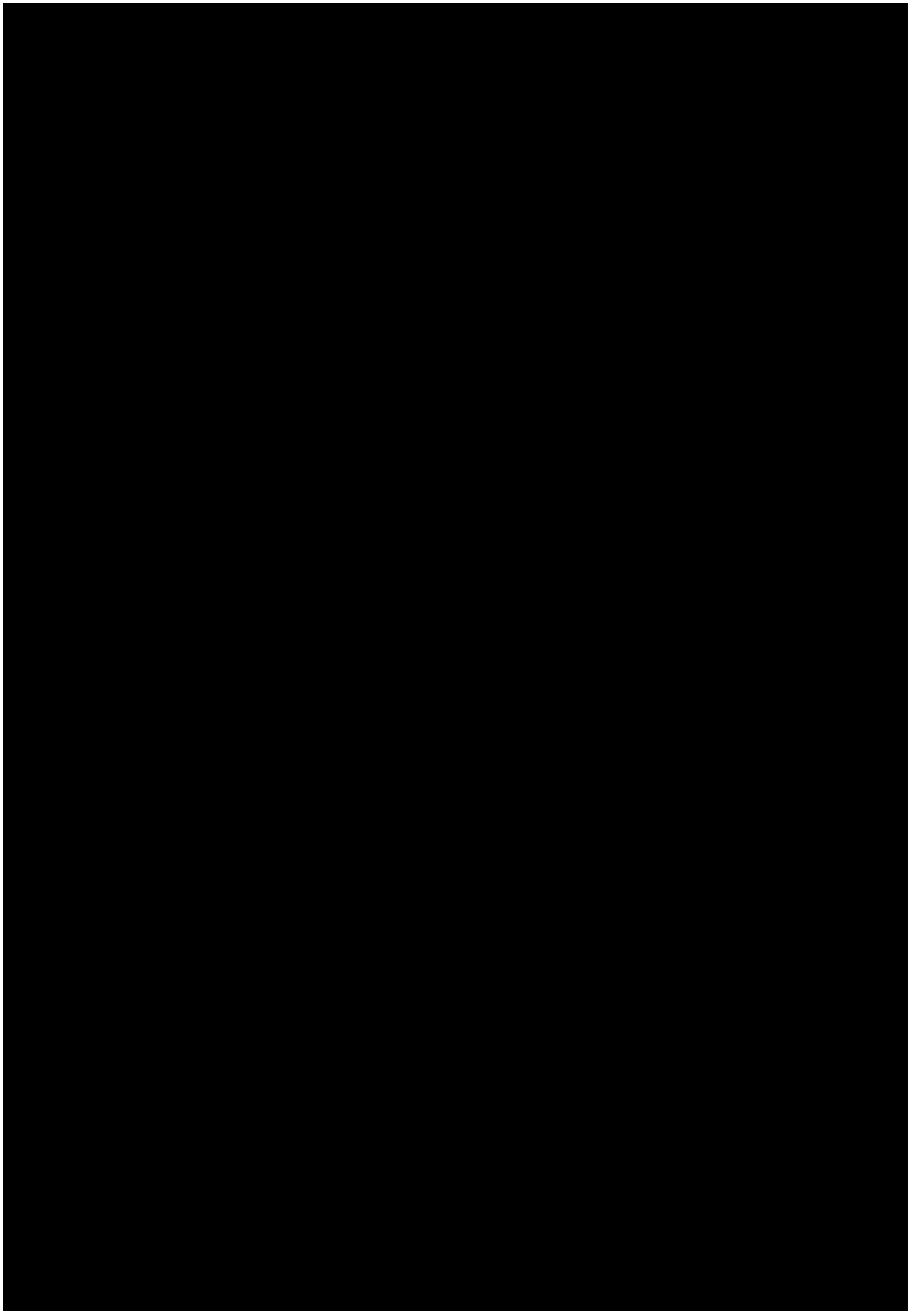
Bazett's formula used to correct QT interval for heart rate is:

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

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.



[redacted]

Appendix 8: Protocol Amendment Changes

AMENDMENT 05

Where the Amendment Applies

This amendment applies to all study sites in all countries.

Amendment Summary of Main Changes

Section	Change	Rationale
Multiple	Delete or replace references to GlaxoSmithKline (GSK) or its staff with that of Novartis	To align with the change of sponsorship from GSK to Novartis
Multiple	Make administrative changes	To align with the change of sponsorship from GSK to Novartis.
Multiple	Style and typographical updates have been made throughout the document but not listed individually	To align with the change of sponsorship from GSK to Novartis
Multiple	Change from medical monitor [or GSK medical monitor] to Medical Lead	To align with the change of sponsorship from GSK to Novartis.

Amendment Details:

Bolded text indicates added text and strikethrough indicates deleted text.

Section: Title Page

Text changed:

The title page was replaced as per Novartis requirements.

Section: Sponsor Information Page

Text changed:

The GSK contact information was removed.

The term medical monitor was replaced by clinical leader and the contact details were updated.

Details of the clinical trial head of Novartis were added.

Section 5.3.6: Other Issues

Text changed:

For pharmacokinetics analyses, assay values below quantifiable limits (BQL) will be handled ~~as described in the GSK Clinical Pharmacokinetics/ Modeling & Simulation Pharmacokinetic (CPK/M&S PK) Methods~~ **according to Novartis procedures**.

Section 5.3.8.1: Safety Analyses

Text changed:

Safety data for Parts 1, 2 and 3 will be presented in tabular and/or graphical format and summarized descriptively according to ~~GSK's Integrated Data Standards Library (IDSL)~~ **Novartis** standards.

Section 6.5.1 Time Period for Collecting Pregnancy Information

Text changed:

The investigator will record pregnancy information on the appropriate form and submit it to ~~GSK~~**Novartis** within ~~2 weeks~~ **24 hours** of learning of a subject's pregnancy.

Section 6.5.2: Action to be taken if pregnancy occurs

Text changed:

The investigator will record pregnancy information on the appropriate form and submit it to ~~GSK~~ **Novartis** within ~~2 weeks~~ **24 hours** of learning of a subject's pregnancy. The subject will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to ~~GSK~~ **Novartis**.

Section 6.5.3: Action to be taken if pregnancy occurs in a female partner of a male study subject

Text changed:

The investigator will record pregnancy information on the appropriate form and submit it to ~~GSK~~ **Novartis** within ~~2 weeks~~ **24 hours** of learning of the partner's pregnancy. The partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to ~~GSK~~ **Novartis**.

Section 6.6.2: Sample Analysis

Text changed:

Plasma analysis will be performed under the management of ~~Bioanalytical Science and Toxicokinetic (BST), Drug Metabolism and Pharmacokinetics, Platform Technology and Sciences, GSK~~ **Novartis**.

Raw data will be stored in the ~~Good Laboratory Practice (GLP) Archives, GlaxoSmithKline~~ **by Novartis**.

Section 10 Study Treatment

Text changed:

Supplies of the investigational products will be provided to sites by Novartis, with the exception of sites in China (if applicable) where GSK will continue to provide supplies.

Section 11: Adverse Events (AE) and Serious Adverse Events (SAE)

Text changed:

AEs will be collected from the time a subject consents to participate in and completes the study (See Section 9.2), all SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy), will be reported promptly to Novartis, as indicated in Section 11.5 from the start of Study Treatment and until the follow-up contact.

Only SAEs relating to study procedures should be reported to ~~GKS~~**Novartis** within 24 hours, as indicated in Section 11.4.

Section 13.3: Quality Control (Study Monitoring)

Text changed:

In accordance with applicable regulations including GCP, and ~~GSK~~**Novartis** procedures, **Novartis personnel (or designated Clinical Research Organization [CRO])** procedures, Novartis study monitors will contact the site 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 Novartis requirements. When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the CRF will serve as the source document.

~~GSK~~**Novartis (or designated CRO) personnel** will monitor the study and site activity to verify that the:

Section 13.5 Study and Site Closure

Text changed:

Upon completion or premature discontinuation of the study, **Novartis personnel (or designated CRO)**~~the monitor~~ will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and ~~GSK~~**Novartis** procedures.

Section 13.6 Records Retention

Text changed:

~~GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, or GSKNovartis standards/procedures; otherwise, the retention period will default to 15 years.~~ **Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless the Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.**

Section 13.7 Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

Text changed:

~~GSK~~**Novartis** aims to post a results summary to the ~~GSK~~**Novartis** Clinical **Trial Results website (www.novartisclinicaltrials.com)** and other publicly available registers no later than ~~8~~**12** months after the last subjects 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~~**upon study completion and finalization of study report, Novartis** aims to ~~publish the full study protocol on the GSK Clinical Study Register at the time the~~ **submit** results of the study ~~are published as a manuscript in the scientific literature~~ for publication.

When ~~manuscript~~ publication ~~in a peer reviewed journal~~ is not feasible, ~~further study information will be posted~~ **please refer** to the ~~GSK~~**Novartis** Clinical **Trial Results website (www.novartisclinicaltrials.com) for a summary of the trial results.**

Section 13.8 Data Management

Text changed:

For this study subject data will be entered into ~~GSK defined~~ **the** electronic case report forms (eCRFs), transmitted electronically to ~~GSK~~ **the sponsor (**or designee**)** and **be** combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable ~~GSK~~**Novartis** standards and data cleaning procedures to ensure the integrity of the data, e.g., ~~removing~~**resolving** errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using the ~~MedDRA (~~**the** Medical Dictionary for Regulatory Activities **(MedDRA**) and ~~an internal validated medication~~a **custom drug** dictionary. eCRFs (including queries and audit trails) will be retained by ~~GSK~~**Novartis**, and copies will be sent to the investigator to maintain as the investigator copy. ~~Subject initials will not be collected or transmitted to GSKNovartis according to GSK policy.~~

AMENDMENT 4

Where the Amendment Applies

This amendment applies to all sites in all countries.

Summary of Amendment Changes with Rationale

Major revisions in this amendment include the additional of Part 2B with revisions to data analysis and statistical considerations; modifications to dose management guidelines; the inclusion of a crossover Time and Event Table; and addition of overall survival to the time and events tables for all Parts of the study.

Throughout the protocol, minor edits have been made to clarify text, including changing of Recommend to Phase 2 Dose (RP2D) to Recommend to Phase 2 Regimen (RP2R), using BRAF mutant and anti-EGFR resistant population in Part 4B

List of Specific Changes

Original text displayed strikethrough indicates replaced or removed text. New text is displayed as underline. Revisions within figures will be displayed first by the original figure, and then followed by the new figure. Revisions within tables will be displayed as text. Formatting changes, corrections to grammatical errors or misspelled words, added abbreviations or references, and changes to Table numbering will not be included in the Summary of Changes for Amendment 4.

SPONSOR SIGNATORY

PREVIOUS TEXT

[redacted] MD, PhD
[redacted]
GlaxoSmithKline

REVISED TEXT

[redacted], MD
[redacted]
GlaxoSmithKline

SPONSOR/MEDICAL MONITOR INFORMATION PAGE

PREVIOUS TEXT

Medical Monitor and Sponsor Contact Information:

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	Fax Number	GSK Address
[redacted] Medical Monitor	[redacted] MD, PhD	[redacted]	[redacted]	[redacted]	GlaxoSmithKline Five Moore Drive Mailstop 5.4300.4B Research Triangle Park, NC 27709 [redacted]
[redacted] Medical Monitor	[redacted] MD, PhD	[redacted]	[redacted]	[redacted]	GlaxoSmithKline 1250 Collegeville Road Mailstop UP4310 Collegeville, PA USA [redacted]
[redacted] Medical Monitor	[redacted] PhD	[redacted]	[redacted]	[redacted]	GlaxoSmithKline 1250 Collegeville Road Mailstop UP4-4210 Collegeville, PA USA [redacted]
SAE fax number	[redacted]	[redacted]	[redacted]		[redacted]

REVISED TEXT

Medical Monitor and Sponsor Contact Information:

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	Fax Number	GSK Address
[redacted] Medical Monitor	[redacted] MD, PhD	[redacted]	[redacted]	[redacted]	GlaxoSmithKline Five Moore Drive Mailstop 5.4300.4B Research Triangle Park, NC 27709 [redacted]
~~[redacted] Medical Monitor~~	~~[redacted] MD, PhD~~	[redacted]	[redacted]	[redacted]	~~GlaxoSmithKline 1250 Collegeville Road Mailstop UP4310 Collegeville, PA USA~~ [redacted]

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	Fax Number	GSK Address
[redacted] Medical Monitor	[redacted] MD, PhD	[redacted]	[redacted]	[redacted]	GlaxoSmithKline 1250 Collegeville Road Mailstop UP4-4210 Collegeville, PA USA [redacted]
SAE fax number	[redacted]	[redacted]	[redacted]		[redacted]

RATIONALE: Update to medical monitor contact information

SECTION 1.1.4 Panitumumab, Vectibix

PREVIOUS TEXT

Panitumumab is a high-affinity (k_d 5 x 10^{-11} M), human immunoglobulin G2 (IgG2) monoclonal antibody directed against human EGFR [Davis, 1999; Yang, 1999]. Panitumumab blocks EGFR binding of epidermal growth factor (EGF), transforming growth factor-alpha (TGFα), amphiregulin, betacellulin, epiregulin, and heparin-binding EGF. Panitumumab [VECTIBIX, 2013] is currently licensed in the United States by the Food and Drug administration (FDA) for single agent use in patients with mCRC that expresses EGFR and is refractory to fluoropyrimidine-, irinotecan-, and oxaliplatin-containing regimens. Use of panitumumab is not recommended for the treatment of colorectal cancer with *KRAS* mutations in codon 12 or 13. Further, panitumumab is approved in the European Union, Canada, Australia, and other regions for use in the treatment of chemotherapy-refractory mCRC that expresses EGFR and wild-type form of the *KRAS* gene. In Japan, panitumumab is approved for treatment of patient with unresectable, advanced or recurrent CRC with wild-type *KRAS*. Panitumumab is administered as an intravenous infusion. The most common adverse events of panitumumab are skin rash, hypomagnesemia, paronychia, fatigue, abdominal pain, nausea and diarrhea.

Refer to the current panitumumab approved labelling for further details [VECTIBIX, 2013]. Please also reference Section 1.4.3 for additional information on the safety profile and the Summary of Risk Mitigation.

REVISED TEXT

Panitumumab is a high-affinity (k_d 5 x 10^{-11} M), human immunoglobulin G2 (IgG2) monoclonal antibody directed against human EGFR [Davis, 1999; Yang, 1999]. Panitumumab blocks EGFR binding of epidermal growth factor (EGF), transforming growth factor-alpha (TGFα), amphiregulin, betacellulin, epiregulin, and heparin-binding EGF. Panitumumab [VECTIBIX, ~~2013~~2014] is currently licensed in the United States by the Food and Drug administration (FDA) for the treatment of patients with wild-type *KRAS* mCRC as determined by an FDA-approved test for this use as first-line therapy in combination with FOLFOX ~~in previously untreated mCRC~~ and ~~for~~ as monotherapy ~~a~~

~~single agent use in patients with mCRC that expresses EGFR and is refractory to~~ following disease progression after prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-~~, and oxaliplatin~~-containing regimens. Use of panitumumab is not indicated for the treatment of patients with *KRAS*–mutant mCRC or for whom *KRAS* mutation status is unknown. ~~not recommended for the treatment of colorectal cancer with *KRAS* mutations in codon 12 or 13.~~ Further, panitumumab is approved in ~~the European Union,~~ Canada~~,~~ ~~Australia,~~ and other regions for use in the treatment of chemotherapy-refractory mCRC that expresses EGFR and wild-type form of the *KRAS* gene. In Japan, panitumumab is approved for treatment of patient with unresectable, advanced or recurrent CRC with wild-type *KRAS.* However in the European Union and Australia, panitumumab is indicated for the treatment of adult patients with wild-type *RAS* mCRC in first- and second-lines as well as monotherapy. Refer to the current regionally-approved labelling for further details.

Panitumumab is administered as an intravenous infusion. The most common adverse events of panitumumab are skin rash, hypomagnesemia, paronychia, fatigue, abdominal pain, nausea and diarrhea.

~~Refer to the current panitumumab approved labelling for further details [VECTIBIX, 2013].~~ Please also reference Section 1.4.3 for additional information on the safety profile and the Summary of Risk Mitigation.

RATIONALE: Updated information from the 2014 Vectibix label

SECTION 1.3 Study Rationale for Parts 1, 2, 3, 4

PREVIOUS TEXT

BRAF-mutation V600E positive CRC is more aggressive than KRAS-mutation positive- or KRAS/BRAF- wild-type colorectal cancer, with a lower overall response rate (ORR), reduced progression-free (PFS) and overall survival (OS) [Di Nicolantonio, 2008; Laurent-Puig, 2009; Maughan, 2011; Souglakos, 2009; Bokemeyer, 2012; Tveit, 2012; Richman, 2009; Tran, 2011; Yokota, 2011; Tie, 2011]. Efforts to target BRAF-mutant CRC with BRAF inhibitors and MEK inhibitors as monotherapies have not been successful to date [Falchook, 2012; Kopetz 2010]. Recently published nonclinical data suggest a role for receptor tyrosine kinase activation (particularly EGFR) in the resistance mechanism and have demonstrated synergistic activity of the combination of a BRAF inhibitor and an EGFR inhibitor in in vitro and in vivo models of BRAF-mutant CRC [Prahallad, 2012; Corcoran, 2012]. Therefore, the combination of potent inhibition of the BRAF pathway (with dabrafenib alone or dabrafenib/trametinib) with an anti-EGFR agent to prevent EGFR-mediated resistance is a rational and promising approach to treat BRAF-mutant CRC.

The study is designed to identify the recommended Phase 2 dose/regimen for the doublet (dabrafenib/panitumumab) and the triplet (dabrafenib/trametinib/panitumumab) in Part 1, identify an initial signal of clinical activity in Part 2 and to perform a randomized comparison of the experimental arms to a chemotherapy comparator arm (a regimen of FOLFOX or FOLFIRI with or without panitumumab or bevacizumab) in Part 3. Extrapolating from the experience in BRAF V600E/V600K -mutation positive melanoma,

it is expected that the triple combination is likely to provide the greatest benefit to subjects, in which case the inclusion of the double combination serves as a control to assess the important "contribution of components" question. However, another possible outcome is that the double combination is superior (e.g., due to poor tolerability of the triple combination), an outcome that this study design will also adequately evaluate.

REVISED TEXT

BRAF-mutation V600E positive CRC is more aggressive than KRAS-mutation positive- or KRAS/BRAF- wild-type colorectal cancer, with a lower overall response rate (ORR), reduced progression-free (PFS) and overall survival (OS) [Di Nicolantonio, 2008; Laurent-Puig, 2009; Maughan, 2011; Souglakos, 2009; Bokemeyer, 2012; Tveit, 2012; Richman, 2009; Tran, 2011; Yokota, 2011; Tie, 2011]. Efforts to target BRAF-mutant CRC with BRAF inhibitors and MEK inhibitors as monotherapies have not been successful to date [Falchook, 2012; Kopetz 2010]. Recently published nonclinical data suggest a role for receptor tyrosine kinase activation (particularly EGFR) in the resistance mechanism and have demonstrated synergistic activity of the combination of a BRAF inhibitor and an EGFR inhibitor in in vitro and in vivo models of BRAF-mutant CRC [Prahallad, 2012; Corcoran, 2012]. Therefore, the combination of potent inhibition of the BRAF pathway (with dabrafenib alone or dabrafenib/trametinib) with an anti-EGFR agent to prevent EGFR-mediated resistance is a rational and promising approach to treat BRAF-mutant CRC.

Thus, this study is designed to identify the recommended Phase 2 dose/regimen (RP2R) for the dabrafenib/panitumumab doublet ~~(dabrafenib/panitumumab)~~ and the dabrafenib/trametinib/panitumumab triplet ~~(dabrafenib/trametinib/panitumumab)~~ in Part 1 and for the trametinib/panitumumab doublet in Part 4A. In part 2 and 4B, the study will identify an initial signal of clinical activity for these combinations.~~in Part 2~~ In part 3, ~~and to perform~~ a randomized comparison of the experimental arms to a chemotherapy comparator arm (a regimen of FOLFOX or FOLFIRI with or without panitumumab or bevacizumab) will be performed~~in Part 3~~.

RATIONALE: Added rationale for evaluation of trametinib and panitumumab combination in Part 4.

SECTION 1.3.2 Study Rationale for Part 4

PREVIOUS TEXT

Anti-EGFR therapies, either in combination with chemotherapy or as monotherapy, are approved therapy for KRAS wild-type (wt) colorectal cancer. Although a significant proportion of patients with KRAS wt CRC derive benefit from anti-EGFR therapy, they inevitably become resistant to this therapy. In a large proportion of cases, the mechanism of resistance to anti-EGFR therapy involves the reactivation of the RAS/MEK/ERK pathway, often through acquisition of mutations to RAS genes (KRAS or NRAS) converging on activation of the RAS/MEK/ERK pathway [Misale, 2012; Misale, 2014]. This is similar to the example of BRAF mutant melanoma in which a frequent mechanism of resistance involves the reactivation of this pathway [Flaherty, 2012].

REVISED TEXT

Part 4 of the study is designed to identify the RP2R for trametinib dosed orally in combination with IV infusions of panitumumab in dose escalation and to identify an initial signal of clinical activity in two populations, subjects with BRAF-V600E mutation-positive CRC (described above) and subjects with CRC that developed secondary resistance to anti-EGFR therapy after initially deriving benefit.

It is also important to understand whether dabrafenib is contributing to the clinical activity that has been seen with the triplet. Therefore, patients with BRAF-mutant CRC will be included in the dose escalation of the trametinib/panitumumab doublet (Part 4A) and an expansion cohort (Part 4B) further evaluating safety and efficacy of the trametinib/panitumumab doublet.

Anti-EGFR therapies, either in combination with chemotherapy or as monotherapy, are approved therapy for KRAS wild-type (wt) colorectal cancer. Although a significant proportion of patients with KRAS wt CRC derive benefit from anti-EGFR therapy, they inevitably become resistant to this therapy. In a large proportion of cases, the mechanism of resistance to anti-EGFR therapy involves the reactivation of the RAS/MEK/ERK pathway, often through acquisition of mutations to RAS genes (KRAS or NRAS) converging on activation of the RAS/MEK/ERK pathway [Misale, 2012; Misale, 2014]. This is similar to the example of BRAF mutant melanoma in which a frequent mechanism of resistance involves the reactivation of this pathway [Flaherty, 2012].

RATIONALE: Added rationale for evaluation of trametinib and panitumumab combination in Part 4.

SECTION 1.3.2.1 Preliminary data from ongoing MEK116833 study

PREVIOUS TEXT

Preliminary clinical data from Parts 1 and 2 of this ongoing study suggest that the triplet combination of dabrafenib/trametinib/panitumumab is more efficacious than the dabrafenib/panitumumab doublet in the BRAF-mutant patient population (see Table 1). Enrollment in this dose combination has been limited to 20 patients, including those enrolled in Part 1 Cohort 1 and those enrolled in Part 2 doublet cohort. Given the difference in activity, it is important to understand whether dabrafenib is contributing to the clinical activity that has been seen with the triplet. Therefore, patients with BRAF-mutant CRC will be included in the dose escalation of the trametinib/panitumumab doublet and an expansion cohort further evaluating safety and efficacy of the trametinib/panitumumab doublet will be included in Part 4 of the study.

Table 1 Best unconfirmed response, Part 1 and Part 2 (preliminary data)

Best unconfirmed response	Doublet Cohort[a], n=13	Triplet Cohorts		
		Cohort 2[b], n=3	Cohort 3A[c] n=4	Cohort 3B[d] n=4
PD	2	0	0	0
SD	9	1	1	3
PR	2	2	2	0
CR	0	0	1	0

a. Doublet cohort combines patients enrolled in Part 1 Cohort 1 and Part 2 doublet expansion cohort; all dosed with Dabrafenib 150mg BID + Panitumumab 6mg/kg/Q2W
b. Dabrafenib 150mg BID + Panitumumab 4.8mg/kg/Q2W + Trametinib 1.5mg QD
c. Dabrafenib 150mg BID + Panitumumab 4.8mg/kg/Q2W + Trametinib 2mg QD
d. Dabrafenib 150mg BID + Panitumumab 6mg/kg/Q2W + Trametinib 1.5mg QD

Part 4 of the study is designed to identify the recommended Phase 2 dose/regimen for trametinib dosed orally in combination with IV infusions of panitumumab in dose escalation and to identify an initial signal of clinical activity in expansion cohorts:

1. subjects with BRAF-V600E mutation-positive CRC

2. subjects with CRC that developed secondary resistance to anti-EGFR therapy after initially deriving benefit.

REVISED TEXT

Preliminary clinical data from Parts 1 and 2A of this ongoing study suggest that the triplet combination of dabrafenib/trametinib/panitumumab is more efficacious than the dabrafenib/panitumumab doublet in the BRAF-mutant patient population (see Table 1).

~~Enrollment in this dose combination has been limited to 20 patients, including those enrolled in Part 1 Cohort 1 and those enrolled in Part 2 doublet cohort.~~

Table 1 Summary of investigator-assessed best ~~un~~confirmed response, Part 1 and Part 2A ~~(preliminary data)~~

Best ~~un~~confirmed response, n (%)	Doublet Cohort[a], n=20~~13~~	Triplet Cohorts			
		Cohort 2[b], n=3	Cohort 3A[c] n=4	Cohort 3B[d] n=4	Cohort 4[e] N=24
Not evaluable	0	0	0	0	1 (4%)
PD	2 (10%)	0	0	2 (50%)~~0~~	3 (13%)
SD	16 (80%)~~9~~	1 (33%)	2 (50%)~~1~~	2 (50%)~~3~~	16 (67%)
PR	1 (5%)~~2~~	2 (67%)	1 (25%)~~2~~	0	4 (17%)
CR	1 (5%)~~0~~	0	1 (25%)	0	0
PR+CR, n (%) (95% CI)	2 (10%) (1.2%, 31.7%)	2 (66%) (9.4%, 99.2%)	2 (50%) (6.8%, 93.2%)	0 (0%) (0%, 60.2%)	4 (16.7%) (4.7%, 37.4%)

From 20 October 2014 data cut-off

a. Doublet cohort combines patients enrolled in Part 1 Cohort 1 and Part 2 doublet expansion cohort; all dosed with Dabrafenib 150mg BID + Panitumumab 6mg/kg/Q2W
b. Dabrafenib 150mg BID + Panitumumab 4.8mg/kg/Q2W + Trametinib 1.5mg QD
c. Dabrafenib 150mg BID + Panitumumab 4.8mg/kg/Q2W + Trametinib 2mg QD

d. Dabrafenib 150mg BID + Panitumumab 6mg/kg/Q2W + Trametinib 1.5mg QD
e. Dabrafenib 150mg BID + Panitumumab 6mg/kg/Q2W + Trametinib 2mg QD

The safety and tolerability of the triplet at multiple doses will be further explored in Part 2B. This will stratify subjects based on prior lines of therapy to obtain a more homogeneous patient population.

~~Given the difference in activity, it is important to understand whether dabrafenib is contributing to the clinical activity that has been seen with the triplet. Therefore, patients with BRAF-mutant CRC will be included in the dose escalation of the trametinib/panitumumab doublet and an expansion cohort further evaluating safety and efficacy of the trametinib/panitumumab doublet will be included in Part 4 of the study.~~

~~Part 4 of the study is designed to identify the recommended Phase 2 dose/regimen for trametinib dosed orally in combination with IV infusions of panitumumab in dose escalation and to identify an initial signal of clinical activity in expansion cohorts:~~

~~3. subjects with BRAF-V600E mutation-positive CRC~~

~~subjects with CRC that developed secondary resistance to anti-EGFR therapy after initially deriving benefit.~~ **RATIONALE: U**pdated data from 20 Oct 2014 data cut-off.

SECTION 1.3.3 Dose Rational

PREVIOUS TEXT

This study will evaluate the safety, tolerability and efficacy of the doublet dabrafenib/panitumumab and triplet trametinib/dabrafenib/panitumumab combinations in subjects with BRAF- mutation V600E positive CRC. Part 1 includes a 3+3 dose escalation that will identify tolerable combination doses for the two combinations. The safety and tolerability of these combination doses will be confirmed in expansion cohorts in Part 2, followed by a randomized evaluation of the efficacy and safety of the combinations in Part 3.

Part 4 of the study includes a 3+3 dose escalation that will identify tolerable combination doses for trametinib dosed orally in combination with IV infusions of panitumumab. The safety and tolerability of the RP2D will be confirmed in the expansion cohorts.

REVISED TEXT

Parts 1-3 of this study will evaluate the safety, tolerability and efficacy of the doublet dabrafenib/panitumumab and triplet trametinib/dabrafenib/panitumumab combinations in subjects with BRAF- ~~mutation~~ V600E mutation positive CRC. Part 1 includes a 3+3 dose escalation that will identify tolerable combination doses for the two combinations. The safety and tolerability of these combination doses will be confirmed in expansion cohorts in Part 2, followed by a randomized evaluation of the efficacy and safety of the combinations in Part 3.

Part 4 of the study includes a 3+3 dose escalation that will identify tolerable combination doses for trametinib dosed orally in combination with IV infusions of panitumumab. The safety and tolerability of the RP2~~D~~R will be confirmed in the expansion cohorts.

RATIONALE FOR CHANGE: Clarify the goals for the specific part of the study

SECTION 1.3.3.2 Potential for Overlapping Toxicities

PREVIOUS TEXT

Fatigue, diarrhea, and nausea are common adverse reactions observed after administration of dabrafenib, trametinib, or panitumumab. In addition, dermatologic toxicities are common after administration of trametinib or panitumumab with severe (National Cancer Institute Common Terminology Criteria for Adverse Events NCI-CTCAE Grade 3 or higher) dermatologic toxicities reported in 16% of all subjects (and ~25% of subjects with KRAS wild-type CRC) with metastatic carcinoma of the colon or rectum after administration of panitumumab alone. In addition, there is an apparent small risk for pneumonitis/interstitial lung disease (ILD) with both trametinib and panitumumab, respectively.

REVISED TEXT

Fatigue, diarrhea, and nausea are common adverse reactions observed after administration of dabrafenib, trametinib, or panitumumab. In addition, dermatologic toxicities are common after administration of trametinib or panitumumab. ~~with S~~severe (National Cancer Institute Common Terminology Criteria for Adverse Events NCI-CTCAE Grade 3 or higher) dermatologic toxicities have been reported in 16% of all subjects (and ~25% of subjects with KRAS wild-type CRC) with metastatic carcinoma of the colon or rectum after administration of panitumumab alone. In addition, there is an apparent small risk for pneumonitis/interstitial lung disease (ILD) with both trametinib and panitumumab, respectively.

RATIONALE FOR CHANGE: Clarify the toxicity attributed to panitumumab in the sentence.

SECTION 1.3.3.3 Part 1

PREVIOUS TEXT

The maximum tolerated dose (MTD)/Recommended Phase 2 Regimen (RP2R) of dabrafenib plus panitumumab will be defined first in Part 1. The starting dose of dabrafenib will be the recommended monotherapy dose of 150mg twice daily (BID). Panitumumab will be administered at the recommended dose of 6mg/kg, administered as an intravenous infusion over 60 minutes, every 14 days. (Additional details regarding dose escalation are provided in Section 3.6.2.) These doses are clinically active with manageable toxicity with prolonged dosing and the potential for overlapping toxicities appears relatively low. However, if unexpected toxicities are observed in Cohort 1, subjects will be enrolled in Cohort -1, in which the dose of one or both agents (depending on the toxicities observed) will be reduced.

Upon definition of a tolerable dose of dabrafenib plus panitumumab, trametinib will be added to the combination in Cohort 2 (see Section 3.1). Dabrafenib will be administered in the triple combination at the dose that was tolerated in combination with panitumumab in Cohort 1. Due to overlapping dermatologic toxicities, the starting doses of panitumumab and trametinib will be reduced. The starting dose of trametinib will be 1.5mg once daily, which is below the current recommended monotherapy dose of 2mg once daily, but is a dose that has demonstrated both pharmacodynamic and clinical activity in subjects with melanoma. The starting dose for panitumumab will be one dose level below the dose that was tolerated in combination with dabrafenib in Cohort 1, administered as an intravenous infusion over 60 minutes, every 14 days. It should be

noted that a recent clinical study of the combination of the MEK inhibitor selumetinib and the chimeric anti-EGFR agent cetuximab were able to achieve the full monotherapy dose for both agents in combination, although there was an increased rate of skin toxicity and an episode of Grade 4 hypomagnesemia [Deming, 2012]. Also of note, panitumumab has demonstrated pharmacodynamic and clinical activity at doses as low as 1 to 2.5 mg/kg weekly [Rowinsky, 2004; Weiner, 2008]. (Dose escalation details are provided in Section 3.6.2, and dose adjustment/ stopping criteria are described in Section 3.9). Doses in combination will not exceed the monotherapy top dose for any single agent.

REVISED TEXT

The maximum tolerated dose (MTD)/Recommended Phase 2 Regimen (RP2R) of dabrafenib plus panitumumab ~~will be~~was defined first in Part 1. The starting dose of dabrafenib ~~will be~~was the recommended monotherapy dose of 150mg twice daily (BID). Panitumumab was~~will be~~ administered at the recommended dose of 6mg/kg, administered as an intravenous infusion over 60 minutes, every 14 days. (Additional details regarding dose escalation are provided in Section 3.6.2.) These doses are clinically active with manageable toxicity with prolonged dosing and the potential for overlapping toxicities appears relatively low. However, if unexpected toxicities were to have been~~are~~ observed in Cohort 1, subjects would have been~~ill be~~ enrolled in Cohort -1, in which the dose of one or both agents (depending on the toxicities observed) would~~ill~~ be reduced.

Upon definition of a tolerable dose of dabrafenib plus panitumumab, trametinib was~~ill be~~ added to the combination in Cohort 2 (see Section 3.1). Dabrafenib was~~ill be~~ administered in the triple combination at the dose that was tolerated in combination with panitumumab in Cohort 1. Due to overlapping dermatologic toxicities, the starting doses of panitumumab and trametinib were~~ill be~~ reduced. The starting dose of trametinib was~~ill be~~ 1.5mg once daily, which is below the current recommended monotherapy dose of 2mg once daily, but is a dose that has demonstrated both pharmacodynamic and clinical activity in subjects with melanoma. The starting dose for panitumumab was~~ill be~~ one dose level below the dose that was tolerated in combination with dabrafenib in Cohort 1, administered as an intravenous infusion over 60 minutes, every 14 days. It should be noted that a recent clinical study of the combination of the MEK inhibitor selumetinib and the chimeric anti-EGFR agent cetuximab was~~ere~~ able to achieve the full monotherapy dose for both agents in combination, although there was an increased rate of skin toxicity and an episode of Grade 4 hypomagnesemia [Deming, 2012]. Also of note, panitumumab has demonstrated pharmacodynamic and clinical activity at doses as low as 1 to 2.5 mg/kg weekly [Rowinsky, 2004; Weiner, 2008].

~~(~~Dose escalation is permitted, details are provided in Section 3.6.2, and dose adjustment/ stopping criteria are described in Section 3.9~~)~~. Doses in combination will not exceed the monotherapy top dose for any single agent.

RATIONALE: Updated text based on the results of the 20 October 2014 data cut.

SECTION 1.3.3.4 Part 2

PREVIOUS TEXT

For each combination (dabrafenib/panitumumab and dabrafenib/trametinib/panitumumab), the optimal safe and tolerable dose combinations defined in Part 1 will be brought forward into Part 2. This will likely be the maximal dose from Part 1 for each combination, although a lower dose combination may be selected if significant delayed or prolonged toxicities require frequent dose modifications. In Part 2, expansion cohorts of approximately 20 subjects with BRAF- mutation V600E positive CRC (including the subjects enrolled at this dose in Part 1) will be enrolled to confirm safety and tolerability, and to generate signals of activity. Based on the safety and tolerability of these combinations, these doses may be modified during Part 2 of the study.

REVISED TEXT

For each combination (dabrafenib/panitumumab and dabrafenib/trametinib/panitumumab), the optimal safe and tolerable dose combinations defined in Part 1 were~~ill be~~ brought forward into Part 2A. This was~~ill likely be~~ the maximal dose from Part 1 for each combination, although a lower dose combination could ~~may~~have been selected if significant delayed or prolonged toxicities required frequent dose modifications. In Part 2A, expansion cohorts of ~~approximately 20~~ 20 and 35 subjects with BRAF- ~~mutation~~ V600E mutation positive CRC (including the subjects enrolled at this dose in Part 1) were ~~will be~~ enrolled to confirm safety and tolerability, and to generate signals of activity of the doublet and triplet regimens, respectively (See Table 1 for clinical data from Parts 1 and 2A).

Preliminary data from Part 2A suggested that compliance of dabrafenib, trametinib and panitumumab was similar between dose cohorts in Weeks 1 to Week4. However, during Weeks 5 to 8, the compliance of dabrafenib, trametinib and panitumumab decreased to 70-80% of the expected dose amounts in Cohort 3B and Cohort 4 compared to Cohort 2 and Cohort 3A. Adverse events leading to dose modifications were greater in the Cohort 3B and Cohort 4 compared to Cohort 2 and Cohort 3A as shown in Table 2.

Table 2 AEs Leading to Dose Modification (Triplet Cohorts)

Preferred Term	Cohort 2 N=3	Cohort 3A N=4	Cohort 3B N=4	Cohort 4 N=24	Total Triplet N=35
AEs Leading to Investigational Product Discontinuation of any Study Treatment					
Any event	0	1 (25%)	0	0	1 (3%)
Subdural haematoma	0	1 (25%)	0	0	1 (3%)
AEs Leading to Dose Reduction of any Study Treatment					
Any event	2 (67%)	1 (25%)	2 (50%)	9 (38%)	14 (40%)
Dermatitis acneiform	0	1 (25%)	2 (50%)	2 (8%)	5 (14%)
Rash	0	1 (25%)	0	1 (4%)	2 (6%)
AEs Leading to Dose Interruption/Delay of any Study Treatment					

Preferred Term	Cohort 2 N=3	Cohort 3A N=4	Cohort 3B N=4	Cohort 4 N=24	Total Triplet N=35
Any event	2 (67%)	3 (75%)	4 (100%)	20 (83%)	29 (83%)
Dermatitis acneiform	0	1 (25%)	2 (50%)	2 (8%)	5 (14%)
Vomiting	1 (33%)	0	3 (75%)	1 (4%)	5 (14%)
Dehydration	0	1 (25%)	1 (25%)	2 (8%)	4 (11%)
Dry skin	0	0	1 (25%)	3 (13%)	4 (11%)
Fatigue	0	0	0	4 (17%)	4 (11%)
Nausea	0	0	3 (75%)	1 (4%)	4 (11%)
ALT increased	0	0	0	3 (13%)	3 (9%)
AST increased	0	0	0	3 (13%)	3 (9%)
Diarrhoea	0	0	2 (50%)	1 (4%)	3 (9%)
Rash	0	1 (25%)	0	2 (8%)	3 (9%)

Based on data from 20 Oct 2014 cut-off

The dose of panitumumab in Cohort 3B and Cohort 4 was 6mg/kg every two weeks. In Part 2B, an additional 60 subjects will be enrolled into 1 of 2 dose cohorts. Subjects will be enrolled at the Cohort 3A dose (Dabrafenib 150mg BID + Panitumumab 4.8mg/kg/Q2W + Trametinib 2mg QD) and Cohort 4 dose (Dabrafenib 150mg BID +Panitumumab 6mg/kg Q2W + Trametinib 2mg QD) to further explore safety, tolerability and clinical activity at the two dose levels. In addition, subjects will be enrolled by lines of therapy in order to provide a more homogeneous patient population.

~~As the dose of panitumumab was the same in Cohort 3B and Cohort 4 (6 mg/kg every 2 weeks), a lower dose panitumumab as used in Cohort 3A (4.8 mg/kg every 2 weeks) will be included in Part 2.~~

~~After the analysis of the preliminary data on the 35 subjects administered the triplet regimen, an additional 60 subjects will be enrolled into 1 of 2 sub-cohorts based on line of therapy. This will provide a more homoegeneous patient population. In addition, the subjects will be enrolled at the Cohort 4 dose and the Cohort 3A dose to further evaluate long-term safety and tolerability of the triplet regimen. Based on the safety and tolerability of these combinations these doses may be modified during Part 2 of the study.~~

RATIONALE: Updated results from 20 October 2014 data cut and inclusion of AEs leading to dose modifications.

SECTION 1.3.3.6 Part 4

PREVIOUS TEXT

Data from Parts 1 and 2 of this ongoing study have demonstrated that both the dabrafenib/panitumumab doublet and the dabrafenib/trametinib/panitumumab triplet are well-tolerated by patients (see Table 2). The triplet combination studies in Cohorts 3A and 3B, in which dabrafenib is dosed at the full marketed dose (150mg po BID) and either trametinib or panitumumab is also dosed at the full marketed dose (2mg po QD or 6 mg/kg IV Q2W, respectively), with the other agent dosed at one dose level lower

(1.5mg po QD or 4.8mg/kg IV Q2W, respectively) have been well tolerated to date, with no DLTs being identified. The highest triplet combination (all three agents at full dose) is currently being evaluated in Cohort 4 of the dose escalation. Based on the tolerability of the triplet in Part 1, the two starting dose trametinib/panitumumab combinations that will be studied in the initial dose escalation cohort of Part 4 will include the doses of trametinib and panitumumab that were tolerated in combination with dabrafenib in Cohorts 3A and 3B of Part 1. If these are well tolerated, the dose will be escalated to the full dose of both agents. If neither of these is well tolerated, there will be an option to dose reduce (see Section 3.4). The optimal safe and tolerable dose combinations defined in dose escalation will be brought forward into expansion cohorts. This will likely be the maximal dose for each combination in dose escalation, although a lower dose combination may be selected if significant delayed or prolonged toxicities require frequent dose modifications. Expansion cohorts of approximately 20 subjects with KRAS wt CRC who progressed on previous anti-EGFR will be enrolled to confirm safety and tolerability, and to generate signals of activity.

Table 2 DLTs, Related AEs ≥Gr 3, and Related SAEs in Part 1 and Part 2 (preliminary data)

	Doublet Cohort[a], n=13	Triplet Cohorts		
		Cohort 2[b], n=3	Cohort 3A[c] n=4	Cohort 3B[d] n=4
DLTs	None	None	None	None
Related SAEs	5	1	None	None
Related AEs ≥Grade 3	1	2	1	2

a. Doublet cohort combines patients enrolled in Part 1 Cohort 1 and Part 2 doublet expansion cohort; all dosed with dabrafenib 150mg BID + panitumumab 6mg/kg/Q2W.
b. Part 1 Cohort 2 dose dabrafenib 150mg BID + panitumumab 4.8mg/kg/Q2W + trametinib 1.5mg QD
c. Part 1 Cohort 3A dose dabrafenib 150mg BID + panitumumab 4.8mg/kg/Q2W + trametinib 2mg QD
d. Part 1 Cohort 3B dose dabrafenib 150mg BID + panitumumab 6mg/kg/Q2W + trametinib 1.5mg QD

REVISED TEXT

Data from Parts 1 and 2A of this ongoing study have demonstrated that both the dabrafenib/panitumumab doublet and the dabrafenib/trametinib/panitumumab triplet are ~~well-~~tolerated by patients (see Table 3~~Table 2~~). The triplet combination studies in Cohorts 3A and 3B, in which dabrafenib is dosed at the full marketed dose (150mg po BID) and either trametinib or panitumumab is also dosed at the full marketed dose (2mg po QD or 6 mg/kg IV Q2W, respectively), with the other agent dosed at one dose level lower (1.5mg po QD or 4.8mg/kg IV Q2W, respectively) have been well tolerated to date, with no DLTs being identified. The highest triplet combination (all three agents at full dose) also has ~~is currently~~ been~~ing~~ evaluated in Cohort 4 of the dose escalation with no DLTs and an additional 20 patients has been enrolled in the expansion cohort at the full dose of all three agents. Based on the tolerability of the triplet at full dose in Part 1, the ~~two~~ starting dose trametinib/panitumumab combinations that is being~~will be~~ studied in the initial dose escalation cohort of Part 4 ~~will include the doses of trametinib and panitumumab that were tolerated in combination with dabrafenib in Cohorts 3A and 3B of Part 1. If these are well tolerated, the dose~~ will be ~~escalated to the~~ full dose of both

agents. If these doses ~~neither of these is~~ are not well tolerated, there will be an option to dose reduce (see Section 3.4). The optimal safe and tolerable dose combinations defined in dose escalation will be brought forward into expansion cohorts. This will likely be the maximal dose for each combination in dose escalation, although a lower dose combination may be selected if significant delayed or prolonged toxicities require frequent dose modifications. Expansion cohorts of approximately 20 subjects with BRAF V600E mutant mCRC or advanced CRC/~~metastatic~~ mCRC who progressed on previous anti-EGFR will be enrolled to confirm safety and tolerability, and to generate signals of activity.

Table ~~3~~2 DLTs, Related AEs ≥Gr 3, and Related SAEs in Part 1 and Part 2 (preliminary data)

	Doublet Cohort[a], n=~~13~~20	Triplet Cohorts			
		Cohort 2[b], n=3	Cohort 3A[c] n=4	Cohort 3B[d] n=4	Cohort 4[e] N=24
DLTs	None	None	None	None	None
Related SAEs	~~5~~6	1	None	~~None~~1	6
Related AEs ≥Grade 3	~~1~~3	2	~~1~~2	2	11

From 20 October 2014 data cut-off

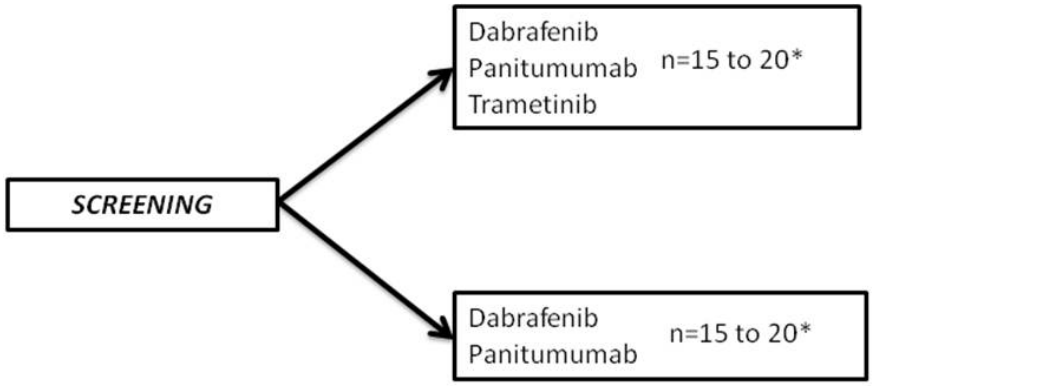
a. Doublet cohort combines patients enrolled in Part 1 Cohort 1 and Part 2 doublet expansion cohort; all dosed with dabrafenib 150mg BID + panitumumab 6mg/kg/Q2W.
b. Part 1 Cohort 2 dose dabrafenib 150mg BID + panitumumab 4.8mg/kg/Q2W + trametinib 1.5mg QD
c. Part 1 Cohort 3A dose dabrafenib 150mg BID + panitumumab 4.8mg/kg/Q2W + trametinib 2mg QD
d. Part 1 Cohort 3B dose dabrafenib 150mg BID + panitumumab 6mg/kg/Q2W + trametinib 1.5mg QD
e. Dabrafenib 150mg BID + Panitumumab 6mg/kg/Q2W + Trametinib 2mg QD

RATIONALE: Updated safety information related to the 20 October 2014

SECTION 3.2 Part 2A: Cohort Expansions Study Design/Schematic

PREVIOUS TEXT

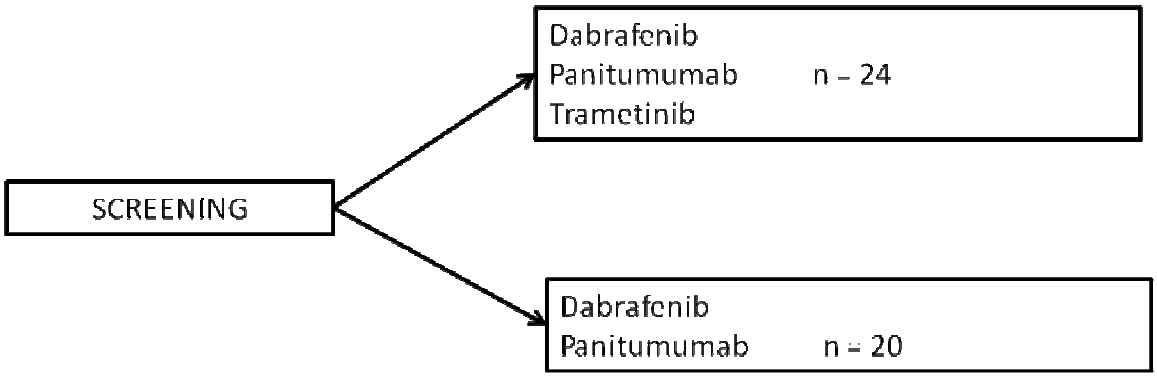
Part 2: Cohort Expansions Study Design/Schematic



*to include subjects enrolled in Part 1 at that dose level/combination

REVISED TEXT

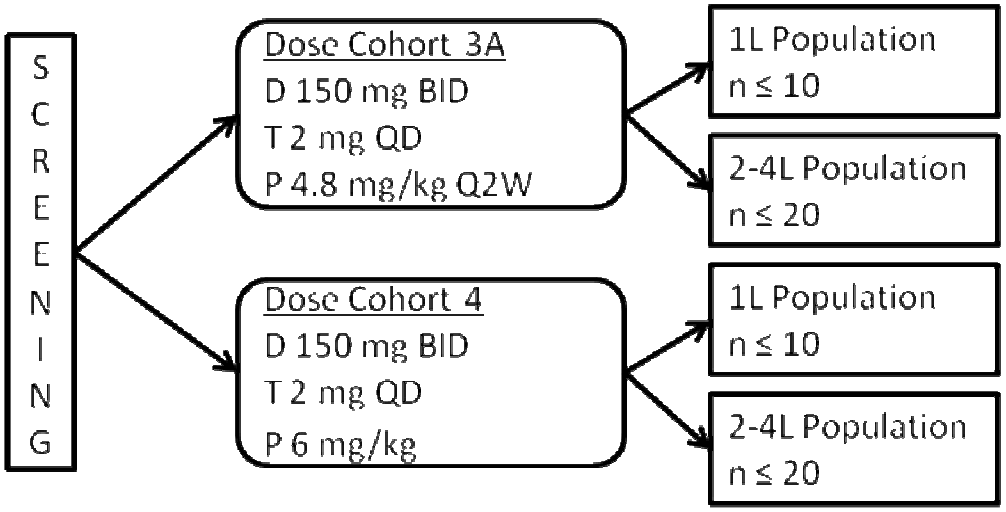
Part 2A: Cohort Expansions Study Design/Schematic



RATIONALE: Updated Schematic to include actual data from the 20 October 2014 data cut and the inclusion of the Part 2B.

ADDITIONAL TEXT

Section 3.3 Part 2B: Cohort Expansion



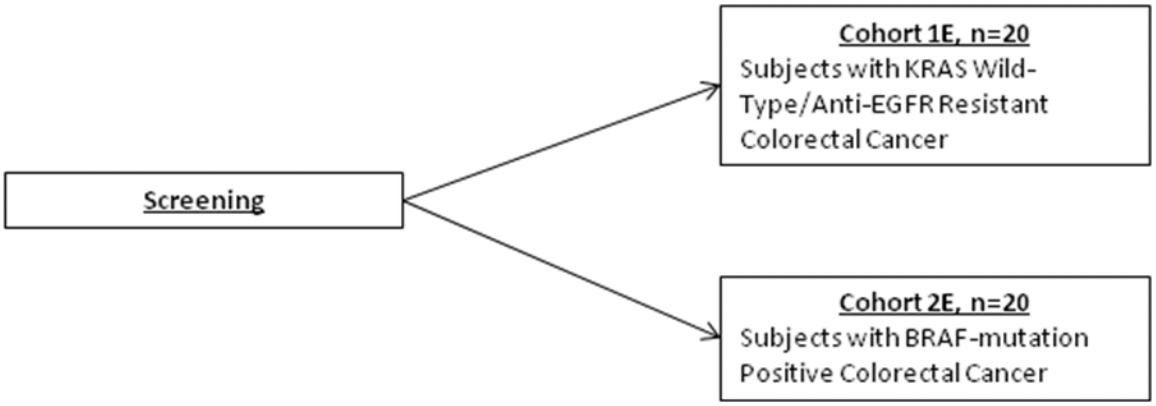
BID, twice daily dosing; D, dabrafenib; L, line of therapy; P, panitumumab; T, trametinib; Q2W, dosing every 2 weeks; QD, once daily dosing;

RATIONALE: Addition of Part 2B to further evaluate the triplet combination at the doses used in Cohort 3A and Cohort 4.

SECTION 3.6 Cohort Expansion

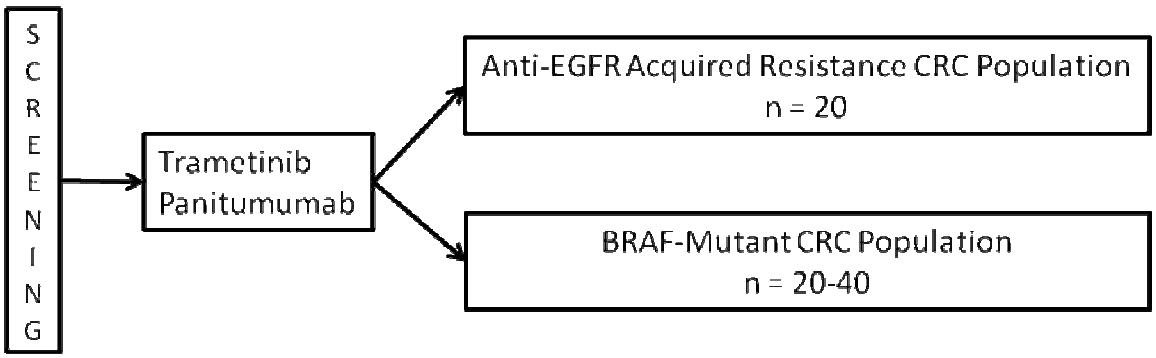
PREVIOUS TEXT

14.1 Part 4B Cohort Expansion



REVISED TEXT

14.2 Part 4B Cohort Expansion



RATIONALE: Schema updated to change from cohort to population for the two populations evaluated in Part 4B

SECTION 3.7.1 Prescreening for KRAS and BRAF Mutation Status

PREVIOUS TEXT

The conduct of the KRAS- and BRAF-mutation screening prior to the baseline assessments is the responsibility of the investigator and must be performed in a CLIA-approved facility. Local testing for KRAS and BRAF mutations for enrollment in the trial can occur any time prior to dosing. If KRAS and BRAF mutation status is unknown at screening, no biopsy for assessment of mutation status in association with this protocol should be taken prior to obtaining consent. Following consent, subjects should be

screened for KRAS and BRAF mutation status (if not already performed) prior to any other study-related screening procedures. The BRAFV600E mutation status will be confirmed centrally using the GSK selected assay. For Part 1 and Part 2, a local test result for KRAS status is adequate for enrollment. Enrollment in Part 3 may only occur following confirmation of KRAS wild-type cancer, as determined by FDA-approved KRAS test for CRC (e.g., Qiagen test) and documented in source. For patients in Part 4 who have acquired secondary resistance to anti-EGFR therapy, repeat testing for RAS mutations is not required.

REVISED TEXT

The conduct of the KRAS- and BRAF-mutation screening prior to the baseline assessments is the responsibility of the investigator and must be performed in a CLIA-approved facility. Local testing for KRAS and BRAF mutations for enrollment in the trial can occur any time prior to dosing. If KRAS and BRAF mutation status is unknown at screening, no biopsy for assessment of mutation status in association with this protocol should be taken prior to obtaining consent. Following consent, subjects should be screened for KRAS and BRAF mutation status (if not already performed) prior to any other study-related screening procedures. ~~The BRAFV600E mutation status will be confirmed centrally using the GSK selected assay.~~ For Part 1 and Part 2, a local test result for KRAS status is adequate for enrollment. Enrollment in Part 3 may only occur following confirmation of KRAS wild-type cancer, as determined by FDA-approved KRAS test for CRC (e.g., Qiagen test) and documented in source. For patients in Part 4 who have acquired secondary resistance to anti-EGFR therapy, repeat testing for RAS mutations is not required.

RATIONALE: Deleted sentence as central confirmation of BRAF mutation status is discussed in the paragraph below.

SECTION 3.7.2 Part 1

PREVIOUS TEXT

If the initial combination dose of dabrafenib and panitumumab in Cohort 1 (starting dose) is not tolerable, lower dose combination(s) defined in de-escalation cohorts (Cohort -1A, -1B and/or -1C) may be evaluated. The actual de-escalation cohorts that are opened will be based on the agent(s) that are most likely causing the intolerance. Once the dabrafenib/panitumumab combination dose is defined, subsequent cohorts in which trametinib is added will be based on the dabrafenib/panitumumab dose defined in Cohort 1 or -1 (e.g., if the maximally tolerated panitumumab dose in the dabrafenib/panitumumab combination is 4.8mg/kg, the panitumumab dose in Cohort 2 will be one dose level lower, or 3.6mg/kg. Cohorts that are designated as “3A” and “3B” may be opened simultaneously once the prior dosing cohort has completed the 28-day DLT window and met dose escalation criteria as specified in Table 4. If the combination doses in both Cohort 3A and Cohort 3B are well-tolerated, available safety and response data will be evaluated to determine the appropriate dose to evaluate in Part 2.

REVISED TEXT

~~If the initial combination dose of dabrafenib and panitumumab in Cohort 1 (starting dose) is not tolerable, lower dose combination(s) defined in de-escalation cohorts (Cohort -1A, -1B and/or -1C) may be evaluated. The actual de-escalation cohorts that are opened will be based on the agent(s) that are most likely causing the intolerance. Once the dabrafenib/panitumumab combination dose is defined, subsequent cohorts in which trametinib is added will be based on the dabrafenib/panitumumab dose defined in Cohort 1 or -1 (e.g., if the maximally tolerated panitumumab dose in the dabrafenib/panitumumab combination is 4.8mg/kg, the panitumumab dose in Cohort 2 will be one dose level lower, or 3.6mg/kg. Cohorts that are designated as "3A" and "3B" may be opened simultaneously once the prior dosing cohort has completed the 28-day DLT window and met dose escalation criteria as specified in Table 4. If the combination doses in both Cohort 3A and Cohort 3B are well-tolerated, available safety and response data will be evaluated to determine the appropriate dose to evaluate in Part 2.~~

RATIONALE: Paragraph deleted as de-escalation cohorts were not used in Part 1

SECTION 3.7.3 Part 2

PREVIOUS TEXT

In Part 2, the primary objectives will be to further assess the safety and preliminary clinical activity of given doses and regimen(s) in subjects with BRAF-V600E mutation-positive CRC. Enrollment in Part 2 doublet will be initiated once dose escalation for the doublet (dabrafenib in combination with panitumumab) has been completed. Enrollment in Part 2 triplet (trametinib plus dabrafenib in combination with panitumumab) will open once dose escalation for the triplet has been completed.

Subjects will be enrolled in the expansion cohorts at a selected dose of dabrafenib in combination with panitumumab and a selected dose of trametinib plus dabrafenib in combination with panitumumab. For each combination, up to 20 evaluable subjects with BRAF-V600E mutation-positive CRC will be enrolled (inclusive of those subjects enrolled at the same dose level in Part 1).

Subjects who participated in Part 1 of the study at the recommended doses will be included in Part 2 analysis, and will contribute to the goal of 15 to 20 subjects enrolled in each arm in Part 2. For this cohort, subjects should follow the assessments in Section 3.10.2.

The responses will be assessed and decisions to continue to Part 3 will be made based on response data are available for up to 20 subjects for each cohort. **In order to proceed to Part 3, sufficient evidence of clinical activity (e.g. observing 4 responses out of up to 20 subjects) should be observed to warrant further development.** Meanwhile**,** the Part 2 portion of the study will employ a Bayesian design that allows the trial to be monitored more frequently at multiple stages.

The trial may also be stopped at any time if excessive toxicities with the drug are observed. For additional details about this approach, see Section 5.

The decision to proceed to Part 3 of the study will take into consideration all available data and will be reviewed by the investigator(s), GSK medical monitor(s), pharmacokineticist and statistician. Data will include the safety profile [redacted] of all dosing cohorts throughout the time subjects are on study. The decision could be based on analysis of a subgroup of responders, so that a single combination arm would be carried forward into Part 3.

REVISED TEXT

In Part 2, the primary objectives will be to further assess the safety and preliminary clinical activity of given doses and regimen(s) in subjects with BRAF-V600E mutation-positive CRC.

For Part 2A and 2B, subjects should follow the assessments in Section 3.10.2.

Part 2 will employ a Bayesian design that allows the trial to be monitored more frequently at multiple stages.

3.7.3.1 Part 2A: Cohort Expansion

Enrollment in Part 2A doublet will be initiated once dose escalation for the doublet (dabrafenib in combination with panitumumab) has been completed. Enrollment in Part 2A triplet (trametinib plus dabrafenib in combination with panitumumab) will open once dose escalation for the triplet has been completed.

Subjects will be enrolled in the expansion cohorts at a selected dose of dabrafenib in combination with panitumumab and a selected dose of trametinib plus dabrafenib in combination with panitumumab. ~~For each combination,~~ Approximately ~~up to~~ 20 evaluable subjects with BRAF-V600E mutation-positive CRC will be enrolled at the Cohort 4 dose, the full monotherapy dose for all three component of the triplet regimen,~~RP2R~~ to obtain preliminary data on the safety and efficacy of the combinations.

Subjects who participated in Part 1 of the study at the doses evaluated in Part 2A will be included in Part 2A analysis, and will contribute to the total count of the 20 subjects enrolled in Part 2A.

For Part 2A, subjects should follow the assessments in Section 3.10.2.

3.7.3.2 Part 2B: Cohort Expansion

After completion of Part 2A, additional subjects will be enrolled into dose cohorts for the triplet of dabrafenib + trametinib +panitumumab. Based on the efficacy (Table 1) and long term tolerability observed in Part 2A, two doses will be evaluated in Part 2B.

~~Enrollement will be.~~ Up to ten subjects with no prior treatment and up to 20 subjects with at least one prior treatment will be enrolled at the Cohort 3A dose (dabrafenib 150mg BID + trametinib 2mg QD + panitumumab 4.8mg/kg IV Q2wks). . Up to 10 subjects with no prior treatment and up to 20 subjects with at least one prior treatment will be

enrolled at the Cohort 4 dose (dabrafenib 150mg BID + trametinib 2mg QD + panitumumab 6mg/kg IV Q2wks).

Enrolment into two patient populations will be dependent on prior therapy for their metastatic disease.

3. First Line Population (1L Population): No prior treatment is defined as subjects with no prior treatment for metastatic disease or metastatic recurrence greater than 6 months following completion of adjuvant therapy;
4. Second to Fourth Line Population (2-4L Population): At least one prior treatment is defined as subjects with progression or intolerance to at least one prior chemotherapy regimen for metastatic disease or recurrence within 6 months following completion of adjuvant therapy. Patients treated with > 4 prior lines of therapy for metastatic disease will not be eligible.

Lines of prior therapy for each subject will be agreed upon by the medical monitor and investigator at the time of enrolment.

This would provide safety, efficacy and tolerability data for the triplet regimen in up to 95 subjects between Part 1, Part 2A and Part 2B. .

For ~~this~~Part 2B subjects should follow the assessments in Section 3.10.2.

~~The~~ Responses will be assessed by patient population, line of therapy, dose cohort and in aggregate for a given combination to inform~~and~~ decisions to continue to Part 3 ~~will be made based on response data are available for up to 20 subjects for each cohort.~~ **In order to proceed to Part 3, sufficient evidence of clinical activity (e.g. observing 4 responses out of up to 20 subjects) should be observed to warrant further development.** ~~Meanwhile, the Part 2 portion of the study will employ a Bayesian design that allows the trial to be monitored more frequently at multiple stages.~~

~~The trial~~ Part 2 may ~~also~~ be stopped at any time if excessive toxicities with the drug are observed. For additional details about this approach, see Section 5.

The decision to proceed to Part 3 of the study will take into consideration all available data and will be reviewed by the investigator(s), GSK medical monitor(s), pharmacokineticist and statistician. Data will include the safety profile [redacted] of all dosing cohorts throughout the time subjects are on study. The decision could be based on analysis of a subgroup of responders, so that a single combination arm would be carried forward into Part 3.

RATIONALE: Addition of Part 2B to further evaluate the efficacy, safety and long-term tolerability of the triplet regimen using the doses evaluated in Cohort 3A and Cohort 4 as well as adding subjects based on line of therapy to ensure a more homogenous patient population.

SECTION 3.7.6 Part 4B Cohort Expansion

PREVIOUS TEXT

In Part 4B cohort expansion, the primary objectives will be to further assess the safety and preliminary clinical activity of given doses and regimen(s) in subjects with advanced/metastatic CRC with either a BRAF-mutation (Cohort 1E) or who developed secondary resistance to prior anti-EGFR therapy (Cohort 2E). Enrollment in expansion cohorts will be initiated once dose escalation for the trametinib /panitumumab combination has been completed.

The trial may also be stopped at any time if excessive toxicities with the study treatment are observed.

REVISED TEXT

In Part 4B cohort expansion, the primary objectives will be to further assess the safety and preliminary clinical activity of trametinib and panitumumab at the MTD determined in Part 4A. Clinical activity will be determined in two patient populations of subjects with advanced/metastatic CRC:

3. BRAF mutant population, subjects with BRAF-V600E mutation-positive CRC (described above)

4. Anti-EGFR resistant population, subjects with CRC that developed secondary resistance to anti-EGFR therapy after initially deriving benefit.

~~given doses and regimen(s) in subjects with advanced/metastatic CRC with either a BRAF-mutation (Cohort 1E) or who developed secondary resistance to prior anti-EGFR therapy (Cohort 2E).~~ Enrollment in expansion cohorts will be initiated once dose escalation for the trametinib /panitumumab combination has been completed. Up to 20 subjects will be enrolled into each population at the starting dose or MTD if lower dose combination is required. This will include the patients from part 4A. An additional 20 subjects with advanced/metastatic CRC with a BRAF mutation and progression or intolerance to one line of prior chemotherapy for metastatic disease or recurrence within 6 months of adjuvant therapy may be enrolled into BRAF mutant CRC population at a lower dose combination defined by the de-escalation cohorts to evaluate the tolerability and efficacy of a lower dose of one or both of the investigational products. The decision to enroll subjects at a lower dose level(s) and the lower dose(s) selected will be at the discretion of the investigators and GSK medical monitor. ~~The trial~~Part 4 may also be stopped at any time if excessive toxicities with the study treatment are observed.

RATIONALE: Change from cohort to population to describe the patients that will be enrolled in Part 4B as well as to add an additional 20 subjects with BRAF mutant disease to be enrolled if evaluation of a lower dose combination of trametinib and panitumumab is undertaken.

SECTION 3.8 Treatment Assignment

PREVIOUS TEXT

All subjects will be assigned to study treatment in accordance with the randomization schedule generated by Discovery Biometrics, prior to the start of the study, using validated internal software. In Part 1, subjects will be assigned to a cohort/ dose level based on evaluation of safety in subjects enrolled in prior cohorts. In Part 2, subjects will be assigned to expansion cohorts at a selected dose of dabrafenib in combination with panitumumab and a selected dose of trametinib plus dabrafenib in combination with panitumumab. In Part 3, subjects will be randomized to study treatment. In Part 4A dose escalation, subjects will be assigned to a cohort/ dose level based on evaluation of safety in subjects enrolled in prior cohorts. In Part 4B cohort expansion, subjects will be assigned to expansion cohorts at a selected dose of trametinib in combination with panitumumab

REVISED TEXT

All subjects will be assigned to study treatment in accordance with the randomization schedule generated by Discovery Biometrics, prior to the start of the study, using validated internal software. In Part 1, subjects will be assigned to a cohort/ dose level based on evaluation of safety in subjects enrolled in prior cohorts. In Part 2, subjects will be assigned to expansion cohorts at a dose cohort from Part 1~~selected dose o~~f dabrafenib in combination with panitumumab and a ~~selected dose~~dose cohort from Part 1 of trametinib plus dabrafenib in combination with panitumumab. In Part 3, subjects will be randomized to study treatment. In Part 4A dose escalation, subjects will be assigned to a cohort/ dose level based on evaluation of safety in subjects enrolled in prior cohorts. In Part 4B cohort expansion, subjects will be assigned to expansion cohorts at ~~a selected dose~~the starting dose cohort or ~~-~~dose de-escalation cohort from Part 4A of trametinib in combination with panitumumab

RATIONALE: Update text to allow for a dose cohort evaluated in Part 1 to be further evaluated in Part 2

SECTION 3.10.1 Continuation on Study

PREVIOUS TEXT

Subjects who have met the criteria for disease progression (PD) according to RECIST v 1.1 may continue to receive study drug if the Investigator believes the subject is receiving clinical benefit and approval to continue is granted by the GSK Medical Monitor. In this case, all study procedures would continue per protocol. The following efficacy and safety criteria must be met during study treatment prior to disease progression in order for investigators to consider continuing study therapy beyond radiographic tumor progression:

- the subject experienced a confirmed tumor response according to RECIST v 1.1 while receiving study treatment OR disease under study had remained no worse than stable for a period of at least 6 months while receiving dabrafenib;

- absence of signs and symptoms of clinical disease progression despite radiographic disease progressive based on RECIST v 1.1 criteria outlined in Appendix 4;

- no treatment-related AEs of CTCAE Grade 4 or SAEs have occurred during the last 4 weeks of dabrafenib treatment.

REVISED TEXT

Subjects who have met the criteria for disease progression (PD) according to RECIST v 1.1 may continue to receive study drug if the Investigator believes the subject is receiving clinical benefit and approval to continue is granted by the GSK Medical Monitor. In this case, all study procedures would continue per protocol. The following efficacy and safety criteria must be met during study treatment prior to disease progression in order for investigators to consider continuing study therapy beyond radiographic tumor progression:

- the subject experienced a confirmed tumor response according to RECIST v 1.1 while receiving study treatment OR disease under study had remained no worse than stable for a period of at least ~~6~~two consecutive scans (approximately 12 weeks)~~months~~ while receiving study treatment~~dabrafenib~~;

- absence of signs and symptoms of clinical disease progression despite radiographic disease progressive based on RECIST v 1.1 criteria outlined in Appendix 4;

no treatment-related AEs of CTCAE Grade 4 or SAEs have occurred during the last 4 weeks of ~~dabrafenib~~ study treatment.

RATIONALE: Changed continuation past progression to account for Part 4, which does not contain trametinib, and allow for continuation past progression after a more modest response to study treatment at the discretion of the investigator and GSK medical monitor.

SECTION 3.10.2 Dose Adjustments

PREVIOUS TEXT

In the event of a DLT (for subjects enrolled in Part 1), or other clinically significant AE in any part of the study, treatment may be withheld and supportive therapy administered as clinically indicated. If the toxicity or event resolves to baseline or Grade 1 in less than or equal to 14 days of stopping therapy, then treatment may be restarted. Dose reduction should be considered as clinically indicated. Any dose adjustment or interruption will be recorded.

REVISED TEXT

In the event of a DLT (for subjects enrolled in ~~Part 1~~a dose escalation cohort), or other clinically significant AE in any part of the study, treatment may be withheld and supportive therapy administered as clinically indicated. If the toxicity or event resolves

to baseline or Grade 1 in less than or equal to 14 days of stopping therapy, then treatment may be restarted. Dose reduction should be considered as clinically indicated. Any dose adjustment or interruption will be recorded.

RATIONALE FOR CHANGE: Clarify DLTs from any dose escalation cohort.

SECTION 3.10.2 Dose Adjustments

PREVIOUS TEXT

Table 7 Dose Level Reduction Guidelines

Dose Level	Dabrafenib Dose/Schedule	Trametinib Dose/Schedule	Panitumumab Dose/Schedule[a]
0	150mg BID	2mg once daily	6 mg/kg every 14 days
-1 (first dose reduction)	100mg BID	1.5mg once daily	4.8 mg/kg every 14 days
-2 (second dose reduction)	75mg BID	1mg once daily	3.6 mg/kg every 14 days

a. In the case of acneiform rash, panitumumab dose may be reduced 50% of the previous dose per Table 11.

REVISED TEXT

Table 8~~7~~ Dose Level Reduction Guidelines

Dose Level	Dabrafenib Dose/Schedule	Trametinib Dose/Schedule	Panitumumab Dose/Schedule[a]
0	150mg BID	2mg once daily	6 mg/kg every 14 days
-1 (first dose reduction)	100mg BID	1.5mg once daily	4.8 mg/kg every 14 days
-2 (second dose reduction)	75mg BID	1mg once daily	3.6 mg/kg every 14 days

~~a. In the case of acneiform rash, panitumumab dose may be reduced 50% of the previous dose per Table 11.~~

RATIONALE: Reduction of panitumumab dose by 50% was modified to "by one dose level"

SECTION 3.10.3 Intra-subject Doublet to Triplet Crossover and Dose Escalation: Part 1, 2 or 4

PREVIOUS TEXT

For BRAF-mutation positive subjects enrolled in Part 1, 2 or 4 doublet dosing, intra-subject doublet to triplet crossover is allowed if a patient has not experienced intolerable toxicity that could not be managed, and has demonstrated radiographic progression on therapy by RECIST v1.1 criteria, and approval will be based on review by GSK Medical Monitor. Dose administered must be from among those for which cohorts have been completed and data has been reviewed for safety.

At the time of crossover, certain safety assessments will be repeated prior to start of triplet dosing (additional information describing assessments is available in Section 6):

- brief physical examination
- vital signs
- dermatological examination
- ECG (single; repeated with 2 additional ECGs if clinically significant abnormalities are observed in the first assessment)
- ECHO/ MUGA
- disease assessment demonstrating radiographic progression on therapy by RECIST v1.1 criteria
- ophthalmic examination, repeated at Week 4 after start of dosing with trametinib

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

All crossover assessments must be completed within 14 days prior to first dose on triplet except informed consent, ophthalmology exam, ECHO/MUGA and Disease Assessment, which can occur within 35 days prior to the first dose on triplet.

The source documents for these assessments should be provided to GSK at least 24 hours in advance to planned start of triplet dosing. The medical monitor will review and provide approval for crossover from doublet to triplet, and site will be notified via email with a signed crossover form (refer to SPM).

Once approved, patients will follow the time and events table for Part 2 Expansion Cohorts, in Section 3.10.3, starting at the column labelled "Continuation Phase" for continued monitoring of safety and efficacy.

Subjects are allowed to crossover once during the study.

Additionally, for subjects who have remained on study for ≥ 6 months in the triplet combination, their dose level for the combination may be increased up to the highest combination dose level that has previously been confirmed as not exceeding the MTD for the combination. The intra-subject dose escalation must be agreed to by the investigator and the GSK Medical Monitor.

REVISED TEXT

For BRAF-mutation positive subjects enrolled in Part 1, 2 or 4 doublet dosing, intra-subject doublet to triplet crossover is allowed if a patient has not experienced intolerable toxicity that could not be managed, and has demonstrated radiographic progression on therapy by RECIST v1.1 criteria, and approval will be based on review by GSK Medical Monitor. Subjects must crossover to triplet within 6 weeks of radiographic progression. All assessments and samples required at progression as described in Section 3.10 must be completed even though the subject crosses over to triplet. Dose administered must be from among those for which cohorts have been completed and data has been reviewed for safety.

At the time of crossover, certain safety assessments will be repeated prior to start of triplet dosing (additional information describing assessments is available in Section 6):

- brief physical examination
- vital signs
- dermatological examination
- ECG (single; repeated with 2 additional ECGs if clinically significant abnormalities are observed in the first assessment)
- ECHO/ MUGA
- disease assessment demonstrating radiographic progression on therapy by RECIST v1.1 criteria
- ophthalmic examination, repeated at Week 4 after start of dosing with trametinib

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

All crossover assessments must be completed within 14 days prior to first dose on triplet except informed consent, ophthalmology exam, ECHO/MUGA and Disease Assessment, which can occur within 35 days prior to the first dose on triplet. Assessments performed as part of the ~~initial~~ follow-up for the doublet will be acceptable if they are performed within these timeframes prior to the first dose on triplet.

The source documents for these assessments should be provided to GSK at least 24 hours in advance to planned start of triplet dosing. The medical monitor will review and provide approval for crossover from doublet to triplet, and site will be notified via email with a signed crossover form (refer to SPM).

Once approved, patients will follow the time and events table ~~for Part 2 Expansion Cohorts,~~ in Section ~~3.10.2~~3.11.5, starting at the column labelled "Continuation Phase" for continued monitoring of safety and efficacy after they receive their first dose on triplet. The Initial Follow-Up and Secondary Follow-Up Assessments should be performed after last dose of triplet. Additional details are provided in the SPM.

Subjects are allowed to crossover once during the study.

Additionally, for subjects who have remained on study for ≥ 6 months in the triplet combination, their dose level for the combination may be increased up to the highest combination dose level that has previously been confirmed as not exceeding the MTD for the combination. The intra-subject dose escalation must be agreed to by the investigator and the GSK Medical Monitor.

RATIONALE: Clarification of assessments to be performed at time of intra-subject crossover and cross reference to inserted crossover time and event table.

SECTION 3.10.4 General Guidelines for Clinical Significant Toxicities

PREVIOUS TEXT

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 8 Dose Modification Algorithms

Non-hematologic and hematologic toxicity (except neutropenia and fever), CTCAE Grade	Dose modification algorithms [a, b, c, d]
Grade 1	• Continue dabrafenib, trametinib and panitumumab at full dose • Monitor closely • Provide supportive care according to institutional standards
Grade 2	• Consider holding dabrafenib, trametinib, and/or panitumumab until resolution to Grade 1 or baseline • Provide supportive care as clinically indicated. • Monitoring of laboratory values should occur as clinically indicated. • For Grade 2 or higher respiratory symptoms (i.e., cough, dyspnea, hypoxia, etc), evaluation by CT scan is recommended.
Grade 3	• Hold dabrafenib, trametinib, and panitumumab until toxicity resolves to Grade 1 or baseline then reduce dose of dabrafenib, trametinib, and/or panitumumab by 1 dose level. • The subject may be continued at the same dose, if in the judgment of the investigator, the toxicity is considered unrelated to dabrafenib, trametinib, and/or panitumumab. • Continue to monitor as clinically indicated.
Grade 4	• Discontinue dabrafenib, trametinib, and panitumumab. Continue to monitor as clinically indicated, and provide supportive care as needed. • If, in the investigator's judgment the toxicity is unlikely to recur, then hold dabrafenib, trametinib, and panitumumab until the toxicity is Grade 1 or baseline, then reduce dose of dabrafenib, trametinib, and/or panitumumab by 1 dose level. • If Grade 4 toxicity recurs after dose reduction, discuss continuation of study drug(s) with the GSK Medical Monitor.

a. The minimum dose of dabrafenib is 75mg BID; the minimum dose of trametinib is 1mg once daily; the minimum dose of panitumumab is 3.6 mg/kg. If a subject requires dose reduction below dabrafenib 75mg BID, trametinib 1mg once daily, or panitumumab 3.6 mg/kg then the subject must be discontinued from study drug(s).
b. For adverse events of abdominal pain or suspected pancreatitis, amylase and lipase laboratory samples should be collected.
c. If the subject has a Grade 3 or 4 laboratory abnormality, that in the judgment of the investigator is not considered clinically significant, dose modification is not required.
d. For subjects who develop symptoms associated with uveitis, including blurry vision, eye pain or erythema, an ophthalmologic consult is required.

REVISED TEXT

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 9~~8~~ Dose Modification Algorithms

Non-hematologic and hematologic toxicity (except ~~neutropenia and~~ fever), CTCAE Grade	**Dose modification algorithms** [a, b, c, d]
Grade 1	• Continue dabrafenib, trametinib and panitumumab at full dose • Monitor closely • Provide supportive care according to institutional standards
Grade 2	• Consider dose de-escalation by 1 dose level or holding dabrafenib, trametinib, and/or panitumumab until resolution to Grade 1 or baseline • Provide supportive care as clinically indicated. • Monitoring of laboratory values should occur as clinically indicated. • For Grade 2 or higher respiratory symptoms (i.e., cough, dyspnea, hypoxia, etc), evaluation by CT scan is recommended.
Grade 3	• Hold dabrafenib, trametinib, and panitumumab until toxicity resolves to Grade 1 or baseline then reduce dose of dabrafenib, trametinib, and/or panitumumab by 1 dose level. • The subject may be continued at the same dose, if in the judgment of the investigator, the toxicity is considered unrelated to dabrafenib, trametinib, and/or panitumumab or clearly related to a particular agent(s). • Continue to monitor as clinically indicated.
Grade 4	• Discontinue dabrafenib, trametinib, and panitumumab. Continue to monitor as clinically indicated, and provide supportive care as needed. • If, in the investigator's judgment the toxicity is unlikely to recur, then hold dabrafenib, trametinib, and panitumumab until the toxicity is Grade 1 or baseline, then reduce dose of dabrafenib, trametinib, and/or panitumumab by 1 dose level. • If Grade 4 toxicity recurs after dose reduction, discuss continuation of study drug(s) with the GSK Medical Monitor.

a. The minimum dose of dabrafenib is 75mg BID; the minimum dose of trametinib is 1mg once daily; the minimum dose of panitumumab is 3.6 mg/kg. If a subject requires dose reduction below dabrafenib 75mg BID, trametinib 1mg once daily, or panitumumab 3.6 mg/kg then the subject must be discontinued from study drug(s).
b. For adverse events of abdominal pain or suspected pancreatitis, amylase and lipase laboratory samples should be collected.
c. If the subject has a Grade 3 or 4 laboratory abnormality that in the judgment of the investigator is not considered clinically significant, dose modification is not required.
d. For subjects who develop symptoms associated with uveitis, including blurry vision, eye pain or erythema, an ophthalmologic consult is required.

RATIONALE: Update guidelines to provide revised guidance on dose modifications.

SECTION 3.10.4.1 Guidelines for Treatment of Pyrexia

PREVIOUS TEXT

Table 11~~10~~ Management and Dose Modification Guidelines for Pyrexia

Pyrexia[a] Management	Action and Dose Modification
All Events: • Clinical evaluation for infection and hypersensitivity[c] • Laboratory work-up[c] • Hydration as required[d]	
1st Event[b]: Administer anti-pyretic treatment if clinically indicated and continue prophylactic treatment[f] if associated with rigors, renal failure, dehydration or hypotension[e]	1st Event: • Interrupt dabrafenib • Continue trametinib and/or panitumumab • Once pyrexia resolves to baseline, restart dabrafenib at the same dose level If fever was associated with dehydration or hypotension, **reduce dabrafenib by one dose level**
2nd Event[g]: • Within 3 days of onset of pyrexia: Optimize anti-pyretic therapy Consider oral cortiocosteroids (i.e., prednisone 10mg) for at least 5 days or as clinically indicated	2nd Event: • **Interrupt dabrafenib** • Continue trametinib and/or panitumumab • Once pyrexia resolves to baseline, restart dabrafenib at the same dose level If fever was associated with rigors, renal failure, dehydration or hypotension, **reduce dabrafenib by one dose level**
Subsequent Events: • Within 3 days of onset of pyrexia: Optimize oral corticosteroid dose as clinically indicated for recalcitrant pyrexia if corticosteroids have been tapered and pyrexia recurs, restart steroids if corticosteroids cannot be tapered consult medical monitor	**Subsequent Events:** • **Interrupt dabrafenib** • Continue trametinib and/or panitumumab Once pyrexia resolves to baseline, restart dabrafenib **reduced by one dose level[h]** If dabrafenib must be reduced to <50mg BID, permanently **discontinue dabrafenib. Trametinib may be continued.**

h. Pyrexia is defined as a body temperature equal to or above 38.5 °Celsius or 101.3° Fahrenheit.
i. For subjects experiencing pyrexia complicated by rigors, severe chills, etc., a clinical evaluation and laboratory work-up is mandatory for each event; anti-pyretic treatment should be started immediately at the first occurrence and prophylactic anti-pyretic treatment is recommended
j. Thorough clinical examination for signs and symptoms of infection or hypersensitivity is required; laboratory workup should include full-blood-count, electrolytes, creatinine, blood urea nitrogen (BUN), C-reactive protein (CRP), liver-function tests, blood culture, and urine culture.
k. Oral hydration should be encouraged in subjects without evidence of dehydration. Intravenous hydration is recommended in subjects experiencing pyrexia complicated by dehydration/hypotension.
l. 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

REVISED TEXT

Table 11~~10~~ Management and Dose Modification Guidelines for Pyrexia

Pyrexia[a] Management	**Action and Dose Modification**
All Events: • Clinical evaluation for infection and hypersensitivity[c] • Laboratory work-up[c] • Hydration as required[d]	
1st Event[b]: Administer anti-pyretic treatment if clinically indicated and continue prophylactic treatment[f] if associated with rigors, renal failure, dehydration or hypotension[e]	1st Event: • Interrupt dabrafenib • Continue trametinib and/or panitumumab • Once pyrexia resolves to baseline, restart dabrafenib at the same dose level If fever was associated with dehydration or hypotension, **reduce dabrafenib by one dose level**
2nd Event[g]: • Within 3 days of onset of pyrexia: Optimize anti-pyretic therapy Consider oral cortiocosteroids (i.e., prednisone 10mg) for at least 5 days or as clinically indicated	2nd Event: • **Interrupt dabrafenib** • Continue trametinib and/or panitumumab • Once pyrexia resolves to baseline, restart dabrafenib at the same dose level If fever was associated with rigors, renal failure, dehydration or hypotension, **reduce dabrafenib by one dose level**
Subsequent Events: • Within 3 days of onset of pyrexia: Optimize oral corticosteroid dose as clinically indicated for recalcitrant pyrexia if corticosteroids have been tapered and pyrexia recurs, restart steroids if corticosteroids cannot be tapered consult medical monitor	**Subsequent Events:** • **Interrupt dabrafenib** • Continue trametinib and/or panitumumab Once pyrexia resolves to baseline, restart dabrafenib **reduced by one dose level[h]** If dabrafenib must be reduced to <50mg BID, permanently **discontinue dabrafenib. Trametinib may be continued.**

a. Pyrexia is defined as a body temperature equal to or above 38.5 °Celsius or 101.3° Fahrenheit.
b. For subjects experiencing pyrexia complicated by rigors, severe chills, etc., a clinical evaluation and laboratory work-up is mandatory for each event; anti-pyretic treatment should be started immediately at the first occurrence and prophylactic anti-pyretic treatment is recommended
c. Thorough clinical examination for signs and symptoms of infection or hypersensitivity is required; laboratory workup 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 subjects without evidence of dehydration. Intravenous hydration is recommended in subjects 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 subject 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.

RATIONALE: Updated text to include missing footnotes.

SECTION 3.10.4.2.2 Acneiform Rash

PREVIOUS TEXT

Table 11 Acneiform Rash Management Guidelines

Step	Rash grading	Rash severity	Management of Rash	Dose Modification for Trametinib and Panitumumab[a]
1	Mild	Localized Minimally symptomatic No impact on activities of daily living (ADL) No sign of superinfection	Initiate prophylactic regimen, including oral antibiotics, if not already started (see Section 3.9.4.2.1). Consider using moderate strength topical steroids[a]	Continue current doses. Reassess after 2 weeks; if rash worsens or does not improve, proceed to Step 2.
2	Moderate	Generalized Mild symptoms (e.g., pruritus, tenderness) Minimal impact on ADL No sign of superinfection	Initiate prophylactic regimen, including oral antibiotics, if not already started (see Section 3.9.4.2.1), using moderate strength topical steroids[a]	Reduce panitumumab dose by 50% or consider interrupting panitumumab until resolution of toxicity to Grade 1. If applicable, reduce trametinib by one dose level or consider interrupting trametinib until resolution of toxicity to Grade 1. If toxicity resolves, then can consider re-escalation to initial dose level. Reassess after 2 weeks; if rash worsens or does not improve, proceed to Step 3.
≥3	Severe	Generalized Severe symptoms (e.g., pruritus, tenderness) Significant impact on ADL Sign of or potential for superinfection	Initiate prophylactic regimen, including oral antibiotics, if not already started, using moderate strength topical steroids[b] plus methylprednisone dose pack (see Section 3.9.4.2.1). Consider obtaining dermatology consultation. Manage rash per dermatologist's recommendation.	Interrupt panitumumab and trametinib until rash improves (moderate or mild), or resolves. If rash worsens or does not improve after 2 weeks, permanently discontinue panitumumab and trametinib. If rash does improve/resolve, restart trametinib and panitumumab, each reduced by a single dose level. 2. If the combination is tolerated for two weeks, consider dose escalating one or both agents to the prior dose level. 3. If it is not tolerated, hold both agents until resolution to Gr1 and

Step	Rash grading	Rash severity	Management of Rash	Dose Modification for Trametinib and Panitumumab[a]
				then restart both agents, each reduced by another dose level.

c. Recommendations for modification of panitumumab dosing may deviate from the package insert [VECTIBIX, 2012].
d. Hydrocortisone 2.5% cream or fluticasone proprionate 0.5% cream.

REVISED TEXT

Table 1211 Acneiform Rash Management Guidelines

Step	Rash grading	Rash severity	Management of Rash	Dose Modification for Trametinib and Panitumumab[a]
1	Mild	Localized Minimally symptomatic No impact on activities of daily living (ADL) No sign of superinfection	Initiate prophylactic regimen, including oral antibiotics, if not already started (see Section 3.9.4.2.1). Consider using moderate strength topical steroids[ab]	Consider reduction of panitumumab dose by one dose level . ~~Continue current doses.~~ Reassess after 2 weeks; if rash worsens or does not improve, proceed to Step 2.
2	Moderate	Generalized Mild symptoms (e.g., pruritus, tenderness) Minimal impact on ADL No sign of superinfection	Initiate prophylactic regimen, including oral antibiotics, if not already started (see Section 3.9.4.2.1), using moderate strength topical steroids[ab]	Reduce panitumumab dose by one dose level ~~50%~~ or consider interrupting panitumumab until resolution of toxicity to Grade 1. ~~If applicable,~~ Rreduce trametinib by one dose level or consider interrupting trametinib until resolution of toxicity to Grade 1. If toxicity resolves, then can consider re-escalation to initial dose level. Reassess after 2 weeks; if rash worsens or does not improve, proceed to Step 3.
≥3	Severe	Generalized Severe symptoms (e.g., pruritus, tenderness) Significant impact on ADL Sign of or potential for superinfection	Initiate prophylactic regimen, including oral antibiotics, if not already started, using moderate strength topical steroids[b] plus methylprednisone dose pack (see Section 3.9.4.2.1). Consider obtaining dermatology	Interrupt panitumumab and trametinib until rash improves (~~moderate or~~ mild), or resolves. If rash worsens or does not improve after 2 weeks, permanently discontinue panitumumab and trametinib. If rash does improve/resolve, restart trametinib and panitumumab, each reduced by a single dose level.

Step	Rash grading	Rash severity	Management of Rash	Dose Modification for Trametinib and Panitumumab[a]
			consultation. Manage rash per dermatologist's recommendation.	~~4. If the combination is tolerated for two weeks, consider dose escalating one or both agents to the prior dose level.~~ 5. If it is not tolerated, hold both agents until resolution to Gr1 and then restart both agents, each reduced by another dose level.

e. Recommendations for modification of panitumumab dosing may deviate from the package insert [VECTIBIX, 2012~~4~~].

Hydrocortisone 2.5% cream or fluticasone proprionate 0.5% cream.

RATIONALE: Updated dose modification guidelines to attempt to better control acneiform rash.

SECTION 3.10.5 Management and Dose Modification Guidelines for Diarrhea

PREVIOUS TEXT

Episodes of diarrhea have occurred in subjects receiving dabrafenib, panitumumab and /or trametinib. Other, frequent causes for diarrhea 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 diarrhea considered to be related to study treatment by the investigator are provided in Table 14.

Table 14 Management and Dose Modification Guidelines for Diarrhea

CTCAE Grade	Adverse Event Management	Action and Dose Modification
Uncomplicated diarrhea[a] Grade 1 or Grade 2	Diet: Stop all lactose-containing products; eat small meals, BRAT diet (bananas, rice, apples, toast) is recommended. Hydration: 8 to 10 large glasses of clear liquids per day (e.g., Gatorade or broth) Loperamide: initially 4mg, followed by 2mg every 4 hours or after every unformed stool, to a maximum of 16mg/ day. Continue until diarrhea-	Continue study treatments If diarrhea is Grade 2 for >48 hours, interrupt study treatments until resolution to ≤Grade 1. Restart study treatments at the current dose level.

CTCAE Grade	Adverse Event Management	Action and Dose Modification
	free for 12 hours. Diarrhea ≥ 24 hours: Loperamide 2mg every two hours to a maximum of 16mg/ day. Consider adding oral antibiotics. Diarrhea ≥48 hours: Loperamide 2mg every two hours to a maximum of 16mg/ day. Add budesonide or other 2nd line therapies (otreotide, or tincture of opium) and oral antibiotics.	
Uncomplicated diarrhea[a] Grade 3 or Grade 4 Any complicated diarrhea[b]	Clinical evaluation is mandatory. Loperamide[c]: initially 4mg, followed by 2mg every 4 hours or after every unformed stool, to a maximum of 16mg/ day. Continue until diarrhea-free for 12 hours. Oral antibiotics and 2nd line therapies should be implemented if clinically indicated. Hydration: intravenous fluids should be administered if clinically indicated. Antibiotics (oral or IV) should be administered if clinically indicated. **Interventions should be continued until the subject is diarrhea-free for ≥24 hours.** **Intervention may require hospitalization for subjects at risk of life-threatening complications.**	Interrupt study treatments until diarrhea recovers to ≤ Grade 1. Restart study treatments with a one dose level reduction. If diarrhea does not recur with this one-level dose reduction, consider re-escalation[d] of study treatment with the following order of priority: 1. Dabrafenib 2. Panitumumab 3. Trametinib If 3 dose reductions of study treatment are clinically indicated, **permanently discontinue study treatments.**

f. Uncomplicated diarrhea is 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 IV fluid substitution.

g. Complicated diarrhea is 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 IV fluid substitution.

h. Loperamide should be made available prior to the start of study treatment so that loperamide administration can begin at the first signs of diarrhea.

Escalation of study treatment to the previous dose level is allowed after consultation with the GSK Medical Monitor and in the absence of another episode of complicated or severe diarrhea in the 4 weeks subsequent to dose reduction.

REVISED TEXT

Episodes of diarrhea have occurred in subjects receiving dabrafenib, panitumumab and /or trametinib. Other, frequent causes for diarrhea 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 diarrhea considered to be related to study treatment by the investigator are provided in Table 15~~Table 14~~.

Table 15~~14~~ Management and Dose Modification Guidelines for Diarrhea

CTCAE Grade	Adverse Event Management	Action and Dose Modification
Uncomplicated diarrhea[a] Grade 1 or Grade 2	Diet: Stop all lactose-containing products; eat small meals, BRAT diet (bananas, rice, apples, toast) is recommended. Hydration: 8 to 10 large glasses of clear liquids per day (e.g., Gatorade or broth) Loperamide: initially 4mg, followed by 2mg every 4 hours or after every unformed stool, to a maximum of 16mg/ day. Continue until diarrhea-free for 12 hours. Diarrhea ≥ 24 hours: Loperamide 2mg every two hours to a maximum of 16mg/ day. Consider adding oral antibiotics. Diarrhea ≥48 hours: Loperamide 2mg every two hours to a maximum of 16mg/ day. Add budesonide or other 2nd line therapies (otreotide, or tincture of opium) and oral antibiotics.	Continue study treatments. Consider dose reduction of trametinib and panitumumab by one dose level. If diarrhea is Grade 2 for >48 hours, interrupt study treatments until resolution to ≤Grade 1. Restart study treatments at the current dose level.
Uncomplicated diarrhea[a] Grade 3 or Grade 4 Any complicated diarrhea[b]	Clinical evaluation is mandatory. Loperamide[c]: initially 4mg, followed by 2mg every 4 hours or after every unformed stool, to a maximum of 16mg/ day. Continue until diarrhea-free for 12 hours.	Interrupt study treatments until diarrhea recovers to ≤ Grade 1. Restart study treatments with a one dose level reduction. ~~If diarrhea does not recur with~~

CTCAE Grade	Adverse Event Management	Action and Dose Modification
	Oral antibiotics and 2nd line therapies should be implemented if clinically indicated. Hydration: intravenous fluids should be administered if clinically indicated. Antibiotics (oral or IV) should be administered if clinically indicated. **Interventions should be continued until the subject is diarrhea-free for ≥24 hours.** **Intervention may require hospitalization for subjects at risk of life-threatening complications.**	~~this one-level dose reduction, consider re-escalation[d] of study treatment with the following order of priority:~~ ~~4. Dabrafenib~~ ~~5. Panitumumab~~ ~~6. Trametinib~~ If 3 dose reductions of study treatment are clinically indicated, **permanently discontinue study treatments.**

i. Uncomplicated diarrhea is 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 IV fluid substitution.

j. Complicated diarrhea is 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 IV fluid substitution.

k. Loperamide should be made available prior to the start of study treatment so that loperamide administration can begin at the first signs of diarrhea.

~~l. Escalation of study treatment to the previous dose level is allowed after consultation with the GSK Medical Monitor and in the absence of another episode of complicated or severe diarrhea in the 4 weeks subsequent to dose reduction.~~

RATIONALE: Update dose modification guidelines for management of diarrhea

SECTION 3.10.7.1 Left Ventricular Ejection Fraction (LVEF)

PREVIOUS TEXT

Table 16 Dose Modification Guidelines and Stopping Criteria for LVEF Decrease

Clinic Presentation	LVEF decrease (%) or CTCAE grade	Action and Dose Modificationd
Asymptomatic	Absolute decrease of >10% in LVEF compared to baseline and ejection fraction below the institutional LLN	Interrupt study treatment with dabrafenib and trametinib and repeat ECHO/MUGA within 2 weeks[a] IF 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 trametinib reduced by one dose level[b] • Restart dabrafenib at previous dose level • Repeat ECHO/MUGA at 2, 4, 8, and 12 weeks after re-start; continue in 12 week intervals thereafter If LVEF **does not recover** within 4 weeks: e. Consult with cardiologist **f. Permanently discontinue dabrafenib and trametinib** **g. Report as SAE** h. Repeat ECHO/MUGA after 2, 4, 8, 12 and 16 weeks or until resolution i. Consult with GSK Medical Monitor[d]
Symptomatic[c]	Grade 3: resting LVEF 39-20% or >20% absolute reduction from baseline	Permanently discontinue study treatment with dabrafenib and trametinib **Report as SAE** Consult with cardiologist Repeat ECHO/MUGA after 2, 4, 8, 12 and 16 weeks or until resolution.
	Grade 4: resting LVEF <20%	

a. Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; ECHO = echocardiogram; GSK = GlaxoSmithKline; LLN = lower limit of normal; LVEF = left ventricular ejection fraction If ECHO/MUGA does not show LVEF recovery after 2 weeks, repeat ECHO/MUGA 2 weeks later.
b. Escalation of trametinib to previous dose level can be considered if LVEF remains stable for 4 weeks after restarting of trametinib. Approval from GSK Medical Monitor is required
c. Symptoms may include: dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema.
d. Once LVEF recovers to baseline, restarting dabrafenib monotherapy may be considered in consultation with the GSK Medical Monitor.

REVISED TEXT

Table 17~~16~~ Dose Modification Guidelines and Stopping Criteria for LVEF Decrease

Clinic Presentation	LVEF decrease (%) or CTCAE grade	Action and Dose Modificationd
Asymptomatic	Absolute decrease of >10% in LVEF compared to baseline and ejection fraction below the institutional LLN	Interrupt ~~study treatment with dabrafenib and~~ trametinib and repeat ECHO/MUGA within 2 weeks[a] IF 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 • If approved, ~~R~~restart trametinib reduced by one dose level[b] • ~~Restart dabrafenib at previous dose level~~ • Repeat ECHO/MUGA at 2, 4, 8, and 12 weeks after re-start; continue in 12 week intervals thereafter If LVEF **does not recover** within 4 weeks:

		e. Consult with cardiologist **f. Permanently discontinue ~~dabrafenib and~~ trametinib** **g. Report as SAE** h. Repeat ECHO/MUGA after 2, 4, 8, 12 and 16 weeks or until resolution i. Consult with GSK Medical Monitor[d]
Symptomatic[c]	Grade 3: resting LVEF 39-20% or >20% absolute reduction from baseline	Permanently discontinue ~~study treatment with dabrafenib and~~ trametinib Interrupt dabrafenib[d]
	Grade 4: resting LVEF <20%	**Report as SAE** Consult with cardiologist Repeat ECHO/MUGA after 2, 4, 8, 12 and 16 weeks or until resolution.

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/MUGA does not show LVEF recovery after 2 weeks, repeat ECHO/MUGA 2 weeks later.
b. Escalation of trametinib to previous dose level can be considered if LVEF remains stable for 4 weeks after restarting of trametinib. Approval from GSK Medical Monitor is required
c. Symptoms may include: dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema.
d. Once LVEF recovers to baseline, restarting dabrafenib monotherapy may be considered in consultation with the GSK Medical Monitor.

RATIONALE: Update to align with current guidance for the dabrafenib and trametinib combination.

SECTION 3.10.10 Liver Stopping Criteria

PREVIOUS TEXT

Liver chemistry threshold stopping criteria have been designed to assure subject safety and evaluate liver event etiology during administration of study treatment(s) and the follow-up period. Study treatment(s) will be stopped if any of the following liver chemistry stopping criteria is/are met:

- Alanine aminotransferase (ALT) ≥3x upper limit of normal (ULN) AND bilirubin ≥2xULN (>35% direct bilirubin) (or ALT≥3xULN and international normalized ratio [INR]>1.5, if INR measured and subject not receiving warfarin therapy).

  NOTE: If serum bilirubin fractionation is not immediately available, study drug 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.

- ALT ≥5xULN.

- ALT ≥3xULN if associated with the appearance or worsening of symptoms of hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia.

- ALT ≥3xULN persists for ≥4 weeks.

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

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

- Immediately discontinue investigational product(s).

- Report the event to GSK within 24 hours of learning its occurrence.

- Complete the liver event eCRF 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 subjects receiving anticoagulants), termed 'Hy's Law', must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
- Complete the liver imaging and/or liver biopsy CRFs if these tests are performed.
- Perform liver event follow up assessments, and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below.
- Follow-up for Overall Survival (OS) is required following permanent discontinuation from investigational product.
- Do not re-challenge with investigational product.

REVISED TEXT

Liver chemistry threshold stopping criteria have been designed to assure subject safety and evaluate liver event etiology during administration of study treatment(s) and the follow-up period. Study treatment(s) will be stopped if any of the following liver chemistry stopping criteria is/are met:

1. Alanine aminotransferase (ALT) ≥3x upper limit of normal (ULN) AND bilirubin ≥2xULN (>35% direct bilirubin) (or ALT≥3xULN and international normalized ratio [INR]>1.5, if INR measured and subject not receiving warfarin therapy).

    - NOTE: If serum bilirubin fractionation is not immediately available, study drug 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 the appearance or worsening of symptoms of hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, 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 5 liver chemistry stopping criteria is met, do the following:

- Immediately discontinue investigational product(s).
- Report the event to GSK within 24 hours of learning its occurrence.
- Complete the liver event eCRF 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 subjects receiving anticoagulants), termed 'Potential Hy's Law', must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
- Complete the liver imaging and/or liver biopsy CRFs if these tests are performed.
- Perform liver event follow up assessments, and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below.
- Follow-up for Overall Survival (OS) is required following permanent discontinuation from investigational product.
- Do not re-challenge with investigational product.

RATIONALE FOR CHANGE: Clarify liver criteria

SECTION 3.11.1 Part 1 Dose Escalation Time and Event Tables

PREVIOUS TEXT

	Screening[1]	**First Treatment Period (Day 1 through Day 28)**			**Continuation Phase[2] (±7 days)**	**Initial follow-up[3]** (14 days [±7 days] from last dose of study drugs)	**Secondary follow-up[3]**	
		Day 1	**Day 15 (± 2 days)**	**Day 21 (± 2 days)**			4 weeks (±7 days) after the last dose of panitumumab	8 weeks (±7 days) after the last dose of panitumumab
Informed Consent	X							
Archival tumor tissue or fresh tumor biopsy (BRAF mutation confirmation)[13]	X							

	Screening[1]	**First Treatment Period (Day 1 through Day 28)**			**Continuation Phase**[2] **(±7 days)**	**Initial follow-up**[3] (14 days [±7 days] from last dose of study drugs)	**Secondary follow-up**[3]	
		Day 1	**Day 15 (± 2 days)**	**Day 21 (± 2 days)**			4 weeks (±7 days) after the last dose of panitumumab	8 weeks (±7 days) after the last dose of panitumumab
Tumor Biopsy (mandatory)[16]	X (pre-dose) [13]		X[10] (to be collected from Day 15 to Day 18)			X[11] (at progression)		
Demographics	X							
Medical history/ Interim History	X	X[6]			At Week 4, then every 4 weeks	X		
Concurrent medications	X	X[6]	X	X	At Week 4, then every 4 weeks	X		
Serum or urine pregnancy test (β-human chorionic gonadotropin [hCG]; women)[4]	X				Every 8 to 12 weeks [4]	X		
Complete physical examination[5]	X					X		
Brief physical examination[5]		X[6]	X		At Week 4, then every 4 weeks			
Dermatological examination[7]	X				At Week 4, then every 8 weeks More frequently if there are new or changing lesions	X		
Height (at screening only) and weight	X	X			Weight: At Week 4, then every 4 weeks	X		
Ophthalmic examination	X				At Week 4, then as symptomatically warranted	X		

	Screening[1]	**First Treatment Period (Day 1 through Day 28)**			**Continuation Phase[2] (±7 days)**	**Initial follow-up[3]** (14 days [±7 days] from last dose of study drugs)	**Secondary follow-up[3]**	
		Day 1	**Day 15 (± 2 days)**	**Day 21 (± 2 days)**			4 weeks (±7 days) after the last dose of panitumumab	8 weeks (±7 days) after the last dose of panitumumab
Eastern Cooperative Oncology Group (ECOG) Performance Status	X	X[6]			At Week 4, then every 4 weeks	X		
Vital signs (BP, HR, Body Temperature)	X	X[14]	X[14]	X	X[14]	X		
12-lead ECG[8]	X	X[6]	X	X	At Week 4, then every 4 weeks until Week 24, then every 8 weeks	X		
Hematology/Clinical Chemistry	X	X[6]	X	X	At Week 4, then every 4 weeks until Week 24, then every 8 weeks	X	X[3]	X[3]
Coagulation Repeat as clinically indicated	X							
CEA	X	X[6]	X	X	At Week 4, then every 4 weeks until Week 24, then every 8 weeks	X	X[3]	X[3]
ECHO (or MUGA)[18]	X				At Week 4, then at Week 12 and every 12 weeks thereafter	X		
Collection of blood PK samples[9]		X	X	X	X[9]	X[9] (at progression)		
[redacted]								

	Screening[1]	**First Treatment Period (Day 1 through Day 28)**			**Continuation Phase**[2] **(±7 days)**	**Initial follow-up**[3] (14 days [±7 days] from last dose of study drugs)	**Secondary follow-up**[3]	
		Day 1	**Day 15 (± 2 days)**	**Day 21 (± 2 days)**			4 weeks (±7 days) after the last dose of panitumumab	8 weeks (±7 days) after the last dose of panitumumab
[redacted]								
Panitumumab dosing[14]		X	X		X Every 2 weeks			
Dabrafenib and trametinib dosing		CONTINUOUS daily dosing; Dabrafenib BID and trametinib once daily should be administered under fasting conditions, either one hour before a meal or 2 hours after a meal.						
AE assessment		CONTINUOUS						
Urinalysis	X	X[6]				X		
Disease Assessment[12]	X				Every 6 weeks until Week 24, then every 8 weeks	X[12]	X[17]	

1. All screening assessments must be completed within 14 days prior to first dose except informed consent, ophthalmology exam, dermatology exam. ECHO/MUGA and Disease Assessment, which can occur within 35 days prior to the first dose. Note: Procedures conducted as part of the subject's routine clinical management (e.g., blood counts, imaging study) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures meet the protocol requirements.
2. Assessments throughout the study are calendar-based starting from the first day of dosing (Day 1) in the first treatment period. Dose interruptions should not alter the assessment schedule for any subsequent treatment period. The Continuation Phase starts with Day 29; events in the Continuation Phase are allowed ±7 days from projected date. Safety lab tests (chemistry/hematology/coag/UA) may be done the day before the visit so that results are ready on the day of the visit, but all assessments should be done within the ±7 day window.
3. Initial follow-up visit should be 14 days from last dose of study drugs (±7 days). If a subject is unable to return to the clinic due to hospitalization, site staff are encouraged to telephone the subject for assessment of AEs. Secondary follow-up visits should occur at 4 weeks and 8 weeks after the last dose of panitumumab.
4. Serum pregnancy test should be performed at screening; all subsequent pregnancy tests may be either serum or urine, and performed every 8 to 12 weeks.
5. Complete physical examination must include integument and genitalia. Note: pelvic exam in female subjects may be completed up to 24 weeks prior to date of first dose. Complete and brief physical examinations are defined in Section 6.2.
6. If within 72 hours of Screening, this assessment does not need to be repeated on Day 1.
7. Baseline skin photography should be performed at Screening. Photographs should be taken of new skin lesions that occur, or skin lesions that change on therapy. Refer to Section 6.2. French sites will perform dermatological exams monthly while on-therapy, and monthly for 6 months following discontinuation of dabrafenib or until initiation of another anti-neoplastic therapy, whichever comes first. Refer to Appendix 7 for full information.
8. Single ECGs will be collected prior to dosing.
9. Blood samples (4 mL) for PK analysis of dabrafenib and metabolites (hydroxy-dabrafenib and desmethyl-dabrafenib) and trametinib will be collected on Day 1 and on Day 15 predose (within 30 minutes of dosing) and at 1, 2, 4, 6,and 8 hours after administration. Blood samples (4 mL) for PK analysis of panitumumab will be collected on Day 1 and Day 15 predose (within 30 minutes of dosing panitumumab) and at 1 hour (end of infusion of panitumumab). A single 4 mL blood sample for analysis of panitumumab will be collected pre-dose on Day 21 during the clinic visit. During the continuation phase, PK samples will be collected pre-dose at Week 8, Week 12, Week 16, and Week 20. PK blood samples for dabrafenib, trametinib, and panitumumab analysis should be collected along with the tumor biopsy taken at progression. On days when serial PK samples are collected, subjects should be instructed to hold doses of dabrafenib and trametinib, report to the clinic for the predose PK blood draw, then dose with dabrafenib and trametinib. Collect PK samples at the time indicated ± 5 minutes up to 2 hour sample, ± 20 minutes up to the 8 hour sample. On all days when a PK sample is collected, date and time of PK sample, date and time of the last doses of dabrafenib, trametinib, and panitumumab prior to the predose PK samples, and the date and time of the doses dabrafenib, trametinib, and panitumumab administered in the clinic must be recorded
10. Collection of on-treatment tumor biopsy for subjects with accessible tumors. On-treatment biopsy may be collected 2 to 4 hours after dosing with oral study medication'from Day 15 to Day 18 (+3 days). Biopsies should be performed on non-target lesions when possible. PK samples for dabrafenib, trametinib and panitumumab analysis will be collected at the time of the post-dose tumor biopsy (±24 hours) (unless the post-dose biopsy occurs on the same day that the Day 15 serial PK samples are collected).
11. Tumor biopsy at tumor progression in subjects who have had a radiologic response (20% or more) or had a stable disease for 6 months is highly encouraged. .
12. CT is the preferred method to measure lesions selected for response assessment. Refer to Appendix 4 for additional information regarding Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 methodology and criteria. Follow-up disease assessment results for subjects who discontinue study medication for any other reason than progression or death. Even if study treatment is withdrawn, radiographic disease assessments (computed tomography [CT] or magnetic resonance imaging [MRI], as appropriate according to the method used at baseline) should continue every 8 weeks until documented disease progression, the start of new anti-cancer therapy, withdrawal of consent or death.
13. Collection of archived tumor tissue or fresh tumor biopsies and determination of the subject's tumor BRAF mutation status is required for enrollment; if a fresh tumor biopsy is collected during screening and up to prior to dosing on Day 1 for BRAF mutation confirmation, this tissue may be used for the day 1/ predose tumor biopsy. [redacted]

[redacted] The Day 1/predose tumor biopsy may be collected at any point after signing consent, after completing wash-out from prior therapies (either 5 half-lives or 14 days from last dose of prior therapy)..

14. Vital signs and temperature should be measured within 30 minutes prior to initiation and upon completion of the panitumumab infusion (up to 15 minutes after the end of infusion).

[redacted]

16. Pre- and post-dose tumor biopsies are mandatory. If the patient's tumors are inaccessible for biopsy, permission to enroll must be granted by the GSK Medical Monitor.
17. After study treatment is withdrawn, disease assessments (the method used at baseline) should continue every 8 weeks until documented disease progression, the start of new anti-cancer therapy, withdrawal of consent, or death.
18. ECHO is preferred. MUGA may be used only if ECHO is not available. The same method must be used consistently from screening throughout the study.

REVISED TEXT

SECTION 3.11.1 Part 1 Dose Escalation

	Screening[1]	**First Treatment Period (Day 1 through Day 28)**			**Continuation Phase[2] (±7 days)**	**Initial follow-up[3]** (14 days [±7 days] from last dose of study drugs)	**Secondary follow-up[3]**	
		Day 1	**Day 15 (± 2 days)**	**Day 21 (± 2 days)**			4 weeks (±7 days) after the last dose of panitumumab	8 weeks (±7 days) after the last dose of panitumumab
Informed Consent	X							
Archival tumor tissue or fresh tumor biopsy (BRAF mutation confirmation)[14]	X							
Tumor Biopsy (mandatory)[10]	X (pre-dose)[14]		X[11] (to be collected from Day 15 to Day 18)			X[12] (at progression)		
Demographics	X							
Medical history/ Interim History	X	X[6]			At Week 4, then every 4 weeks	X		
Concurrent medications	X	X[6]	X	X	At Week 4, then every 4 weeks	X		

	Screening[1]	**First Treatment Period (Day 1 through Day 28)**			**Continuation Phase[2] (±7 days)**	**Initial follow-up[3]** (14 days [±7 days] from last dose of study drugs)	**Secondary follow-up[3]**	
		Day 1	**Day 15 (± 2 days)**	**Day 21 (± 2 days)**			4 weeks (±7 days) after the last dose of panitumumab	8 weeks (±7 days) after the last dose of panitumumab
Serum or urine pregnancy test (β-human chorionic gonadotropin [hCG]; women)[4]	X				Every 8 to 12 weeks[4]	X		
Complete physical examination[5]	X					X		
Brief physical examination[5]		X[6]	X		At Week 4, then every 4 weeks			
Dermatological examination[7]	X				At Week 4, then every 8 weeks More frequently if there are new or changing lesions	X		
Height (at screening only) and weight	X	X			Weight: At Week 4, then every 4 weeks	X		
Ophthalmic examination	X				At Week 4, then as symptomatically warranted	X		
Eastern Cooperative Oncology Group (ECOG) Performance Status	X	X[6]			At Week 4, then every 4 weeks	X		
Vital signs (BP, HR, Body Temperature)	X	X[15]	X[15]	X	X[15]	X		
12-lead ECG[8]	X	X[6]	X	X	At Week 4, then every 4 weeks until Week 24, then every 8 weeks	X		
Hematology/Clinical Chemistry	X	X[6]	X	X	At Week 4, then every 4 weeks until Week 24, then every 8 weeks	X	X[3]	X[3]

	Screening[1]	**First Treatment Period (Day 1 through Day 28)**			**Continuation Phase[2] (±7 days)**	**Initial follow-up[3]** (14 days [±7 days] from last dose of study drugs)	**Secondary follow-up[3]**	
		Day 1	**Day 15 (± 2 days)**	**Day 21 (± 2 days)**			4 weeks (±7 days) after the last dose of panitumumab	8 weeks (±7 days) after the last dose of panitumumab
Coagulation Repeat as clinically indicated	X							
CEA	X	X[6]	X	X	At Week 4, then every 4 weeks until Week 24, then every 8 weeks	X	X[3]	X[3]
ECHO (or MUGA)[18]	X				At Week 4, then at Week 12 and every 12 weeks thereafter	X		
Collection of blood PK samples[9]		X	X	X	X[9]	X[9] (at progression)		
[redacted]								
Panitumumab dosing[15]		X	X		X Every 2 weeks			
Dabrafenib and trametinib dosing		CONTINUOUS daily dosing; Dabrafenib BID and trametinib once daily should be administered under fasting conditions, either one hour before a meal or 2 hours after a meal.						
AE assessment		CONTINUOUS						
Urinalysis	X	X[6]				X		

	Screening[1]	First Treatment Period (Day 1 through Day 28)			Continuation Phase[2] (±7 days)	Initial follow-up[3]	Secondary follow-up[3]	
		Day 1	Day 15 (± 2 days)	Day 21 (± 2 days)		(14 days [±7 days] from last dose of study drugs)	4 weeks (±7 days) after the last dose of panitumumab	8 weeks (±7 days) after the last dose of panitumumab
Disease Assessment[12]	X				Every 6 weeks until Week 24, then every 8 weeks	X[12]	X[17]	
Long-term survival follow-up								X[19]

AE, Adverse Event; BP, blood pressure; CEA, ; ECHO, echocardiogram; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; HR, heart rate; MUGA,

1. **SCREENING WINDOW**: All screening assessments must be completed within 14 days prior to first dose except informed consent, ophthalmology exam, dermatology exam. ECHO/MUGA and Disease Assessment, which can occur within 35 days prior to the first dose. Note: Procedures conducted as part of the subject's routine clinical management (e.g., blood counts, imaging study) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures meet the protocol requirements.
2. **TREATMENT PHASE**: Assessments throughout the study are calendar-based starting from the first day of dosing (Day 1) in the first treatment period. Dose interruptions should not alter the assessment schedule for any subsequent treatment period. The Continuation Phase starts with Day 29; events in the Continuation Phase are allowed ±7 days from projected date. Safety lab tests (chemistry/hematology/coag/UA) may be done the day before the visit so that results are ready on the day of the visit, but all assessments should be done within the ±7 day window.
3. **FOLLOW-UP VISIT**: Initial follow-up visit should be 14 days from last dose of study drugs (±7 days). If a subject is unable to return to the clinic due to hospitalization, site staff are encouraged to telephone the subject for assessment of AEs. Secondary follow-up visits should occur at 4 weeks and 8 weeks after the last dose of panitumumab.
4. **PREGNANCY TEST**: Serum pregnancy test should be performed at screening; all subsequent pregnancy tests may be either serum or urine, and performed every 8 to 12 weeks.
5. **PHYSICAL EXAMINATION**: Complete physical examination must include integument and genitalia. Note: pelvic exam in female subjects may be completed up to 24 weeks prior to date of first dose. Complete and brief physical examinations are defined in Section 6.2.
6. **DAY1 ASSESSMENTS**: If within 72 hours of Screening, this assessment does not need to be repeated on Day 1.
7. **DERMALOGICAL EVALUATION**: Baseline skin photography should be performed at Screening. Photographs should be taken of new skin lesions that occur, or skin lesions that change on therapy. Refer to Section 6.2. French sites will perform dermatological exams monthly while on-therapy, and monthly for 6 months following discontinuation of dabrafenib or until initiation of another anti-neoplastic therapy, whichever comes first. Refer to Appendix 7 for full information.
8. **ECG**: Single ECGs will be collected prior to dosing.
9. **PHARMACOKINETIC SAMPLES**: Blood samples (4 mL) for PK analysis of dabrafenib and metabolites (hydroxy-dabrafenib and desmethyl-dabrafenib) and trametinib will be collected on Day 1 and on Day 15 predose (within 30 minutes of dosing) and at 1, 2, 4, 6,and 8 hours after administration. Blood samples (4 mL) for PK analysis of panitumumab will be collected on Day 1 and Day 15 predose (within 30 minutes of dosing panitumumab) and at 1 hour (end of infusion of panitumumab). A single 4 mL blood sample for analysis of panitumumab will be collected pre-dose on Day 21 during the clinic visit. During the continuation phase, PK samples will be collected pre-dose at Week 8, Week 12, Week 16, and Week 20. PK blood samples for dabrafenib, trametinib, and panitumumab analysis should be collected along with the tumor biopsy taken at progression. On days when serial PK samples are collected, subjects should be instructed to hold doses of dabrafenib and trametinib, report to the clinic for the predose PK blood draw, then dose with

dabrafenib and trametinib. Collect PK samples at the time indicated ± 5 minutes up to 2 hour sample, ± 20 minutes up to the 8 hour sample. On all days when a PK sample is collected, date and time of PK sample, date and time of the last doses of dabrafenib, trametinib, and panitumumab prior to the predose PK samples, and the date and time of the doses dabrafenib, trametinib, and panitumumab administered in the clinic must be recorded

10. **BIOPSY**: Pre- and post-dose tumor biopsies are mandatory. If the patient's tumors are inaccessible for biopsy, permission to enroll must be granted by the GSK Medical Monitor.
11. **BIOPSY**: Collection of on-treatment tumor biopsy for subjects with accessible tumors. On-treatment biopsy may be collected 2 to 4 hours after dosing with oral study medication'from Day 15 to Day 18 (+3 days). Biopsies should be performed on non-target lesions when possible. PK samples for dabrafenib, trametinib and panitumumab analysis will be collected at the time of the post-dose tumor biopsy (±24 hours) (unless the post-dose biopsy occurs on the same day that the Day 15 serial PK samples are collected).
12. **BIOPSY**: Tumor biopsy at tumor progression in subjects who have had a radiologic response (20% or more) or had a stable disease for 6 months is highly encouraged. .
13. **DISEASE ASSESSMENT**: CT is the preferred method to measure lesions selected for response assessment. Refer to Appendix 4 for additional information regarding Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 methodology and criteria. Follow-up disease assessment results for subjects who discontinue study medication for any other reason than progression or death. Even if study treatment is withdrawn, radiographic disease assessments (computed tomography [CT] or magnetic resonance imaging [MRI], as appropriate according to the method used at baseline) should continue every 8 weeks until documented disease progression, the start of new anti-cancer therapy, withdrawal of consent or death.
14. **TUMOR TISSUE SAMPLE**: Collection of archived tumor tissue or fresh tumor biopsies and determination of the subject's tumor BRAF mutation status is required for enrollment; if a fresh tumor biopsy is collected during screening and up to prior to dosing on Day 1 for BRAF mutation confirmation, this tissue may be used for the day 1/ predose tumor biopsy. [redacted] The Day 1/predose tumor biopsy may be collected at any point after signing consent, after completing wash-out from prior therapies (either 5 half-lives or 14 days from last dose of prior therapy)..
15. **VITAL SIGNS**: Vital signs and temperature should be measured within 30 minutes prior to initiation and upon completion of the panitumumab infusion (up to 15 minutes after the end of infusion).
16. [redacted]
17. After study treatment is withdrawn, disease assessments (the method used at baseline) should continue every 8 weeks until documented disease progression, the start of new anti-cancer therapy, withdrawal of consent, or death.
18. **ECHO**: ECHO is preferred. MUGA may be used only if ECHO is not available. The same method must be used consistently from screening throughout the study.
19. **OVERALL SURVIVAL**: Subjects will be followed for Overall Survival every 8 weeks after last dose of study drugs. See Section 6.3.1.for additional information.

RATIONALE: Update Time and Events Table footnote with label and include Overall Survival follow up.

SECTION 3.11.2 Part 2 Dose Escalation Time and Event Tables

PREVIOUS TEXT

	Screening[1]	First Treatment Period (Day 1 through Day 28)		Continuation Phase[2] (±7 days)	Initial Follow-up[3]	Secondary Follow-up[3]	
		Day 1	Day 15 (± 2 days)			4 weeks (±7 days) after the last dose of panitumumab	8 weeks (±7 days) after the last dose of panitumumab
Informed Consent	X						
Archival tumor tissue or fresh tumor biopsy (BRAF mutation confirmation)[11]	X						
Tumor tissue biopsy (mandatory)[16]	X (pre-dose)[11]		X (to be collected from Day 15 to Day 18) [9]		X[12] (at progression)		
Demographics	X						
Medical history/ Interim History	X	X[5]		At Week 4, then every 4 weeks	X		
Concurrent Medications	X	X[5]	X	At Week 4, then every 4 weeks	X		
Serum or urine pregnancy test (β-hCG; women)[4]	X			Every 8 to 12 weeks [4]	X		
Complete physical examination[6]	X				X		
Brief physical examination[6]		X[5]	X	At Week 4, then every 4 weeks			

	Screening[1]	**First Treatment Period (Day 1 through Day 28)**		**Continuation Phase[2] (±7 days)**	**Initial Follow-up[3]**	**Secondary Follow-up[3]**	
		Day 1	**Day 15 (± 2 days)**			4 weeks (±7 days) after the last dose of panitumumab	8 weeks (±7 days) after the last dose of panitumumab
Dermatological examination[7]	X			At Week 4, then every 8 weeks More frequently if there are new or changing lesions	X		
Height (at screening only) and weight	X			Weight: At Week 4, then every 4 weeks	X		
Ophthalmic examination	X			at Week 4, then as symptomatically warranted	X		
ECOG Performance Status	X	X[5]		At Week 4, then every 4 weeks	X		
Vital signs (BP, HR, Body Temperature)	X	X[14]	X[14]	X[14]	X		
12-lead ECG[8]	X	X[5]	X	At Week 4, then every 4 weeks until Week 24, then every 8 weeks	X		
Hematology/Clinical Chemistry)	X	X[5]	X	At Week 4, then every 4 weeks until Week 24, then every 8 weeks	X[3]	X[3]	X[3]
Coagulation Repeat as clinically indicated	X						

	Screening[1]	First Treatment Period (Day 1 through Day 28)		Continuation Phase[2] (±7 days)	Initial Follow-up[3]	Secondary Follow-up[3]	
		Day 1	Day 15 (± 2 days)			4 weeks (±7 days) after the last dose of panitumumab	8 weeks (±7 days) after the last dose of panitumumab
CEA	X	X[5]	X	At Week 4, then every 4 weeks until Week 24, then every 8 weeks	X[3]	X[3]	X[3]
ECHO (or MUGA)[18]	X			At Week 4, then at Week 12 and every 12 weeks thereafter	X		
Pharmacokinetics collection: blood		X[10]	X[9],[10]	Predose; At Week 4[10]	X[10] (at progression)		
[redacted]							
Panitumumab dosing[14]		X	X	X Every 2 weeks			
Dabrafenib and trametinib dosing		CONTINUOUS daily dosing; Dabrafenib BID and trametinib once daily should be administered under fasting conditions, either one hour before or 2 hours after a meal.					
Urinalysis	X	X[5]			X		

	Screening[1]	First Treatment Period (Day 1 through Day 28)		Continuation Phase[2] (±7 days)	Initial Follow-up[3]	Secondary Follow-up[3]	
		Day 1	Day 15 (± 2 days)			4 weeks (±7 days) after the last dose of panitumumab	8 weeks (±7 days) after the last dose of panitumumab
AE assessment		CONTINUOUS					
Disease Assessment[13]	X			Every 6 weeks until Week 24, then every 8 weeks	X[13]	X[17]	
[redacted]							

1. All screening assessments must be completed within 14 days prior to first dose except informed consent, ophthalmic exam, dermatological exam, ECHO/MUGA, and Disease Assessment, which can occur within 35 days prior to the first dose. Note: Procedures conducted as part of the subject's routine clinical management (e.g., blood counts, imaging study) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures meet the protocol requirements.
2. Assessments throughout the study are calendar-based starting from the first day of dosing (Day 1) in the first treatment period. Dose interruptions should not alter the assessment schedule for any subsequent treatment period. The Continuation Phase starts with Day 29; events in the Continuation Phase are allowed ±7 days from projected date. Safety lab tests (chemistry/hematology/coag/UA) may be done the day before the visit so that results are ready on the day of the visit, but all assessments should be done within the ±7 day window.
3. Initial follow-up visit should be 14 days from last dose of study drugs (±7 days). If a subject is unable to return to the clinic due to hospitalization, site staff are encouraged to telephone the subject for assessment of AEs. Secondary follow-up visits should occur at 4 weeks and 8 weeks after the last dose of panitumumab.
4. Serum pregnancy test should be performed at screening; all subsequent pregnancy tests may be either serum or urine, and performed every 8 to 12 weeks.
5. If within 72 hours of Screening, this assessment does not need to be repeated on Day 1.
6. Complete physical examination must include integument and genitalia. Note: pelvic exam in female subjects may be completed up to 24 weeks prior to date of first dose. Complete and brief physical examinations are defined in Section 6.2.
7. Baseline skin photography should be performed at Screening. Photographs should be taken of new skin lesions that occur, or skin lesions that change on therapy. Refer to Section 6.2. French sites will perform dermatological exams monthly while on-therapy, and monthly for 6 months following discontinuation of dabrafenib or until initiation of another anti-neoplastic therapy, whichever comes first. Refer to Appendix 7 for full information
8. Single ECGs will be collected prior to dosing.
9. Collection of on-treatment tumor biopsy for subjects with accessible tumors. On-treatment biopsy may be collected 2 to 4 hours after dosing with oral study medication'from Day 15 to Day 18 (+3 days). Biopsies should be performed on non-target lesions when possible. A single PK samples for dabrafenib, trametinib, and panitumumab will be collected at the time of the post-dose tumor biopsy (±24 hours) (unless the post-dose biopsy occurs on the same day that the Day 15 serial PK samples are collected).
10. Blood samples (4 mL) for PK analysis of dabrafenib and metabolites (hydroxy-dabrafenib and desmethyl-dabrafenib) and trametinib will be collected on Day 1 and Day 15 predose (within 30 minutes of dosing) and at 1, 2, 4, 6,and 8 hours after administration. Blood samples (4 mL) for PK analysis of panitumumab will be collected on Day 1 and Day

15 predose (within 30 minutes of dosing panitumumab) and at 1 hour (end of infusion of panitumumab). A single 4 mL blood sample for analysis of panitumumab will be collected predose at the Week 4 clinic visit. On days when serial PK samples are collected, subjects should be instructed to hold doses of dabrafenib and trametinib, report to the clinic for the predose PK blood draw, then dose with dabrafenib and trametinib. Collect PK samples at the time indicated ± 5 minutes up to 2 hour sample, ± 20 minutes up to the 8 hour sample. On all days when PK samples are collected, date and time of the PK sample(s), date and time of the last doses of dabrafenib, trametinib, and panitumumab prior to the predose PK sample, and date and time of the dose of dabrafenib, trametinib, and panitumumab in the clinic must be recorded. A single blook sample for dabrafenib, trametinib, and panitumumab analysis should be collected along with the tumor biopsy taken at progression.

11. Collection of archived tumor tissue or fresh tumor biopsies and determination of the subject's tumor BRAF mutation status is required for enrollment; if a fresh tumor biopsy is collected during screening and up to prior to dosing on Day1 for BRAF mutation confirmation, this tissue may be used for the day 1/ predose tumor biopsy. [redacted] The Day 1/predose tumor biopsy may be collected at any point after signing consent, after completing wash-out from prior therapies (either 5 half-lives or 14 days from last dose of prior therapy).
12. Optional tumor biopsy for subjects who had a radiologic response (20% or more decrease) or had a stable disease for 6 months at disease progression (if feasible). A single PK sample will be collected at the time of tumor progression Refer to Section 6.7.2.
13. CT is the preferred method to measure lesions selected for response assessment. Refer to Appendix 4 for additional information regarding RECIST 1.1 methodology and criteria. Even if study treatment is withdrawn, radiographic disease assessments (CT or MRI, as appropriate according to the method used at baseline) should continue every 8 weeks until documented disease progression, the start of new anti-cancer therapy, withdrawal of consent or death.
14. Vital signs and temperature should be measured within 30 minutes prior to initiation and upon completion of the panitumumab infusion (up to 15 minutes after the end of infusion). [redacted]
16. Pre- and post-dose tumor biopsies are mandatory. If the patient's tumors are inaccessible for biopsy, permission to enroll must be granted by the GSK Medical Monitor.
17. After study treatment is withdrawn, disease assessments (the method used at baseline) should continue every 8 weeks until documented disease progression, the start of new anti-cancer therapy, withdrawal of consent, or death.
18. ECHO is preferred. MUGA may be used only if ECHO is not available. The same method must be used consistently from screening throughout the study. [redacted]

REVISED TEXT

SECTION 3.11.2 Part 2 Expansion Cohorts

	Screening[1]	First Treatment Period (Day 1 through Day 28)		Continuation Phase[2] (±7 days)	Initial Follow-up[3]	Secondary Follow-up[3]	
		Day 1	Day 15 (± 2 days)			4 weeks (±7 days) after the last dose of panitumumab	8 weeks (±7 days) after the last dose of panitumumab
Informed Consent	X						
Archival tumor tissue or fresh tumor biopsy (BRAF mutation confirmation)[12]	X						
Tumor tissue biopsy (mandatory)[9]	X (pre-dose)[12]		X (to be collected from Day 15 to Day 18)[10]		X[13] (at progression)		
Demographics	X						
Medical history/ Interim History	X	X[5]		At Week 4, then every 4 weeks	X		
Concurrent Medications	X	X[5]	X	At Week 4, then every 4 weeks	X		
Serum or urine pregnancy test (β-hCG; women)[4]	X			Every 8 to 12 weeks[4]	X		
Complete physical examination[6]	X				X		
Brief physical examination[6]		X[5]	X	At Week 4, then every 4 weeks			

	Screening[1]	**First Treatment Period (Day 1 through Day 28)**		**Continuation Phase[2] (±7 days)**	**Initial Follow-up[3]**	**Secondary Follow-up[3]**	
		Day 1	**Day 15 (± 2 days)**			4 weeks (±7 days) after the last dose of panitumumab	8 weeks (±7 days) after the last dose of panitumumab
Dermatological examination[7]	X			At Week 4, then every 8 weeks More frequently if there are new or changing lesions	X		
Height (at screening only) and weight	X			Weight: At Week 4, then every 4 weeks	X		
Ophthalmic examination	X			at Week 4, then as symptomatically warranted	X		
ECOG Performance Status	X	X[5]		At Week 4, then every 4 weeks	X		
Vital signs (BP, HR, Body Temperature)	X	X[15]	X[15]	X[15]	X		
12-lead ECG[8]	X	X[5]	X	At Week 4, then every 4 weeks until Week 24, then every 8 weeks	X		
Hematology/Clinical Chemistry)	X	X[5]	X	At Week 4, then every 4 weeks until Week 24, then every 8 weeks	X[3]	X[3]	X[3]
Coagulation Repeat as clinically indicated	X						
CEA	X	~~X~~[5]	~~X~~	At Week 4<u>6</u>, then every 4 <u>6</u> weeks until Week 24, then every 8 weeks	X[3]	X[3]	X[3]

	Screening[1]	First Treatment Period (Day 1 through Day 28)		Continuation Phase[2] (±7 days)	Initial Follow-up[3]	Secondary Follow-up[3]	
		Day 1	Day 15 (± 2 days)			4 weeks (±7 days) after the last dose of panitumumab	8 weeks (±7 days) after the last dose of panitumumab
ECHO (or MUGA)[18]	X			At Week 4, then at Week 12 and every 12 weeks thereafter	X		
Pharmacokinetics collection: blood		X[11]	X[10,11]	Predose; At Week 4[10]	X[11](at progression)		
[redacted]							
Panitumumab dosing[15]		X	X	X Every 2 weeks			
Dabrafenib and trametinib dosing		CONTINUOUS daily dosing; Dabrafenib BID and trametinib once daily should be administered under fasting conditions, either one hour before or 2 hours after a meal.					
Urinalysis	X	X[5]			X		
AE assessment		CONTINUOUS					
Disease Assessment[13]	X			Every 6 weeks until Week 24, then every 8 weeks	X[14]	X[17]	
[redacted]							

	Screening[1]	First Treatment Period (Day 1 through Day 28)		Continuation Phase[2] (±7 days)	Initial Follow-up[3]	Secondary Follow-up[3]	
		Day 1	Day 15 (± 2 days)			4 weeks (±7 days) after the last dose of panitumumab	8 weeks (±7 days) after the last dose of panitumumab
Long-term survival follow-up							X[20]

AE, Adverse Event; BP, blood pressure; CEA, ; ECHO, echocardiogram; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; HR, heart rate; MUGA,

1. **SCREENING**: All screening assessments must be completed within 14 days prior to first dose except informed consent, ophthalmic exam, dermatological exam, ECHO/MUGA, and Disease Assessment, which can occur within 35 days prior to the first dose. Note: Procedures conducted as part of the subject's routine clinical management (e.g., blood counts, imaging study) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures meet the protocol requirements.
2. **TREATMENT PHASE**: Assessments throughout the study are calendar-based starting from the first day of dosing (Day 1) in the first treatment period. Dose interruptions should not alter the assessment schedule for any subsequent treatment period. The Continuation Phase starts with Day 29; events in the Continuation Phase are allowed ±7 days from projected date. Safety lab tests (chemistry/hematology/coag/UA) may be done the day before the visit so that results are ready on the day of the visit, but all assessments should be done within the ±7 day window.
3. **FOLLOW-UP VISIT**: Initial follow-up visit should be 14 days from last dose of study drugs (±7 days). If a subject is unable to return to the clinic due to hospitalization, site staff are encouraged to telephone the subject for assessment of AEs. Secondary follow-up visits should occur at 4 weeks and 8 weeks after the last dose of panitumumab. Subjects are to be followed until progression for collection of PFS data and until death for collection of overall survival (OS) data. If a subject who is eligible for crossover to the triplet combination has not crossed over by 14 days past the last dose of study treatment, the Initial Follow-Up assessments should be done. If a subject who is eligible for crossover to the triplet combination has not crossed over by 4 weeks past the last dose of panitumumab, the Secondary Follow-Up assessments should be done.
4. **PREGNANCY TEST**: Serum pregnancy test should be performed at screening; all subsequent pregnancy tests may be either serum or urine, and performed every 8 to 12 weeks.
5. **PHYSICAL EXAM**: If within 72 hours of Screening, this assessment does not need to be repeated on Day 1.
6. **PHYSICAL EXAM**: Complete physical examination must include integument and genitalia. Note: pelvic exam in female subjects may be completed up to 24 weeks prior to date of first dose. Complete and brief physical examinations are defined in Section 6.2.
7. **DERMALOGICAL EVALUATION**: Baseline skin photography should be performed at Screening. Photographs should be taken of new skin lesions that occur, or skin lesions that change on therapy. Refer to Section 6.2. French sites will perform dermatological exams monthly while on-therapy, and monthly for 6 months following discontinuation of dabrafenib or until initiation of another anti-neoplastic therapy, whichever comes first. Refer to Appendix 7 for full information
8. **ECG**: Single ECGs will be collected prior to dosing.
9. **BIOPSY**: Pre- and post-dose tumor biopsies are mandatory. If the patient's tumors are inaccessible for biopsy, permission to enroll must be granted by the GSK Medical Monitor.
10. **BIOPSY**: Collection of on-treatment tumor biopsy for subjects with accessible tumors. On-treatment biopsy may be collected 2 to 4 hours after dosing with oral study medication'from Day 15 to Day 18 (+3 days). Biopsies should be performed on non-target lesions when possible. A single PK samples for dabrafenib, trametinib, and

panitumumab will be collected at the time of the post-dose tumor biopsy (±24 hours) (unless the post-dose biopsy occurs on the same day that the Day 15 serial PK samples are collected).

11. **PHARMACOKINETIC SAMPLES**: Blood samples (4 mL) for PK analysis of dabrafenib and metabolites (hydroxy-dabrafenib and desmethyl-dabrafenib) and trametinib will be collected on Day 1 and Day 15 predose (within 30 minutes of dosing) and at 1, 2, 4, 6,and 8 hours after administration. Blood samples (4 mL) for PK analysis of panitumumab will be collected on Day 1 and Day 15 predose (within 30 minutes of dosing panitumumab) and at 1 hour (end of infusion of panitumumab). A single 4 mL blood sample for analysis of panitumumab will be collected predose at the Week 4 clinic visit. On days when serial PK samples are collected, subjects should be instructed to hold doses of dabrafenib and trametinib, report to the clinic for the predose PK blood draw, then dose with dabrafenib and trametinib. Collect PK samples at the time indicated ± 5 minutes up to 2 hour sample, ± 20 minutes up to the 8 hour sample. On all days when PK samples are collected, date and time of the PK sample(s), date and time of the last doses of dabrafenib, trametinib, and panitumumab prior to the predose PK sample, and date and time of the dose of dabrafenib, trametinib, and panitumumab in the clinic must be recorded. A single blood sample for dabrafenib, trametinib, and panitumumab analysis should be collected along with the tumor biopsy taken at progression.
12. **TUMOR TISSUE SAMPLE**: Collection of archived tumor tissue or fresh tumor biopsies and determination of the subject's tumor BRAF mutation status is required for enrollment; if a fresh tumor biopsy is collected during screening and up to prior to dosing on Day1 for BRAF mutation confirmation, this tissue may be used for the day 1/ predose tumor [redacted] The Day 1/predose tumor biopsy may be collected at any point after signing consent, after completing wash-out from prior therapies (either 5 half-lives or 14 days from last dose of prior therapy).
13. **BIOPSY AT PROGRESSION**: Optional tumor biopsy for subjects who had a radiologic response (20% or more decrease) or had a stable disease for 6 months at disease progression (if feasible). A single PK sample will be collected at the time of tumor progression Refer to Section 6.7.2.
14. **DISEASE ASSESSMENT**: CT is the preferred method to measure lesions selected for response assessment. Refer to Appendix 4 for additional information regarding RECIST 1.1 methodology and criteria. Even if study treatment is withdrawn, radiographic disease assessments (CT or MRI, as appropriate according to the method used at baseline) should continue every 8 weeks until documented disease progression, the start of new anti-cancer therapy, withdrawal of consent or death.
15. **VITAL SIGNS**: Vital signs and temperature should be measured within 30 minutes prior to initiation and upon completion of the panitumumab infusion (up to 15 minutes after the end of infusion).

[redacted]

17. **DISEASE ASSESSMENT**: After study treatment is withdrawn, disease assessments (the method used at baseline) should continue every 8 weeks until documented disease progression, the start of new anti-cancer therapy, withdrawal of consent, or death.
18. **ECHO**: ECHO is preferred. MUGA may be used only if ECHO is not available. The same method must be used consistently from screening throughout the study.

[redacted]

20. **OVERALL SURVIVAL**: Subjects will be followed for Overall Survival every 8 weeks after last dose of study drugs. See Section 6.3.1.for additional information.

RATIONALE: Update Time and Events Table footnote with label and include Overall Survival follow up.

SECTION 3.11.4 Part 4 Dose Escalation Time and Event Tables

PREVIOUS TEXT

Day:	Screening[1]	Screening[1]	First treatment period, Day 1 thru Day 28/end of Week 4			Continuation phase ≥ Day 29/start of Week 5[2]	Initial follow-up[3]	Secondary follow-up[3]	Tertiary follow-up[3]
Visit Window (relative to Day 1)	-35 to -1 days	-14 to -1 days	on Day 1	on Day 15 (± 2 days)	on Day 21 (± 2 days)		14 (±7) days from last dose of trametinib	4 weeks (±7 days) after the last dose of panitumumab	8 weeks (±7 days) after the last dose of panitumumab
Informed Consent	X								
Demographics		X							
Collection of archival tissue[12]	X								
Complete physical[5]	X						X		
Brief physical[5]			X	X		At Week 4, then every 4 wks			
Medical/medication/ drug/alcohol history		X	X[6]			X	X		
Concurrent medications	X	X	X			At Week 4, then every 4 weeks	X		
12-lead ECG[7]		X	X[6]	X	X	At Week 4, then every 4 weeks until Week 24, then every 8 weeks	X		
Vital signs [13] (including weight)		X	X	X	X	X	X		
Height		X							
Ophthalmic examination	X					At Week 4, then as symptomatically warranted			
ECOG		X	X[6]			At Week 4, then every 4 wks	X		

Day:	**Screening[1]**	**Screening[1]**	**First treatment period, Day 1 thru Day 28/end of Week 4**			**Continuation phase ≥ Day 29/start of Week 5[2]**	**Initial follow-up[3]**	**Secondary follow-up[3]**	**Tertiary follow-up[3]**
Visit Window (relative to Day 1)	**-35 to -1 days**	**-14 to -1 days**	**on Day 1**	**on Day 15 (± 2 days)**	**on Day 21 (± 2 days)**		**14 (±7) days from last dose of trametinib**	**4 weeks (±7 days) after the last dose of panitumumab**	**8 weeks (±7 days) after the last dose of panitumumab**
ECHO/MUGA[17]	X					At Week 4, then at Week 12, then every 12 weeks	X		
Serum or urine pregnancy test (β-hCG;women)[4]			X			Every 8 to 12 weeks [4]			
Hema/Chem/Urinalysis tests		X	X[6]			At Week 4, then every 4 weeks until Week 24, then every 8 weeks		X	X
Coagulation Repeat as clinically indicated	X								
CEA		X	X			At Week 4, then every 4 weeks until Week 24, then every 8 weeks		X	X
Tumor biopsy[15]	X (pre-dose)[15]			X[9] (to be collected from Day 15 to Day 18)			X[10] (at progression)		
[redacted]									

Day:	Screening[1]	Screening[1]	First treatment period, Day 1 thru Day 28/end of Week 4			Continuation phase ≥ Day 29/start of Week 5[2]	Initial follow-up[3]	Secondary follow-up[3]	Tertiary follow-up[3]
Visit Window (relative to Day 1)	**-35 to -1 days**	**-14 to -1 days**	**on Day 1**	**on Day 15 (± 2 days)**	**on Day 21 (± 2 days)**		**14 (±7) days from last dose of trametinib**	**4 weeks (±7 days) after the last dose of panitumumab**	**8 weeks (±7 days) after the last dose of panitumumab**
[redacted]									
AE assessment			CONTINUOUS						
PK blood sample[8]			X	X	X	X			
Panitumumab Dosing			X	X		X every 2 weeks from Day 1			
Trametinib dosing			X	X	X	X			
Disease assessments[11]	x					Every 6 weeks until Week 24, then every 8 weeks.[16]			
[redacted]									

1. All screening assessments must be completed within 14 days prior to first dose except informed consent, ophthalmology exam, dermatological exam, ECHO/MUGA and Disease Assessment, which can occur within 35 days prior to the first dose. Note: Procedures conducted as part of the subject's routine clinical management (e.g., blood counts, imaging study) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures meet the protocol requirements.
2. Assessments throughout the study are calendar-based starting from the first day of dosing (Day 1) in the first treatment period. Dose interruptions should not alter the assessment schedule for any subsequent treatment period. The continuation phase starts with Day 29; events in the continuation phase are allowed ± 7 days from projected date. Safety lab tests (chemistry/hematology/UA) may be done the day before the visit so that results are available on the day of the visit, but all assessments should be done within the ±7 day window.
3. Initial follow-up visit should be 14 days (±7 days) from last dose of trametinib. If a subject is unable to return to the clinic due to hospitalization, site staff are encouraged to telephone the subject for assessment of AEs. Secondary follow-up visits should occur at 4 weeks and 8 weeks after the last dose of panitumumab.
4. Serum pregnancy test should be performed at screening; all subsequent pregnancy tests may be either serum or urine, and performed every 8 to 12 weeks.
5. Complete physical examination must include integument and genitalia. Note: pelvic exam in female subjects may be completed up to 24 weeks prior to date of first dose. Complete and brief physical examinations are defined in Section 6.2.
6. If within 72 hours of Screening, this assessment does not need to be repeated on Day 1.

7. Single ECGs will be collected prior to dosing.
8. Blood samples (2 mL) for PK analysis of trametinib will be collected on Day 1 and on Day 15 predose (within 30 minutes of dosing) and at 1, 2 and 4 hours after administration. Blood samples (4 mL) for PK analysis of panitumumab will be collected on Day 1 and on Day 15 predose (within 30 minutes of dosing with panitumumab) and at 1 hour (at the end of infusion of panitumumab). A single 4 mL blood sample for analysis of panitumumab will be collected pre-dose on Day 21 during the clinic visit. During the continuation phase, PK samples (for trametinib and panitumumab) will be collected pre-dose at Week 8, Week 12, Week 16, and Week 20. PK blood samples for trametinib, and panitumumab analysis should be collected along with the tumor biopsy taken at progression. On days when serial PK samples are collected, subjects should be instructed to hold doses of trametinib, report to the clinic for the predose PK blood draw, then dose with trametinib. Collect PK samples at the time indicated ±5 minutes up to 2 hour sample, ±20 minutes up to the 4 hour sample.
9. Collection of on-treatment tumor biopsy for subjects with accessible tumors. On-treatment biopsy may be collected 2 to 4 hours after dosing with oral study medication from Day 15 to Day 18. Biopsies should be performed on non-target lesions when possible. PK samples for trametinib and panitumumab analysis will be collected at the time of the post-dose tumor biopsy (±24 hours) (unless the post-dose biopsy occurs on the same day that the Day 15 serial PK samples are collected).
10. Tumor biopsy at tumor progression in subjects who have had a response is highly encouraged. PK blood samples for trametinib, and panitumumab analysis should be collected along with the tumor biopsy taken at progression.
11. CT is the preferred method to measure lesions selected for response assessment. Refer to Appendix 4 for additional information regarding Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 methodology and criteria. Even if study treatment is withdrawn, radiographic disease assessments (computed tomography [CT] or magnetic resonance imaging [MRI], as appropriate according to the method used at baseline) should continue every 8 weeks until documented disease progression, the start of new anti-cancer therapy, withdrawal of consent or death.
12. Collection of archived tumor tissue or fresh tumor biopsies is required for enrollment; if a fresh tumor biopsy is collected at screening, this tissue may be used for the day 1/ predose tumor biopsy. [redacted] The Day 1/predose tumor biopsy may be collected at any point after signing consent, up to 14 days prior to first dose.
13. Vital signs and temperature should be measured within 30 minutes prior to initiation and upon completion of the panitumumab infusion (up to 15 minutes after the end of infusion). [redacted]
15. Collection of archived tumor tissue or fresh tumor biopsies and determination of the subject's tumor BRAF mutation status is required for enrollment; if a fresh tumor biopsy is collected during screening and up to prior to dosing on Day1 for BRAF mutation confirmation, this tissue may be used for the day 1/ predose tumor biopsy. [redacted] The Day 1/predose tumor biopsy may be collected at any point after signing consent, after completing wash-out from prior therapies (either 5 half-lives or 14 days from last dose of prior therapy). Pre- and post-dose tumor biopsies are mandatory. If the patient's tumors are inaccessible for biopsy, permission to enroll must be granted by the GSK Medical Monitor
16. After study treatment is withdrawn, disease assessments (the method used at baseline) should continue every 8 weeks until documented disease progression, the start of new anti-cancer therapy, withdrawal of consent, or death
17. ECHO is preferred. MUGA may be used only if ECHO is not available. The same method must be used consistently from screening throughout the study. [redacted]

REVISED TEXT

SECTION 3.11.4 Part 4 Dose Escalation and Cohort Expansion

Day:	~~Screening~~[1]	Screening[1]	First treatment period~~,~~ ~~Day 1 thru Day 28/end of Week 4~~			Continuation phase ~~≥ Day 29/start of Week 5~~[2] (±7 Days)	Initial follow-up[3]	Secondary follow-up[3]	Tertiary follow-up[3]
Visit Window (relative to Day 1)	~~-35 to -1 days~~	-14 to -1 days	on Day 1	on Day 15 (± 2 days)	on Day 21 (± 2 days)		14 (±7) days from last dose of trametinib	4 weeks (±7 days) after the last dose of panitumumab	8 weeks (±7 days) after the last dose of panitumumab
Informed Consent	~~X~~								
Demographics		X							
Collection of archival tissue[14]	~~X~~								
Complete physical[5]	~~X~~						X		
Brief physical[5]			X	X		At Week 4, then every 4 wks			
Medical/medication/ drug/alcohol history		X	X[6]			X	X		
Concurrent medications	~~X~~	X	X	X	X	At Week 4, then every 4 weeks	X	X	
12-lead ECG[7]		X	X[6]	X	X	At Week 4, then every 4 weeks until Week 24, then every 8 weeks	X		
Vital signs [12] **(including weight)**		X	X	X	X	X[13]	X		
Height		X							
Ophthalmic examination	~~X~~					At Week 4, then as symptomatically warranted			
ECOG		X	X[6]			At Week 4, then every 4 wks	X		

Day:	~~**Screening**~~[1]	**Screening**[1]	**First treatment period**~~**, Day 1 thru Day 28/end of Week 4**~~			**Continuation phase** ~~**≥ Day 29/start of Week 5**~~[2] **(±7 Days)**	**Initial follow-up**[3]	**Secondary follow-up**[3]	**Tertiary follow-up**[3]
Visit Window (relative to Day 1)	~~**-35 to -1 days**~~	**-14 to -1 days**	**on Day 1**	**on Day 15 (± 2 days)**	**on Day 21 (± 2 days)**		**14 (±7) days from last dose of trametinib**	**4 weeks (±7 days) after the last dose of panitumumab**	**8 weeks (±7 days) after the last dose of panitumumab**
ECHO/MUGA[16]	~~X~~					At Week 4, then at Week 12, then every 12 weeks	X		
Serum or urine pregnancy test (β-hCG;women)[4]		X				Every 8 to 12 weeks[4]			
Hematology/Clinical Chemistry~~**Hema/Chem/Urinalysis tests**~~		X	X[6]			At Week 4, then every 4 weeks until Week 24, then every 8 weeks		X	X
Urinalysis		X	X[6]				X		
Coagulation Repeat as clinically indicated	~~X~~								
CEA	~~X~~	X				At Week 6~~4~~, then every 6~~4~~ weeks until Week 24, then every 8 weeks		X	X
Tumor biopsy[15~~9~~]	X (pre-dose)[15~~9~~]			X[9] (to be collected from Day 15 to Day 18)			X[11] (at progression)		
[redacted]									

Day:	**~~Screening~~[1]**	**Screening[1]**	**First treatment period~~,~~ ~~Day 1 thru Day 28/end of Week 4~~**			**Continuation phase ~~≥ Day 29/start of Week 5~~[2] (±7 Days)**	**Initial follow-up[3]**	**Secondary follow-up[3]**	**Tertiary follow-up[3]**
Visit Window (relative to Day 1)	**~~-35 to -1 days~~**	**-14 to -1 days**	**on Day 1**	**on Day 15 (± 2 days)**	**on Day 21 (± 2 days)**		**14 (±7) days from last dose of trametinib**	**4 weeks (±7 days) after the last dose of panitumumab**	**8 weeks (±7 days) after the last dose of panitumumab**
[redacted]									
AE assessment			CONTINUOUS						
PK blood sample[8]			X	X	X	Predose, at Week 4			
Panitumumab Dosing			X	X		X every 2 weeks ~~from Day 1~~			
Trametinib dosing			X	X	~~X~~	~~X~~CONTINUOUS daily dosing; Trametinib once daily should be administered under fasting conditions, either one hour before or 2 hours after a meal.			

Day:	~~Screening~~[1]	Screening[1]	First treatment period~~,~~ ~~Day 1 thru Day 28/end of Week 4~~			Continuation phase ~~≥ Day 29/start of Week 5~~[2] (±7 Days)	Initial follow-up[3]	Secondary follow-up[3]	Tertiary follow-up[3]
Visit Window (relative to Day 1)	~~-35 to -1 days~~	-14 to -1 days	on Day 1	on Day 15 (± 2 days)	on Day 21 (± 2 days)		14 (±7) days from last dose of trametinib	4 weeks (±7 days) after the last dose of panitumumab	8 weeks (±7 days) after the last dose of panitumumab
Disease assessments[12]	x					Every 6 weeks until Week 24, then every 8 weeks.[15]			
[redacted]									
Long-term survival follow-up									X[18]

AE, Adverse Event; BP, blood pressure; CEA, ; ECHO, echocardiogram; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; HR, heart rate; MUGA,

1. **SCREENING ASSESSMENTS**: All screening assessments must be completed within 14 days prior to first dose except informed consent, ophthalmology exam, dermatological exam, ECHO/MUGA and Disease Assessment, which can occur within 35 days prior to the first dose. Note: Procedures conducted as part of the subject's routine clinical management (e.g., blood counts, imaging study) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures meet the protocol requirements.
2. **TREATMENT PERIOD**: Assessments throughout the study are calendar-based starting from the first day of dosing (Day 1) in the first treatment period. Dose interruptions should not alter the assessment schedule for any subsequent treatment period. ~~The continuation phase starts with Day 29; e~~Events in the continuation phase are allowed ± 7 days from projected date. Safety lab tests (chemistry/hematology/UA) may be done the day before the visit so that results are available on the day of the visit, but all assessments should be done within the ±7 day window.
3. **FOLLOW-UP VISIT**: Initial follow-up visit should be 14 days (±7 days) from last dose of trametinib. If a subject is unable to return to the clinic due to hospitalization, site staff are encouraged to telephone the subject for assessment of AEs. Secondary follow-up visits should occur at 4 weeks and 8 weeks after the last dose of panitumumab. Subjects are to be followed until progression for collection of PFS data and until death for collection of overall survival (OS) data. If a subject who is eligible for crossover to the triplet combination has not crossed over by 14 days past the last dose of study treatment, the Initial Follow-Up assessments should be done. If a subject who is eligible for crossover to the triplet combination has not crossed over by 4 weeks past the last dose of panitumumab, the Secondary Follow-Up assessments should be done.
4. **PREGNANCY TEST**: Serum pregnancy test should be performed at screening; all subsequent pregnancy tests may be either serum or urine, and performed every 8 to 12 weeks.
5. **PHYSICAL EXAMINATION**: Complete physical examination must include integument ~~and genitalia~~. Note: pelvic exam in female subjects is not required in Part 4 ~~may be completed up to 24 weeks prior to date of first dose~~. Complete and brief physical examinations are defined in Section 6.2.
6. **PHYSICAL EXAMINATION**: If within 72 hours of Screening, this assessment does not need to be repeated on Day 1.
7. **ECG**: Single ECGs will be collected prior to dosing.
8. **PHARMACOKINETIC SAMPLES**: Blood samples (2 mL) for PK analysis of trametinib will be collected on Day 1 and on Day 15 predose (within 30 minutes of dosing) and at 1, 2 and 4 hours after administration. Blood samples (4 mL) for PK analysis of panitumumab will be collected on Day 1 and on Day 15 predose (within 30 minutes of dosing with panitumumab) and at 1 hour (at the end of infusion of panitumumab). A single 4 mL blood sample for analysis of panitumumab will be collected pre-dose on Day 21 during the

clinic visit. During the continuation phase, PK samples (for trametinib and panitumumab) will be collected pre-dose at Week 8, Week 12, Week 16, and Week 20. PK blood samples for trametinib, and panitumumab analysis should be collected along with the tumor biopsy taken at progression. On days when serial PK samples are collected, subjects should be instructed to hold doses of trametinib, report to the clinic for the predose PK blood draw, then dose with trametinib. Collect PK samples at the time indicated ±5 minutes up to 2 hour sample, ±20 minutes up to the 4 hour sample.

9. **TUMOR TISSUE SAMPLE/DAY1**: Collection of archived tumor tissue or fresh tumor biopsies and determination of the subject's tumor BRAF mutation status is required for enrollment; if a fresh tumor biopsy is collected during screening and up to prior to dosing on Day1 for BRAF mutation confirmation, this tissue may be used for the day 1/ predose tumor biopsy. [redacted] The Day 1/predose tumor biopsy may be collected at any point after signing consent, after completing wash-out from prior therapies (either 5 half-lives or 14 days from last dose of prior therapy). Pre- and post-dose tumor biopsies are mandatory. If the patient's tumors are inaccessible for biopsy, permission to enroll must be granted by the GSK Medical Monitor
10. **BIOPSY**: Collection of on-treatment tumor biopsy for subjects with accessible tumors. On-treatment biopsy may be collected 2 to 4 hours after dosing with oral study medication from Day 15 to Day 18. Biopsies should be performed on non-target lesions when possible. PK samples for trametinib and panitumumab analysis will be collected at the time of the post-dose tumor biopsy (±24 hours) (unless the post-dose biopsy occurs on the same day that the Day 15 serial PK samples are collected).
11. **BIOPSY**: Tumor biopsy at tumor progression in subjects who have had a response is highly encouraged. PK blood samples for trametinib and panitumumab analysis should be collected along with the tumor biopsy taken at progression.
12. **DISEASE ASSESSMENT**: CT is the preferred method to measure lesions selected for response assessment. Refer to Appendix 4 for additional information regarding Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 methodology and criteria. Even if study treatment is withdrawn, radiographic disease assessments (computed tomography [CT] or magnetic resonance imaging [MRI], as appropriate according to the method used at baseline) should continue every 8 weeks until documented disease progression, the start of new anti-cancer therapy, withdrawal of consent or death.
13. ~~Collection of archived tumor tissue or fresh tumor biopsies is required for enrollment; if a fresh tumor biopsy is collected at screening, this tissue may be used for the day 1/ predose tumor biopsy.~~ [redacted] ~~The Day 1/predose tumor biopsy may be collected at any point after signing consent, up to 14 days prior to first dose.~~
14. **VITAL SIGNS**: Vital signs and temperature should be measured within 30 minutes prior to initiation and upon completion of the panitumumab infusion (up to 15 minutes after the end of infusion).

[redacted]

16. ~~Collection of archived tumor tissue or fresh tumor biopsies and determination of the subject's tumor BRAF mutation status is required for enrollment; if a fresh tumor biopsy is collected during screening and up to prior to dosing on Day1 for BRAF mutation confirmation, this tissue may be used for the day 1/ predose tumor biopsy.~~ [redacted] ~~The Day 1/predose tumor biopsy may be collected at any point after signing consent, after completing wash-out from prior therapies (either 5 half-lives or 14 days from last dose of prior therapy). Pre- and post-dose tumor biopsies are mandatory. If the patient's tumors are inaccessible for biopsy, permission to enroll must be granted by the GSK Medical Monitor~~
17. **DISEASE ASSESSMENT**: After study treatment is withdrawn, disease assessments (the method used at baseline) should continue every 8 weeks until documented disease progression, the start of new
anti-cancer therapy, withdrawal of consent, or death
18. **ECHO**: ECHO is preferred. MUGA may be used only if ECHO is not available. The same method must be used consistently from screening throughout the study.

[redacted]

20. **OVERALL SURVIVAL**: Subjects will be followed for Overall Survival every 8 weeks after last dose of study drugs. See Section 6.3.1.for additional information.

RATIONALE: Update Time and Events Table footnote with label and include Overall Survival follow up.

SECTION 3.11.5 Intra-Subject Crossover Time and Event Tables

ADDITIONAL TEXT

3.11.5.1 Intra-subject Doublet to Triplet Crossover

	Crossover Screening[1]	Crossover Day 1	Crossover Treatment Phase[2] (±7 days)	Initial Follow-up[3]	Secondary Follow-up[3]	
					4 weeks (±7 days) after the last dose of panitumumab	8 weeks (±7 days) after the last dose of panitumumab
Medical history/ Interim History	X		Every 4 weeks	X		
Concurrent Medications		X	At Week 4, then every 4 weeks	X		
Serum or urine pregnancy test (β-hCG; women)			Every 8 to 12 weeks	X		
Physical examination[4]	X		Every 4 weeks	X[4]		
Dermatological examination[5]	X		At Week 4, then every 8 weeks More frequently if there are new or changing lesions	X		
Weight	X		Every 4 weeks	X		
Ophthalmic examination	X		at Week 4, then as symptomatically warranted	X		
ECOG Performance Status	X		Every 4 weeks	X		
Vital signs (BP, HR, Body Temperature)	X	X[6]	Before and after panitumumab infusion[6]	X		
12-lead ECG	X		At Week 4, then every 4 weeks until Week 24, then every 8 weeks	X		

	Crossover Screening[1]	Crossover Day 1	Crossover Treatment Phase[2] (±7 days)	Initial Follow-up[3]	Secondary Follow-up[3]	
					4 weeks (±7 days) after the last dose of panitumumab	8 weeks (±7 days) after the last dose of panitumumab
Hematology/Clinical Chemistry)	X		At Week 4, then every 4 weeks until Week 24, then every 8 weeks	X	X	X
Coagulation			As clinically indicated			
CEA	X		At Week 6, then every 6 weeks until Week 24, then every 8 weeks	X	X	
ECHO (or MUGA)[7]	X		At Week 4, then at Week 12 and every 12 weeks thereafter	X		
[redacted]						
Panitumumab dosing[6]		X	Every 2 weeks			
Dabrafenib and trametinib dosing		CONTINUOUS daily dosing; Dabrafenib BID and trametinib once daily should be administered under fasting conditions, either one hour before or 2 hours after a meal.				
Urinalysis				X		
AE assessment		CONTINUOUS				
Disease Assessment[9]	X		Every 6 weeks until Week 24, then every 8 weeks	X[9]	X[10]	

	Crossover Screening[1]	Crossover Day 1	Crossover Treatment Phase[2] (±7 days)	Initial Follow-up[3]	Secondary Follow-up[3]	
					4 weeks (±7 days) after the last dose of panitumumab	8 weeks (±7 days) after the last dose of panitumumab
Long-term survival follow-up						X[11]

AE, Adverse Event; BP, blood pressure; CEA, ; ECHO, echocardiogram; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; HR, heart rate; MUGA,

1. **SCREENING ASSESSMENTS**: All screening assessments must be completed within 14 days prior to first crossover dose except ophthalmic exam, dermatological exam, ECHO/MUGA, and Disease Assessment, which can occur within 35 days prior to the first dose. Note: Procedures conducted as part of the subject's initial follow-up assessments may be utilized for screening or baseline purposes provided these procedures meet the protocol requirements.
2. **TREATMENT PHASE**: Assessments throughout the study are calendar-based starting from the first day of dosing (Day 1) in the first treatment period. Dose interruptions should not alter the assessment schedule for any subsequent treatment period. Safety lab tests (chemistry/hematology/coag/UA) may be done the day before the visit so that results are ready on the day of the visit, but all assessments should be done within the ±7 day window.
3. **FOLLOW_UP VISITS**: Initial follow-up visit should be 14 days from last dose of study drugs (±7 days). If a subject is unable to return to the clinic due to hospitalization, site staff are encouraged to telephone the subject for assessment of AEs. Secondary follow-up visits should occur at 4 weeks and 8 weeks after the last dose of panitumumab.
4. **PHYSICAL EXAM**: A brief physical exam should be conducted at screening and every 4 weeks. A complete physical examination including integument and genitalia should be performed during the initial follow-up visit. Note: pelvic exam in female subjects may be completed up to 24 weeks prior to date of first dose. Complete and brief physical examinations are defined in Section 6.2.
5. **DERMATOLOGICAL EVALUATION**: Baseline skin photography should be performed at Screening. Photographs should be taken of new skin lesions that occur, or skin lesions that change on therapy. Refer to Section 6.2. French sites will perform dermatological exams monthly while on-therapy, and monthly for 6 months following discontinuation of dabrafenib or until initiation of another anti-neoplastic therapy, whichever comes first. Refer to Appendix 7 for full information.
6. **VITAL SIGNS**: Vital signs and temperature should be measured within 30 minutes prior to initiation and upon completion of the panitumumab infusion (up to 15 minutes after the end of infusion).
7. **ECHO**: ECHO is preferred. MUGA may be used only if ECHO is not available. The same method must be used consistently from screening throughout the study.
8. [redacted].
9. **DISEASE ASSESSMENT**: CT is the preferred method to measure lesions selected for response assessment. Refer to Appendix 4 for additional information regarding RECIST 1.1 methodology and criteria. Even if study treatment is withdrawn, radiographic disease assessments (CT or MRI, as appropriate according to the method used at baseline) should continue every 8 weeks until documented disease progression, the start of new anti-cancer therapy, withdrawal of consent or death.
10. **DISEASE ASSESSMENT**: After study treatment is withdrawn, disease assessments (the method used at baseline) should continue every 8 weeks until documented disease progression, the start of new anti-cancer therapy, withdrawal of consent, or death.
11. **OVERALL SURVIVAL**: Subjects will be followed for Overall Survival every 8 weeks after last dose of study drugs. See Section 6.3.1.for additional information.

SECTION 4.1 Number of Subjects

PREVIOUS TEXT

The number of dose levels and the level at which the MTD will be reached cannot be determined in advance. An adequate number of subjects will be enrolled into the study to establish a recommended dose(s) and schedule(s) for the further study of dabrafenib/panitumumab and dabrafenib/trametinib/panitumumab combinations.

To complete Part 1, it is estimated that 24 evaluable subjects (~4 per cohort) will be enrolled. Part 2 will enroll approximately 30 subjects in total. In order to confirm safety in Japanese patients, up to three additional Japanese patients may be enrolled in Japan in each expansion cohort. Approximately 20 subjects will be evaluated at the RP2D/R for each combination tested by the end of Part 2, including those subjects enrolled at the RP2D/R in Part 1. For Part 3, approximately 47 subjects per arm will be enrolled. For Part 4A (dose escalation), it is estimated that up to 18 evaluable subjects (~6 per cohort) will be enrolled. Part 4B (expansion cohorts 1E and 2E) will enroll approximately 17 additional subjects in each of two expansion cohorts (n=34). This will be a total of approximately 20 patients at the RP2D/R for each patient population, including the subjects enrolled in Part 4A.

If subjects discontinue the study before completing Week 4, additional subjects may be enrolled at the discretion of the Sponsor in consultation with the investigator.

REVISED TEXT

The number of dose levels and the level at which the MTD will be reached cannot be determined in advance. An adequate number of subjects will be enrolled into the study to establish a recommended dose(s) and schedule(s) for the further study of dabrafenib/panitumumab and dabrafenib/trametinib/panitumumab combinations.

To complete Part 1, it is estimated that 24 evaluable subjects (~4 per cohort) will be enrolled. Part 2 will enroll approximately ~~30~~120 subjects in total. In order to confirm safety in Japanese patients, up to three additional Japanese patients may be enrolled in Japan in each expansion cohort. By the end of Part 2, approximately 30 subjects will be evaluated for each dose cohort. ~~Approximately 20 subjects will be evaluated at the RP2D/R for each combination tested by the end of Part 2,~~ including ~~those subjects enrolled at the RP2R in Part 1.~~ For Part 3, approximately 47 subjects per arm will be enrolled. For Part 4A (dose escalation), it is estimated that up to 18 evaluable subjects (~6 per cohort) will be enrolled. Part 4B ~~(expansion cohorts 1E and 2E)~~ will enroll approximately 17 additional subjects in each of two expansion ~~cohorts~~ populations (n=34). This will be a total of approximately 20 patients at the ~~RP2D/R~~MTD for each patient population, including the subjects enrolled in Part 4A. In order to confirm safety in Japanese patients, three additional Japanese patients may be enrolled in Japan in each expansion population for Part 4. Up to an additional 20 subjects with BRAF mutant CRC may be enrolled in Part 4 to further explore safety and efficacy of the trametinib plus panitumumab doublet.

If subjects discontinue the study before completing Week 4, additional subjects may be enrolled at the discretion of the Sponsor in consultation with the investigator.

RATIONALE: Enrolment updated to include the additional subjects of Part 2B and allow for additional subjects from Japan to be enrolled in Part 4B.

SECTION 4.2.1.2 Part 1, Part 2, and Part 4 Exclusion Criteria

ADDITIONAL TEXT

9. Part 2B ONLY: Patients treated with > 4 prior lines of therapy for metastatic disease will not be eligible.

RATIONALE: Additional exclusion criteria to limit the number of prior lines of therapy for subjects enrolled into Part 2B to collect data on a more homogeneous patient population.

SECTION 5.2.1.1 Part 1 and Part 4 Dose Escalation

PREVIOUS TEXT

The total number of subjects in Part 1 and Part 4 dose escalation will depend on the number of dose escalations needed. However, the maximum anticipated number of subjects will be approximately 24 in Part 1 and approximately 12 in Part 4 dose escalation.

REVISED TEXT

The total number of subjects in Part 1 and Part 4 dose escalation will depend on the number of dose escalations needed. However, the maximum anticipated number of subjects will be approximately 24 in Part 1 and approximately ~~12~~ 22 in Part 4 dose escalation.

RATIONALE: Change to allow for dose de-escalation in Part 4A.

SECTION 5.1.2 Part 2 and Part 4 Cohort Expansion

PREVIOUS TEXT

For Part 2 and Part 4 cohort expansion, efficacy will be evaluated for each cohort to decide whether to proceed with further development based on the clinical activity seen in Part 1. Futility analysis criteria at the end of Part 2 and Part 4 will be based on 2-stage Green-Dahlberg design's [Green, 1992] interim analysis criteria. The criteria will be based on a historically unimportant response rate of 15% versus a response rate of interest of 30%. The Part 2 and Part 4B portion of the study will employ a Bayesian design that allows the trial to be monitored more frequently at multiple stages. Bayesian statistics will be employed to calculate the predictive probability that the response rate ≥30% and ≥15% at interim assuming a Beta prior for the Binomial distributed data. Predictive probability calculates the probability that the response rate ≥30% or ≥15% at the end of Part 2 (after 20 subjects) given the responses have already been observed. It

predicts what is likely to happen at the end of Part 2 and Part 4 so is more meaningful and straightforward than posterior probability. A weak prior Beta (0.003, 0.007) is used, which is equivalent to the information present in 0.01 subject. Futility analysis criteria based on 2-stage Green-Dahlberg design's are only used at the end of Part 2 and Part 4B when all subjects are enrolled. Bayesian design based criteria are only used for interim data monitoring before the end of Part 2 or Part 4B data analysis allowing early stop for futility. An initial total of 10 subjects will be recruited at a dose level based on the recommended dose for each treatment/cohort (including the subjects treated in Part 1 or Part 4A at the same dose with the same mutation status). The number of subjects will be increased up to a total of 20 per treatment cohort depending on the results observed. The tables below show the decision rules for the 10^{th} to 19^{th} evaluable subjects, specifying the number of subjects with a confirmed response needed for continuing enrolment or stopping for futility. The methodology is based on the predictive probability of success if enrolment continues to 20 subjects [Lee, 2008]. These rules are intended as a guideline. Actual decisions will depend on the totality of the data.

Table 24 Decision Making Criteria at Interim Analysis for Futility and Efficacy

Number of Evaluable Patients	≤ This Number of Confirmed Responses to Stop Early for Futility	≥ This Number of Confirmed Responses to Declare ORR≥0.3
10	0	5
11	0	5
12	0	6
13	0	6
14	0	6
15	0	7
16	1	7
17	1	7
18	1	8
19	1	8

For the interim looks in each cohort separately, if the predictive probability that the confirmed response rate ≥15% (historical control) is small (i.e., less than 10% chance), or equivalent to observe no confirmed response in the first enrolled 10-15 evaluable subjects in that cohort (e.g., after they have either progressed, or withdrew from the study, or lost to follow-up, or ongoing but have completed at least one post treatment disease assessment) and observe less than 1 confirmed response in the first 16-19 evaluable subjects, the enrollment for that cohort may be stopped due to futility. Otherwise, the enrolment of the respective cohort will continue to the target sample size of 20. If the predictive probability that the response rate of ≥30% is large (i.e., greater than 80% chance), strong statistical evidence has been provided in favor of further development of the treatment for the target population.

When at least 4 responders out of 20 subjects are observed in a treatment arm, after each subject has been followed at least 12 weeks, further development of the corresponding

treatment in Part 3 will follow. If less than 4 responders are observed, the accrued efficacy data will be evaluated for possibility of further development to Part 3.
The final decision with respect to continuation of the trial to Part 3 will be made by the Sponsor based on safety considerations as well as available efficacy data with input from participating investigators.

REVISED TEXT

For Part 2 and Part 4 cohort expansion, efficacy will be evaluated for each cohort to decide whether to proceed with further development based on the clinical activity seen in Part 1 and Part 4. Analyses will be descriptive [redacted] Subjects treated with the same starting dose will be analysed together.

Futility analysis criteria at the end of Part 2 and Part 4 will be ~~based on 2-stage Green-Dahlberg design's [Green, 1992] interim analysis criteria~~based on Bayesian predictive adaptive design [Lee, 2008]. The criteria will be based on a historically unimportant response rate of 15% versus a response rate of interest of 30%. The Part 2 and Part 4~~B~~ portion of the study will employ a Bayesian design that allows the trial to be monitored more frequently at multiple stages. Bayesian statistics will be employed to calculate the predictive probability that the response rate ≥30% and ≥15% at interim assuming a Beta prior for the Binomial distributed data. Predictive probability calculates the probability that the response rate ≥30% or ≥15% at the end of Part 2 ~~(after 20 subjects)~~ given the responses have already been observed. It predicts what is likely to happen at the end of Part 2 and Part 4 so is more meaningful and straightforward than posterior probability. A weak prior Beta (0.003, 0.007) is used, which is equivalent to the information present in 0.01 subject. ~~Futility analysis criteria based on 2-stage Green-Dahlberg design's are only used at the end of Part 2 and Part 4B when all subjects are enrolled. Bayesian design based criteria are only used for interim data monitoring before the end of Part 2 or Part 4B data analysis allowing early stop for futility.~~ An initial total of 10 subjects will be recruited at a dose level based on the recommended dose for each treatment/cohort (including the subjects treated in Part 1 or Part 4A at the same dose with the same mutation status). The number of subjects will be increased by 30~~up to a total of 20 10055~~ per treatment cohort depending on the results observed. Table 25~~The tables below~~ shows the decision rules for the 10th to 19th evaluable subjects, specifying the number of subjects with a confirmed response needed for continuing enrolment or stopping for futility when total sample size is 20. The methodology is based on the predictive probability of success if enrolment continues to 20 subjects [Lee, 2008]. Table 26 shows the decision rules for the 10th to 54th evaluable subjects, specifying the number of subjects with a confirmed response needed for continuing enrolment or stopping for futility when total sample size is 55. These rules are intended as a guideline. Actual decisions will depend on the totality of the data.

Table 2524 Decision Making Criteria at Interim Analysis for Futility and Efficacy when enrolling up to 20 subjects

~~Number of Evaluable Patients~~	~~≤ This Number of Confirmed Responses to Stop Early for Futility~~	~~≥ This Number of Confirmed Responses to Declare ORR≥0.3~~
~~10~~	~~0~~	~~5~~
~~11~~	~~0~~	~~5~~
~~12~~	~~0~~	~~6~~
~~13~~	~~0~~	~~6~~
~~14~~	~~0~~	~~6~~
~~15~~	~~0~~	~~7~~
~~16~~	~~1~~	~~7~~
~~17~~	~~1~~	~~7~~
~~18~~	~~1~~	~~8~~
~~19~~	~~1~~	~~8~~

Table 25 Sample sizes for different analysis cohorts using Bayesian predictive adaptive design.

Part	Cohorts/Population	Target sample size	Minimum sample size needed for first interim analysis
Part 1 and Part 2	D 150mg BID+P 6mg/kg	20	10
Part 1 and Part 2	D 150mg BID+ T 2mg QD +P 6mg/kg	54	10
Part 1 and Part 2	D 150mg BID+T 2mg QD+P 6mg/kg 1L	10-15	10
Part 1 and Part 2	D 150mg BID+T 2mg QD+P 6mg/kg 2L-4L	40-44	10
Part 1 and Part 2	D 150mg BID+T 2mg QD+P 4.8mg/kg	34	10
Part 1 and Part 2	D 150mg BID+T 2mg QD+P 4.8mg/kg 1L	10-14	10
Part 1 and Part 2	D 150mg BID+T 2mg QD+P 4.8mg/kg 2L-4L	20-24	10
Part 4	T+P Anti-EGFR CRC population	20	10
Part 4	T+ P BRAF+ CRC population	20-40	10

Table 26 Decision Making Criteria at Interim Analysis for Futility when enrolling up to 55 subjects

Number of Evaluable Subjects	≤ This Number of Confirmed Responses to Stop Early for Futility	Probability of continuing when ORR=0.15	Probability of continuing when ORR=0.3
10	0	0.8031	0.9718
11	0	0.8031	0.9718
12	0	0.8031	0.9718
13	0	0.8031	0.9718
14	0	0.8031	0.9718

Number of Evaluable Subjects	≤ This Number of Confirmed Responses to Stop Early for Futility	Probability of continuing when ORR=0.15	Probability of continuing when ORR=0.3
15	0	0.8031	0.9718
16	1	0.6721	0.9575
17	1	0.6721	0.9575
18	1	0.6721	0.9575
19	1	0.6721	0.9575
20	1	0.6721	0.9575
25	2	0.5943	0.9522
30	3	0.5203	0.9476
35	4	0.4559	0.9439
40	5	0.4009	0.941
45	6	0.3457	0.9378
50	8	0.2430	0.9298
54	10	0.1471	0.9144

~~For the interim looks in each cohort separately, if the predictive probability that the confirmed response rate ≥15% (historical control) is small (i.e., less than 10% chance), or equivalent to observe no confirmed response in the first enrolled 10-15 evaluable subjects in that cohort (e.g., after they have either progressed, or withdrew from the study, or lost to follow-up, or ongoing but have completed at least one post treatment disease assessment) and observe less than 1 confirmed response in the first 16-19 evaluable subjects, the enrollment for that cohort may be stopped due to futility.~~For the separate interim looks in each cohort, the enrollment for that cohort may be stopped due to futility if the predictive probability that the confirmed response rate ≥15% (historical control) is small (e.g., less than 10% chance for a total sample size of 20 subjects or less than a 2% chance for a total sample size of 54 subjects). Enrollment may also be stopped due to futility if the equivalent of no confirmed response is observed in the first 10-15 enrolled evaluable subjects in that cohort or less than 1 confirmed response is observed in the first 16-19 evaluable subjects. For example, if all (10-15) or all but one (16-19) of the subjects have either progressed, withdrew from the study, were lost to follow-up, or are ongoing and have completed at least one post treatment disease assessment without a confirmed response then the cohort may be stopped for futility. Otherwise, the enrolment of the respective cohort will continue to the target sample size~~of 20~~. If the predictive probability that the response rate of ≥30% is large (i.e., greater than 80% chance) is observed during the interim looks, strong statistical evidence has been provided in favor of further development of the treatment for the target population.

When the total sample size in a treatment arm/cohort is 20 and at least ~~4~~ 2 confirmed responders out of 20 subjects are observed~~ in a treatment arm~~, ~~after each subject has been followed at least 12 weeks,~~ further development of the corresponding treatment in Part 3 may~~will~~ follow. ~~If less than 4 responders are observed, the accrued efficacy data will be evaluated for possibility of further development to Part 3.~~

When the total sample size in a cohort is 55 and at least 12 confirmed responders out of 55 subjects are observed, after each subject has been followed at least 12 weeks, further development of the corresponding treatment in Part 3 may follow.

RATIONALE: Update sample size to add Part 2B and update decision making criteria rules based on the addition of Part 2B subjects

SECTION 5.2.1.2 Part 2 and Part 4 Cohort Expansions

PREVIOUS TEXT

Part 2 will enroll approximately 30 subjects in total. Approximately 40 subjects will be evaluated at the end of Part 2, including those enrolled in Part 1 at the same dose levels. Part 4 cohort expansion will enroll approximately 40 subjects in total (20 subjects in Cohort 1E and 20 subjects in Cohort 2E). For each cohort, approximately 20 subjects will be evaluated separately at the end of Part 4, including those enrolled in dose escalation at the same dose levels and the same mutation status.

To determine the maximum sample size for each cohort, a traditional, 2-stage Green-Dahlberg design [Green, 1992] was evaluated and the sample size for the first stage will be used for the futility analysis. To test the hypotheses (RR=30% vs RR=15%), using a Green-Dahlberg design, 20 subjects per arm would be needed for Stage 1 (assuming a type 1 error of 5% and power of 95%). The chance to effectively terminate the trial after 20 subjects due to futility (true RR=15%) is 65%; the risk to incorrectly stop the trial after 20 subjects if the treatment is effective (true RR =40%) is less than 2% (Table 26).

Table 26 Futility Analysis Design Performance

True RR	Probability of Early Termination, after 20 pts
15%	0.648
20%	0.411
30%	0.107
40%	0.016

A Bayesian posterior probability will also be calculated to further inform decision making. Since neither BRAF in combination with panitumumab nor MEK in combination with BRAF and panitumumab has been tested previously in the clinic in CRC subjects, a Beta (0.003, 0.007) prior is assumed. This prior is equivalent to the prior information from 0.01 subject. The posterior probabilities of RR exceeding 20%, 30% and 40% based on 20 subjects are shown in Table 27.

Table 27 Bayesian Posterior Probabilities of Response Rate for Given Number of Observed Responses

# of Responses Observed out of 20 Subjects	Posterior Probability RR ≥20%	Posterior Probability RR ≥30%	Posterior Probability RR ≥40%
4	0.45	0.14	0.024
5	0.69	0.29	0.075
6	0.83	0.48	0.17
7	0.93	0.66	0.31
8	0.97	0.81	0.49

Using this sample size, a Bayesian design that allows the trial to be monitored more frequently at multiple stages was evaluated. A Bayesian analysis expresses uncertainty about a parameter in terms of probability. A prior is defined to characterize the level of knowledge about a parameter before the data are collected. Once the data are collected, a posterior distribution is formed using the prior and the likelihood (i.e., the data). Since none of the treatment has been tested previously in the clinic in the target population, a weak prior Beta (0.003, 0.007) is assumed. Thus, the posterior distribution for the response rate will be primarily driven by the data and can be derived as follows: Let p denote the response rate for the treatment, the number of responses in the current n patients, x, follows a binomial distribution, Binomial (n, p). Taking the Bayesian method and combining the weak prior and the likelihood of the observed data x, the posterior distribution of the response rate follows a beta distribution, *i.e.,* $p \sim \text{Beta}(0.003 + x, 0.007 + n-x)$ with the posterior mean $(0.003 + x)/(0.01 + n)$.

Based on this posterior distribution of the response rate, the predictive probability that the response rate >15% or ≥30% after 19 subjects will be calculated for decision-making as described in the Section 5.1.2 (Hypotheses). The decision rule and a minimal required sample size of 10 patients for the first interim look is determined to generate the design that leads to a reasonable chance of early termination due to futility.

The design property, by utilizing the decision rule specified in Section 5.1.2, and sample size of 20 patients are shown (Table 28). The probability of early termination of the trial is calculated by simulations. The probability of early termination after the first 19 evaluable subjects is 33% under the null hypothesized response rate, and the risk to incorrectly stop the trial early if the drug is effective is approximately 5%. Thus, the study will employ the Bayesian design that allows the trial to be monitored more frequently at multiple stages with the constraint of satisfactory stop for futility rate.

Table 28 Bayesian Design Performance by Response Rate

If True Response Rate to The Treatment is: (%)	Prob (early stop for futility)
0.15	0.326
0.2	0.180
0.3	0.047

REVISED TEXT

Part 2 will enroll ~~approximately 30~~up to 115 subjects in total. ~~Approximately 40 subjects will be evaluated at the end of Part 2, including~~This will include those enrolled in Part 1 at the same dose levels. Each population and dose cohort will be evaluated separately. Part 4 cohort expansion will enroll ~~approximately~~ 40-60 subjects in total (20 subjects in ~~Cohort 1E~~the anti-EGFR acquired resistance CRC population and 20-40 subjects in the BRAF mutant CRC population~~Cohort 2E~~). Subjects will be evaluated separately by dose cohort and population at the end of Part 4~~For each cohort, approximately 20 subjects will be evaluated separately at the end of Part 4, including those enrolled in dose escalation at the same dose levels and the same mutation status~~.

To determine the ~~maximum~~ sample size for ~~each~~ dabrafenib in combination with panitumumab expansion cohort, ~~cohort1E and cohort 2E in cohort 4~~and trametinib in combination with panitumumab expansion cohort, a traditional, 2-stage Green-Dahlberg design [Green, 1992] was evaluated and the sample size for the first stage will be used for the futility analysis. To test the hypotheses (RR=30% vs RR=15%), using a Green-Dahlberg design, 20 subjects per arm would be needed for Stage 1 (assuming a type 1 error of 10~~5~~% and power of 80~~95~~%). The chance to effectively terminate the trial after 20 subjects due to futility (true RR=15%) is 33~~65~~%; the risk to incorrectly stop the trial after 20 subjects if the treatment is effective (true RR =40%) is less than 1~~2~~% (Table 28~~Table 26~~). To determine the maximum sample size for any cohort or population in trametinib plus dabrafenib in combination with panitumumab, Bayesian predictive adaptive design will be used for testing hypotheses:

H_0: RR≤15%

H_A:RR≥30%

When maximum sample size is 55, the design will have a Type I error (α) of 0.10 and 89% power with the probability of termination is 0.898 when the treatment is futile and probability of early termination 0.104 when the treatment is effective (true RR=0.3).

Table 28~~26~~ Futility Analysis Design Performance

True RR	Probability of ~~Early~~ Termination, after 20 pts	Probability of Termination, after 55 pts
15%	0.329~~0.648~~	0.898
20%	0.180~~0.411~~	0.619
30%	0.044~~0.107~~	0.104
40%	0.007~~0.016~~	0.010

A Bayesian posterior probability will also be calculated to further inform decision making. Since neither ~~BRAF~~ dabrafenib in combination with panitumumab, trametinib in combination with panitumumab, nor ~~MEK~~ trametinib in combination with ~~BRAF~~ dabrafenib and panitumumab has been tested previously in the clinic in CRC subjects, a Beta (0.003, 0.007) prior is assumed. This prior is equivalent to the ~~prior~~ information from 0.01 subject. The posterior probabilities of RR exceeding 20%, 30% and 40%

based on 20 subjects and the posterior probabilities of RR exceeding 20%, 30% and 40% based on 55 subjects are shown in Table 29~~Table 27~~.

Table 29~~27~~ Bayesian Posterior Probabilities of Response Rate for Given Number of Observed Responses

# of Responses Observed out of 20 Subjects	Posterior Probability RR ≥20%	Posterior Probability RR ≥30%	Posterior Probability RR ≥40%
4	0.45	0.14	0.024
5	0.69	0.29	0.075
6	0.83	0.48	0.17
7	0.93	0.66	0.31
8	0.97	0.81	0.49
# of Responses Observed out of 55 Subjects	**Posterior Probability RR ≥20%**	**Posterior Probability RR ≥30%**	**Posterior Probability RR ≥40%**
11	0.47	0.04	0.001
12	0.61	0.08	0.002
13	0.73	0.13	0.005
14	0.82	0.21	0.011
15	0.89	0.31	0.022
16	0.94	0.43	0.043
17	0.97	0.54	0.076

Using these~~this~~ sample sizes, a Bayesian design that allows the trial to be monitored more frequently at multiple stages was evaluated. A Bayesian analysis expresses uncertainty about a parameter in terms of probability. A prior is defined to characterize the level of knowledge about a parameter before the data are collected. Once the data are collected, a posterior distribution is formed using the prior and the likelihood (i.e., the data). Since none of the treatment has been tested previously in the clinic in the target population, a weak prior Beta (0.003, 0.007) is assumed. Thus, the posterior distribution for the response rate will be primarily driven by the data and can be derived as follows: Let p denote the response rate for the treatment, the number of responses in the current n patients, x, follows a binomial distribution, Binomial (n, p). Taking the Bayesian method and combining the weak prior and the likelihood of the observed data x, the posterior distribution of the response rate follows a beta distribution, *i.e.,* $p \sim \text{Beta}(0.003 + x, 0.007 + n-x)$ with the posterior mean $(0.003 + x)/(0.01 + n)$.

Based on this posterior distribution of the response rate, the predictive probability that the response rate >15% or ≥30% after 19 or 54 subjects will be calculated for decision-making as described in the Section 5.1.2 (Hypotheses). The decision rule and a minimal required sample size of 10 patients for the first interim look is determined to generate the design that leads to a reasonable chance of early termination due to futility.

The design property, by utilizing the decision rule specified in Section 5.1.2, and sample size of 20 ~~patients~~ subjects or 55 subjects are shown (Table 30~~Table 28~~). The probability

of early termination of the trial is calculated by simulations. The probability of early termination after the first 19 evaluable subjects is 33% under the null hypothesized response rate, and the risk to incorrectly stop the trial early if the drug is effective is approximately 5%. Thus, the study will employ the Bayesian design that allows the trial to be monitored more frequently at multiple stages with the constraint of satisfactory stop for futility rate

Table 3028 Bayesian Design Performance by Response Rate

If True Response Rate to The Treatment is: (%)	Prob (early stop for futility) after 19 subjects	Prob (early stop for futility) after 54 subjects
0.15	0.326	0.853
0.2	0.180	0.483
0.3	0.0437	0.086

RATIONALE: Update sample size in the Bayesian design to accommodate the additional subjects in Part 2B

SECTION 5.2.3 Analysis Populations

PREVIOUS TEXT

The **Intent-to-Treat (ITT) population** will comprise all randomized subjects regardless of whether or not treatment was administered. This population will be based on the treatment to which the subject was randomized and will be the primary population for the analysis of efficacy data in Part 3.

The **All Treated Population** will consist of all subjects that received at least one dose of investigational product. Safety and clinical activity data will be evaluated based on this population.

The **PK Population** will consist of those subjects in All Treated Population and for whom a PK sample is obtained and analyzed.

The **Crossover Population** will comprise the subset of subjects in Part 1, Part 2 and Part 4 who had intra-subject dose escalation or intra-subject doublet to triplet crossover. It will be the primary population when summarizing data in Part 1, Part 2 and Part 4 crossover phase.

REVISED TEXT

The **Intent-to-Treat (ITT) population** will comprise all randomized subjects regardless of whether or not treatment was administered. This population will be based on the treatment to which the subject was randomized and will be the primary population for the analysis of efficacy data in Part 3.

The **All Treated Population** will consist of all subjects that received at least one dose of investigational product. Safety and clinical activity data for Parts 1, 2 and 4 will be evaluated based on this population.

The **PK Population** will consist of those subjects in All Treated Population and for whom a PK sample is obtained and analyzed.

The **Crossover Population** will comprise the subset of subjects in Part 1, Part 2 and Part 4 who had intra-subject dose escalation or intra-subject doublet to triplet crossover. It will be the primary population when summarizing data in Part 1, Part 2 and Part 4 crossover phase.

RATIONALE: To clarify that Part 1, Part 2 and Part 4 will use all subjects that were treated with one dose of either doublet or triplet regimen will be included in the efficacy and safety populations.

SECTION 5.3.8.7.1 Part 1, Part 2 and Part 4

PREVIOUS TEXT

The ORR endpoint will be tabulated based on number and percentage of subjects attaining either a confirmed or unconfirmed overall best response of CR or PR in the ITT population. Per RECIST, version 1.1, confirmation of response is not required. Subjects 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.

PFS will be estimated using the Kaplan Meier method. PFS will be defined as the time from randomization until the first date of either disease progression or death due to any cause. The date of objective disease progression will be defined as the earliest date of disease progression as assessed by the investigator using RECIST, version 1.1. For subjects who have not progressed or died at the time of the PFS analysis, censoring will be performed using the date of the last adequate disease assessment. In addition, subjects with an extended loss to follow-up or who start a new anti-cancer therapy prior to a PFS event will be censored at the date of the last adequate disease assessment prior to the extended loss to follow-up or start of new anti-cancer therapy, respectively. Further details on censoring rules will be outlined in the RAP.

For Part 1 and Part 2, anti-tumor activities will be evaluated based on clinical evidence and response criteria. If the data warrant, the response data from both parts will be combined and summarized by dose level. Subjects who crossover from dabrafenib/panitumumab combination or trametinib/panitumumab to dabrafenib/trametinib/panitumumab combination will not be included in the main efficacy analysis for dabrafenib/trametinib/panitumumab combinations. The efficacy for these subjects will be summarized separately.

REVISED TEXT

The ORR endpoint will be tabulated based on number and percentage of subjects attaining either a confirmed or unconfirmed overall best response of CR or PR in the ~~ITT~~ all treated population. Per RECIST, version 1.1, confirmation of response is not required. Subjects 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.

All responses are investigator-assessed. Independent central review may be performed.

PFS will be estimated using the Kaplan Meier method. PFS will be defined as the time from ~~randomization~~study treatment start until the first date of either disease progression or death due to any cause. The date of objective disease progression will be defined as the earliest date of disease progression as assessed by the investigator using RECIST, version 1.1. For subjects who have not progressed or died at the time of the PFS analysis, censoring will be performed using the date of the last adequate disease assessment. In addition, subjects with an extended loss to follow-up or who start a new anti-cancer therapy prior to a PFS event will be censored at the date of the last adequate disease assessment prior to the extended loss to follow-up or start of new anti-cancer therapy, respectively. Further details on censoring rules will be outlined in the RAP.

For Part 1 and Part 2, anti-tumor activities will be evaluated based on clinical evidence and response criteria. If the data warrant, the response data from both parts will be combined and summarized by dose level. The efficacy data collected after crossover for those subjects who crossover from dabrafenib/panitumumab combination or trametinib/panitumumab to dabrafenib/trametinib/panitumumab combination will not be included in the main efficacy analysis for dabrafenib/trametinib/panitumumab combinations. The crossover efficacy data for these subjects will be summarized separately.

RATIONALE: Added to allow for independent review of scans as well as clarify PFS definition and handling of crossover data.

Section 6.2 Safety

PREVIOUS TEXT

Physical Exams/ Dermatological Exams

A complete physical examination will be performed by a qualified physician according to local practices. At minimum, the examination should include assessments of the head and neck, skin, neurological, lungs, cardiovascular, abdomen (liver and spleen), thyroid, lymph nodes and extremities. 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 not required unless clinically indicated.) Rectal exam must include digital rectal exam and

visual inspection of the anus and perianal area. Height (at baseline only) and weight will also be measured and recorded.

UPDATED TEXT

Physical Exams/ Dermatological Exams

A complete physical examination will be performed by a qualified physician according to local practices. At minimum, the examination should include assessments of the head and neck, skin, neurological, lungs, cardiovascular, abdomen (liver and spleen), thyroid, lymph nodes and extremities. For subjects treated with dabrafenib in Part 1, 2, and 3, ~~C~~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 for subjects in Parts 1, 2 and 3. (Pap smear and colposcopy are not required unless clinically indicated.) Rectal exam must include digital rectal exam and visual inspection of the anus and perianal area. Height (at baseline only) and weight will also be measured and recorded.

RATIONALE: Removal of dabrafenib specific monitoring from Part 4.

SECTION 6.2 Safety

PREVIOUS TEXT

Clinical Chemistry

Albumin	Sodium	AST (SGOT)	Magnesium
BUN	Potassium	ALT (SGPT)	Total and direct bilirubin
Creatinine	Chloride	Gamma glutamyl transferase (GGT)	Uric Acid
Glucose fasting glucose at screening only; all other glucose measurements may be non-fasting	Total carbon dioxide (CO_2)	Alkaline phosphatase	Inorganic phosphorus
Lactacte dehydrogenase (LDH)	Calcium		Total Protein

Routine Urinalysis

Color, appearance, pH, specific gravity, glucose, protein, blood, ketones, WBC esterase, urobiligen
Microscopic examination (if blood or protein is abnormal)

Other screening tests

FSH and estradiol (as needed in women of non-child bearing potential only)
Coagulation (at screening, repeated only if clinically indicated)

REVISED TEXT

Clinical Chemistry

Albumin	Sodium	AST (SGOT)	Magnesium
BUN	Potassium	ALT (SGPT)	Total and direct bilirubin[1]
Creatinine	Chloride	Gamma glutamyl transferase (GGT)	Uric Acid
Glucose fasting glucose at screening only; all other glucose measurements may be non-fasting	Total carbon dioxide (CO_2)	Alkaline phosphatase	Inorganic phosphorus
Lactacte dehydrogenase (LDH)	Calcium		Total Protein

1. Direct bilirubin is only required when total bilirubin is above the upper limit of normal.

Routine Urinalysis

Color, appearance, pH, specific gravity, glucose, protein, blood, ketones, WBC esterase, urobiligen
Microscopic examination (if blood or protein is abnormal)

Other screening tests

FSH and estradiol (as needed in women of non-child bearing potential only)
Coagulation (at screening, repeated only if clinically indicated)

Progressively decreasing serum magnesium levels leading to severe (grade 3-4) hypomagnesemia occurred in up to 7% (in Study 2) of patients across clinical trials. Monitor patients for hypomagnesemia and hypocalcemia prior to initiating panitumumab treatment, periodically during panitumumab treatment, and for up to 8 weeks after the completion of treatment. Other electrolyte disturbances, including hypokalemia, have also been observed. Replete magnesium and other electrolytes as appropriate.

RATIONALE: Clarification that direct bilirubin is only necessary to test as part of the clinical chemistry panel if total bilirubin is above the upper limit of normal per standard clinical practice. Added language around hypomagnesemia and hypocalcemia from panitumumab.

SECTION 6.7.1 Fresh Pre- and Post-dose Tumour Tissues

PREVIOUS TEXT

Tumor specimens that are accessible and can be sampled easily will be requested in Part 1 and Part 2. These biopsies will be taken during the screening period, e.g., within 14 days before treatment, and within 2 to 4 hrs after dosing on Day 15 (+3 days) in those subjects who have signed the corresponding section of the informed consent. Details of the tumor biopsy collection including processing, storage and shipping procedures will be provided in the SPM.

REVISED TEXT

Tumor specimens that are accessible and can be sampled easily will be requested in Part 1~~and~~, Part 2 and Part 4. These biopsies will be taken during the screening period, e.g., within 14 days before treatment, and within 2 to 4 hrs after dosing on Day 15 (+3 days) in those subjects who have signed the corresponding section of the informed consent. Details of the tumor biopsy collection including processing, storage and shipping procedures will be provided in the SPM.

RATIONALE: Include Part 4 to be consistent with Time and Event Table

[redacted]

SECTION 6.7.4 Archival tissue collection

PREVIOUS TEXT

Collection of archival primary tumor tissue is required. These samples will be used to confirm or determine the BRAF or KRAS mutation status of subjects. [redacted]

REVISED TEXT

Collection of archival primary tumor tissue is required. These samples will be used to confirm or determine the BRAF or KRAS mutation status of subjects. [redacted]

[redacted]

SECTION 8.2 Prohibited Medications

PREVIOUS TEXT

The use of certain medications, and illicit drugs within 5 half-lives or 28 days, whichever is shorter prior to the first dose of study drug and for the duration of the trial will not be allowed. If a prohibited medication is required for single use (such as for a procedure) while study drug is held, the GSK medical monitor can approve such use.

The following medications or non-drug therapies are prohibited:

- Other anti-cancer therapy while on treatment in this study.
- Antiretroviral drugs.
- Herbal remedies (e.g., St. John's wort).
- Dabrafenib is metabolized primarily by Cytochrome P450 (CYP) 2C8 and CYP3A4. Co-administration of dabrafenib with ketoconazole, a CYP3A4 inhibition, or with gemfibrozil, a CYP2C8 inhibitor, resulted in increases in dabrafenib AUC of 71% and 47%, respectively. Drugs that are strong inhibitors or inducers of CYP3A and CYP2C8 (see list in Tablel 30) may only be used under special circumstances (e.g. as a single use for a procedure) while treatment with study drug is interrupted as they may alter dabrafenib concentrations; consider therapeutic substitutions for these medications. Approval of the GSK medical monitor is required in these situations. The list may be modified based on emerging data.

Oral contraceptives (either combined or progesterone only), estrogenic vaginal ring/percutaneous contraceptive patches, or implants of levonorgestrel/Injectable progesterone is prohibited in this study as it is not known if there is the potential of inhibition/induction of enzymes that affect the metabolism of estrogens and/or progestins.

Table 30 Prohibited Medications

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

REVISED TEXT
The use of certain medications, and illicit drugs within 5 half-lives or 28 days, whichever is shorter prior to the first dose of study drug and for the duration of the trial will not be allowed. If a prohibited medication is required for single use (such as for a procedure) while study drug is held, the GSK medical monitor can approve such use.

The following medications or non-drug therapies are prohibited:

- Other anti-cancer therapy while on treatment in this study.
- Antiretroviral drugs.
- Herbal remedies (e.g., St. John's wort).
- Dabrafenib is metabolized primarily by Cytochrome P450 (CYP) 2C8 and CYP3A4. Co-administration of dabrafenib with ketoconazole, a CYP3A4 inhibition, or with gemfibrozil, a CYP2C8 inhibitor, resulted in increases in dabrafenib AUC of 71% and 47%, respectively. Drugs that are strong inhibitors or inducers of CYP3A and CYP2C8 (see list in Table 32~~30~~) may only be used under special circumstances (e.g. as a single use for a procedure) while treatment with study drug is interrupted as they may alter dabrafenib concentrations; consider therapeutic substitutions for these medications. Approval of the GSK medical monitor is required in these situations. The list may be modified based on emerging data.
- Oral contraceptives (either combined or progesterone only), estrogenic vaginal ring/percutaneous contraceptive patches, or implants of levonorgestrel/Injectable progesterone is prohibited in this study as it is not known if there is the potential of inhibition/induction of enzymes that affect the metabolism of estrogens and/or progestins. HRT is permitted.

Table 3230 Prohibited Medications

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

a. Topical formulations of these drugs/agents can be used.

RATIONALE FOR CHANGE: Updated to allow HRT for female patients and topical formulation of certain drugs.

SECTION 9.2 Subject Completion Criteria

PREVIOUS TEXT

For Part 1 (dose-escalation phase) subjects who are not treated with the RP2D, a completed subject is one who has discontinued study treatment for reasons listed in Section 3.9 and was followed to progression, or to death.

For Part 1 subjects who are treated at RP2D, for Part 2 (expansion cohorts) subjects and for Part 3 (randomized Phase 2) subjects, a completed subject is one who has discontinued study treatment for reasons listed in Section 3.9 and was followed to death or has died while receiving study treatment.

REVISED TEXT

~~For Part 1 (dose-escalation phase) subjects who are not treated with the RP2D, a completed subject is one who has discontinued study treatment for reasons listed in Section 3.9 and was followed to progression, or to death.~~

~~For Part 1 subjects who are treated at RP2D, for Part 2 (expansion cohorts) subjects and for Part 3 (randomized Phase 2) subjects, a~~A completed subject is one who has discontinued study treatment for reasons listed in Section 3.9 and was followed to death or has died while receiving study treatment.

RATIONALE: Updated to collect overall survival on all subjects in the study regardless of Part or dose cohort.

APPENDIX 4 RECIST 1.1

PREVIOUS TEXT

Frequency of tumor re-evaluation

Target and non-target lesions will be re-evaluated every 8 weeks, or more frequently, based on clinical judgment.

REVISED TEXT

Frequency of tumor re-evaluation

Target and non-target lesions will be re-evaluated every 6 weeks for the first 24 weeks and every 8 weeks thereafter, or more frequently, based on clinical judgment.

RATIONALE: Update to match the Time and Event Table.

AMENDMENT 3

Where the Amendment Applies

This protocol amendment applies to all participating sites in all countries.

Summary of Amendment Changes with Rationale

List of Specific Changes

TITLE PAGE

PREVIOUS TITLE

An Open-Label, Three-Part, Phase I/II Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of the MEK Inhibitor GSK1120212, BRAF Inhibitor GSK2118436 and the anti-EGFR Antibody Panitumumab in Combination in Subjects with BRAF-mutation V600E Positive Colorectal Cancer

REVISED TITLE

An Open-Label, ~~Three~~Four-Part, Phase I/II Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of the MEK Inhibitor GSK1120212, BRAF Inhibitor GSK2118436 and the anti-EGFR Antibody Panitumumab in Combination in Subjects with BRAF-mutation V600E Positive Colorectal Cancer and in Subjects with CRC With Secondary Resistance to Prior Anti-EGFR Therapy

PREVIOUS TEXT

This is an open-label, three-part Phase I/II study to investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity of trametinib (GSK1120212) and dabrafenib (GSK2118436) when administered in combination with the anti-EGFR

antibody panitumumab in subjects with BRAF-mutation V600E positive colorectal cancer (CRC). **Part 1** of the study will consist of dose-escalation cohorts, following a 3 + 3 enrollment scheme. **Part 2** of the study will consist of expansion cohorts to investigate safety and clinical activity of dabrafenib in combination with panitumumab and trametinib plus dabrafenib in combination with panitumumab. **Part 3** of the study will be a randomized Phase II study comparing dosing with dabrafenib in combination with panitumumab and trametinib plus dabrafenib in combination with panitumumab as compared to the chemotherapy comparator (a regimen of FOLFOX, FOLFIRI or irinotecan with or without panitumumab or bevacizumab). Subjects will be assigned to treatment groups in a randomized fashion to compare safety and clinical activity.

REVISED TEXT

This is an open-label, ~~three~~four-part Phase I/II study to investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity of trametinib (GSK1120212) and dabrafenib (GSK2118436) when administered in combination with the anti-EGFR antibody panitumumab in subjects with BRAF-mutation V600E positive colorectal cancer (CRC) and in subjects with CRC with secondary resistance to prior anti-EGFR therapy. **Part 1** of the study will consist of dose-escalation cohorts, following a 3 + 3 enrollment scheme. **Part 2** of the study will consist of expansion cohorts to investigate safety and clinical activity of dabrafenib in combination with panitumumab and trametinib plus dabrafenib in combination with panitumumab. **Part 3** of the study will be a randomized Phase II study comparing dosing with dabrafenib in combination with panitumumab and trametinib plus dabrafenib in combination with panitumumab as compared to the chemotherapy comparator (a regimen of FOLFOX, FOLFIRI or irinotecan with or without panitumumab or bevacizumab). Subjects will be assigned to treatment groups in a randomized fashion to compare safety and clinical activity. **Part 4** of the study will investigate the trametinib/panitumumab combination, including dose escalation and subsequent cohort expansion in two patient populations: 1) BRAF-mutation V600E positive CRC and 2) subjects with CRC who developed secondary resistance to prior anti-EGFR therapy. The objective of Part 4 is to identify the recommended Phase 2 dose/regimen for trametinib dosed in combination with panitumumab in dose escalation and to identify an initial signal of clinical activity in expansion cohorts.

RATIONALE: Additional text describes subject population and dosing regimen for Part 4.

SPONSOR SIGNATORY

PREVIOUS TEXT

[redacted] MD, PhD
[redacted]
GlaxoSmithKline

REVISED TEXT

[redacted] MD, PhD
[redacted]
GlaxoSmithKline

Section 1.1.1, Paragraph 2

PREVIOUS TEXT

One improvement in CRC therapy has been the inclusion of anti-epidermal growth factor receptor (EGFR) therapy. Cetuximab, the first anti-EGFR therapy approved for the treatment of CRC, was demonstrated to have a benefit on progression free survival (PFS) and overall survival (OS) as a single agent in subjects with CRC that was resistant to standard chemotherapy [Jonker, 2007]. Subsequently it was demonstrated that cetuximab also demonstrated improvement in PFS when combined with standard chemotherapy (leucovorin calcium, fluorouracil, irinotecan hydrochloride; FOLFIRI) in previously untreated CRC subjects [Van Cutsem, 2009]. However, subsequent analyses of these studies, and a randomized Phase 2 evaluation of cetuximab with FOLFOX (leucovorin calcium, fluorouracil, oxaliplatin) demonstrated that the improvement in PFS was limited to cancers that harboured the wild-type version of the proto-oncogene KRAS [Karapetis, 2008; Bokemeyer, 2009; Van Cutsem, 2009]. Furthermore, a benefit in overall survival could also be demonstrated in wild-type KRAS subjects. More recently, the fully humanized anti-EGFR antibody panitumumab (Vectibix) was demonstrated to have very similar efficacy in the first line and second line settings with less frequent dosing (once every two weeks) and a lower rate of infusion reactions [VECTIBIX, 2013; Douillard, 2010; Peeters, 2010]. Again, the therapeutic benefit was limited to the KRAS wild-type population. Subsequent ~~meta-~~analyses of studies that have investigated anti-EGFR therapy (cetuximab and panitumumab) in CRC have confirmed that the clinical benefit of these therapies is limited to subjects with wild-type KRAS CRC [DeRoock, 2010].

REVISED TEXT

One improvement in CRC therapy has been the inclusion of anti-epidermal growth factor receptor (EGFR) therapy. Cetuximab, the first anti-EGFR therapy approved for the treatment of CRC, was demonstrated to have a benefit on progression free survival (PFS) and overall survival (OS) as a single agent in subjects with CRC that was resistant to standard chemotherapy [Jonker, 2007]. Subsequently it was demonstrated that cetuximab also demonstrated improvement in PFS when combined with standard chemotherapy (leucovorin calcium, fluorouracil, irinotecan hydrochloride; FOLFIRI) in previously untreated CRC subjects [Van Cutsem, 2009]. However, subsequent analyses of these studies, and a randomized Phase 2 evaluation of cetuximab with FOLFOX (leucovorin calcium, fluorouracil, oxaliplatin) demonstrated that the improvement in PFS was limited to cancers that harboured the wild-type version of the proto-oncogene KRAS [Karapetis, 2008; Bokemeyer, 2009; Van Cutsem, 2009]. Furthermore, a benefit in overall survival could also be demonstrated in wild-type KRAS subjects. More recently, the fully humanized anti-EGFR antibody panitumumab (Vectibix) was demonstrated to have very similar efficacy in the first line and second line settings with less frequent dosing (once every two weeks) and a lower rate of infusion reactions [VECTIBIX, 2013; Douillard,

2010; Peeters, 2010]. Again, the therapeutic benefit was limited to the KRAS wild-type population. Subsequent ~~meta-~~analyses of studies that have investigated anti-EGFR therapy (cetuximab and panitumumab) in CRC have confirmed that the clinical benefit of these therapies is limited to subjects with wild-type KRAS ~~CRC~~/NRAS [DeRoock, 2010, Schwartzberg 2014; Douillard 2013].

RATIONALE: Additional documentation in support of the ongoing study.

Section 1.1.1, Paragraph 9

PREVIOUS TEXT

The current study is designed to test the hypothesis that the combination of an anti-EGFR antibody with either a BRAF inhibitor (dabrafenib; GSK2118436) alone or with the combination of a BRAF inhibitor and a MEK inhibitor (trametinib; GSK1120212) will result in clinically meaningful anti-tumor activity that represents an improvement over the chemotherapy comparator (a regimen of FOLFOX, FOLFIRI or irinotecan with or without panitumumab or bevacizumab) for BRAF-mutant CRC. This will include the evaluation of the safety and tolerability of the two combinations, a preliminary assessment of clinical activity and then a randomized evaluation relative to the chemotherapy comparator therapy.

REVISED TEXT

The current study is designed to test the hypothesis that the combination of an anti-EGFR antibody with either a BRAF inhibitor (dabrafenib; GSK2118436) alone or with the combination of a BRAF inhibitor and a MEK inhibitor (trametinib; GSK1120212) will result in clinically meaningful anti-tumor activity that represents an improvement over the chemotherapy comparator (a regimen of FOLFOX, FOLFIRI or irinotecan with or without panitumumab or bevacizumab) for BRAF-mutant CRC. This will include the evaluation of the safety and tolerability of the two combinations, a preliminary assessment of clinical activity and then a randomized evaluation relative to the chemotherapy comparator therapy. In addition, the study will test the hyposthesis that the combination of panitumumab and trametinib can overcome secondary resistance to an abti-EGFR therapy in patients that initially derived benefit from the anti-EGFR therapy (further rationale in Section1.3.2).

RATIONALE: Additional documentation in support of the ongoing study.

Section 1.3.1, Heading

PREVIOUS TEXT

Study Rationale

REVISED TEXT

Study Rationale for Parts 1, 2 3

Section 1.3.2: Added Section

RATIONALE: Addition of text describing incorporation of Part 4 in the ongoing study.

1.3.2. Study Rationale for Part 4

Anti-EGFR therapies, either in combination with chemotherapy or as monotherapy, are approved therapy for KRAS wild-type (wt) colorectal cancer. Although a significant proportion of patients with KRAS wt CRC derive benefit from anti-EGFR therapy, they inevitably become resistant to this therapy. In a large proportion of cases, the mechanism of resistance to anti-EGFR therapy involves the reactivation of the RAS/MEK/ERK pathway, often through acquisition of mutations to RAS genes (KRAS or NRAS) converging on activation of the RAS/MEK/ERK pathway [Misale 2012; Misale 2014]. This is similar to the example of BRAF mutant melanoma in which a frequent mechanism of resistance involves the reactivation of this pathway [Flaherty 2012].

Vertical pathway inhibition can be an effective therapeutic strategy in tumors that are highly dependent on a single signaling pathway [Flaherty 2012]. The addition of a MEK inhibitor, trametinib, to the BRAF inhibitor dabrafenib results in a significant improvement in both the depth and durability of responses in preclinical models of or in patients with BRAF mutant melanoma [TAFINLAR prescribing information January 2014]. Using a similar rationale, the combination of an anti-EGFR agent and a MEK inhibitor demonstrated efficacy in preclinical models of CRC that had developed resistance to anti-EGFR therapy [Misale 2014].

Based on above data, the combination of the anti-EGFR agent panitumumab with the MEK inhibitor trametinib is of great interest to study in patients who were eligible for and derived benefit from anti-EGFR therapy and have subsequenty developed secondary resistance to anti-EGFR therapy.

1.3.2.1. Preliminary data from ongoing MEK116833 study

Preliminary clinical data from Parts 1 and 2 of this ongoing study suggest that the triplet combination of dabrafenib/trametinib/panitumumab is more efficacious than the dabrafenib/panitumumab doublet in the BRAF-mutant patient population (see Table 1). Enrollment in this dose combination has been limited to 20 patients, including those enrolled in Part 1 Cohort 1 and those enrolled in Part 2 doublet cohort. Given the difference in activity, it is important to understand whether dabrafenib is contributing to the clinical activity that has been seen with the triplet. Therefore, patients with BRAF-mutant CRC will be included in the dose escalation of the trametinib/panitumumab doublet and an expansion cohort further evaluating safety and efficacy of the trametinib/panitumumab doublet will be included in Part 4 of the study.

Table 1 Best unconfirmed response, Part 1 and Part 2 (preliminary data)

Best unconfirmed response	Doublet Cohort[a], n=13	Triplet Cohorts		
		Cohort 2[b], n=3	Cohort 3A[c] n=4	Cohort 3B[d] n=4
PD	2	0	0	0
SD	9	1	1	3
PR	2	2	2	0
CR	0	0	1	0

a. Doublet cohort combines patients enrolled in Part 1 Cohort 1 and Part 2 doublet expansion cohort; all dosed with Dabrafenib 150mg BID + Panitumumab 6mg/kg/Q2W
b. Dabrafenib 150mg BID + Panitumumab 4.8mg/kg/Q2W + Trametinib 1.5mg QD
c. Dabrafenib 150mg BID + Panitumumab 4.8mg/kg/Q2W + Trametinib 2mg QD
d. Dabrafenib 150mg BID + Panitumumab 6mg/kg/Q2W + Trametinib 1.5mg QD

Part 4 of the study is designed to identify the recommended Phase 2 dose/regimen for trametinib dosed orally in combination with IV infusions of panitumumab in dose escalation and to identify an initial signal of clinical activity in expansion cohorts:

1. subjects with BRAF-V600E mutation-positive CRC

2. subjects with CRC that developed secondary resistance to anti-EGFR therapy after initially deriving benefit.

Section 1.3.3 Dose Rationale: Added Paragraph 2

Part 4 of the study includes a 3+3 dose escalation that will identify tolerable combination doses for trametinib dosed orally in combination with IV infusions of panitumumab. The safety and tolerability of the RP2D will be confirmed in the expansion cohorts.

RATIONALE: Addition of text describing incorporation of Part 4 in the ongoing study

Section 1.3.3.6 Dose Rationale, Part 4: Added Section

RATIONALE: Addition of text describing incorporation of Part 4 in the ongoing study

1.3.3.6 Part 4

Data from Parts 1 and 2 of this ongoing study have demonstrated that both the dabrafenib/panitumumab doublet and the dabrafenib/trametinib/panitumumab triplet are well-tolerated by patients (see Table 2). The triplet combination studies in Cohorts 3A and 3B, in which dabrafenib is dosed at the full marketed dose (150mg po BID) and either trametinib or panitumumab is also dosed at the full marketed dose (2mg po QD or 6 mg/kg IV Q2W, respectively), with the other agent dosed at one dose level lower (1.5mg po QD or 4.8mg/kg IV Q2W, respectively) have been well tolerated to date, with no DLTs being identified. The highest triplet combination (all three agents at full dose) is currently being evaluated in Cohort 4 of the dose escalation. Based on the tolerability of the triplet in Part 1, the two starting dose trametinib/panitumumab combinations that will be studied in the initial dose escalation cohort of Part 4 will include the doses of

trametinib and panitumumab that were tolerated in combination with dabrafenib in Cohorts 3A and 3B of Part 1. If these are well tolerated, the dose will be escalated to the full dose of both agents. If neither of these is well tolerated, there will be an option to dose reduce (see Section 3.4). The optimal safe and tolerable dose combinations defined in dose escalation will be brought forward into expansion cohorts. This will likely be the maximal dose for each combination in dose escalation, although a lower dose combination may be selected if significant delayed or prolonged toxicities require frequent dose modifications. Expansion cohorts of approximately 20 subjects with KRAS wt CRC who progressed on previous anti-EGFR will be enrolled to confirm safety and tolerability, and to generate signals of activity.

Table 2 DLTs, Related AEs ≥Gr 3, and Related SAEs in Part 1 and Part 2 (preliminary data)

	Doublet Cohort[a], n=13	Triplet Cohorts		
		Cohort 2[b], n=3	Cohort 3A[c] n=4	Cohort 3B[d] n=4
DLTs	None	None	None	None
Related SAEs	5	1	None	None
Related AEs ≥Grade 3	1	2	1	2

a. Doublet cohort combines patients enrolled in Part 1 Cohort 1 and Part 2 doublet expansion cohort; all dosed with dabrafenib 150mg BID + panitumumab 6mg/kg/Q2W.
b. Part 1 Cohort 2 dose dabrafenib 150mg BID + panitumumab 4.8mg/kg/Q2W + trametinib 1.5mg QD
c. Part 1 Cohort 3A dose dabrafenib 150mg BID + panitumumab 4.8mg/kg/Q2W + trametinib 2mg QD
d. Part 1 Cohort 3B dose dabrafenib 150mg BID + panitumumab 6mg/kg/Q2W + trametinib 1.5mg QD

Section 2.4 Part 4A Dose Escalation: Added Section

RATIONALE: Addition of text describing objectives and endpoints associated with Part 4 in the ongoing study

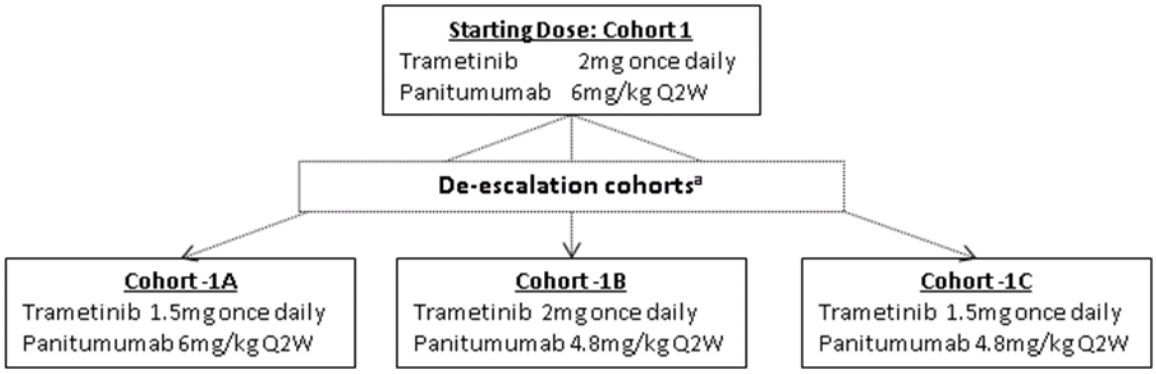
	Objectives	Endpoints
Primary	To determine the safety, tolerability and range of tolerated combination doses in of the combination of panitumumab and trametinib in subjects with advanced/metastatic CRC	Adverse events and changes in laboratory values, vital signs and dose interruptions, modifications and discontinuations
Secondary	To describe the pharmacokinetics of trametinib and panitumumab after combination therapy	Maximum observed concentration (Cmax), time of occurrence of Cmax (tmax), and area under the concentration-time curve from zero (pre-dose) the time of the last quantifiable concentration (AUC(0-t)), pre-dose (trough) concentration at the end of the dosing interval ($C\tau$) of trametinib. Predose ($C\tau$) and Cmax concentrations of panitumumab.
	To determine preliminary clinical activity of panitumumab/trametinib	

	Objectives	**Endpoints**
	combination therapy in two patient populations: • subjects with BRAF-V600E mutation-positive CRC • subjects with CRC that developed secondary resistance to anti-EGFR therapy after initially deriving benefit To evaluate the pharmacodynamic response in colorectal tumors following combination therapy	Response rate (complete response [CR] + partial response [PR]) Progression free survival Duration of response Change in levels of proteins/RNA implicated in MAPK/PI3K/EGFR pathways in pre- and post-dose tumor tissue.
[redacted]		

Section 2.5 Part 4B Cohort Expansion: Added Section

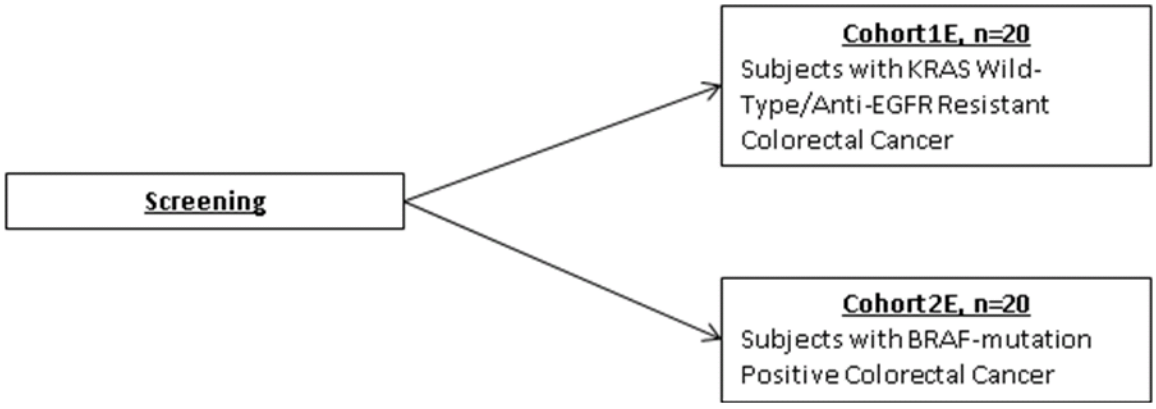
	Objectives	Endpoints
Primary	To confirm the safety and tolerability of RP2D/R of the panitumumab/trametinib combination in an expansion cohorts of • subjects with BRAF-V600E mutation-positive CRC • subjects with CRC that developed secondary resistance to anti-EGFR therapy after initially deriving benefit To determine clinical activity of combination therapy in this patient population	Adverse events and changes in laboratory values, vital signs and dose interruptions, modifications and discontinuations Response rate (CR +PR)
Secondary	To characterize the population PK parameters of trametinib dosed orally in combination with anti-EGFR antibody (panitumumab) To characterize the durability of response with trametinib dosed in combination with panitumumab To evaluate the pharmacodynamic response in colorectal tumors following combination treatment	Population PK parameters, oral clearance (CL/F), oral volume of distribution (V/F), and absorption rate constant (Ka) Duration of response Progression-free survival Overall survival Change in levels of proteins/RNA implicated in MAPK/PI3K/EGFR pathways in pre- and post-dose tumor tissue
[redacted]		

Section 3.4 Part 4A Dose Escalation: Added Schematic



a. If the initial combination dose of trametinib and panitumumab in Cohort 1 (starting dose) is not tolerable, the lower dose combination defined in de-escalation cohorts (Cohort -1A, -1B and/or -1C) may be evaluated.

Section 3.5 Part 4B Cohort Expansion: Added Schematic



Section 3.6 Discussion of Design

PREVIOUS TEXT

This three-part Phase 1/2 multi-center study allows for the phased evaluation of safety, tolerability, and activity of dabrafenib and trametinib in combination with panitumumab in subjects with BRAF-V600E mutation-positive CRC. The planned number of subjects per part is described in Section 4.1. Dose adjustment and stopping criteria are described in Section 3.9. All study treatments, including investigational products, will be referred to as "study treatment(s)" for ease of presentation throughout the protocol, except for Section 3.8.

REVISED TEXT

This ~~three~~four-part Phase 1/2 multi-center study allows for the phased evaluation of safety, tolerability, and activity of dabrafenib and/or trametinib in combination with panitumumab in subjects with BRAF-V600E mutation-positive CRC and in subjects with

CRC with secondary resistance to prior anti-EGFR therapy. The planned number of subjects per part is described in Section 4.1. Dose adjustment and stopping criteria are described in Section 3.9. All study treatments, including investigational products, will be referred to as "study treatment(s)" for ease of presentation throughout the protocol, except for Section 3.8.

RATIONALE: Addition of text describing population enrolling into Part 4 in the ongoing study

Section 3.6.1 Prescreening for KRAS and BRAF Mutation Status, Paragraph 2 & 3

PREVIOUS TEXT

The conduct of the KRAS- and BRAF-mutation screening prior to the baseline assessments is the responsibility of the investigator and must be performed in a CLIA-approved facility. Local testing for KRAS and BRAF mutations for enrollment in the trial can occur any time prior to dosing. If KRAS and BRAF mutation status is unknown at screening, no biopsy for assessment of mutation status in association with this protocol should be taken prior to obtaining consent. Following consent, subjects should be screened for KRAS and BRAF mutation status (if not already performed) prior to any other study-related screening procedures. The BRAFV600E mutation status will be confirmed centrally using the GSK selected assay. For Part 1 and Part 2, a local test result for KRAS status is adequate for enrollment. Enrollment in Part 3 may only occur following confirmation of KRAS wild-type cancer, as determined by FDA-approved KRAS test for CRC (e.g., Qiagen test) and documented in source.

For subjects with known BRAFV600E mutations, confirmation of mutation must occur following registration in Part 1 and Part 2. Subjects will not be excluded if centralized testing is later found to be discordant or uninformative (e.g., inadequate sample), but additional subjects may be enrolled as replacement subjects at the discretion of the Sponsor and in consultation with the investigator.

REVISED TEXT

The conduct of the KRAS- and BRAF-mutation screening prior to the baseline assessments is the responsibility of the investigator and must be performed in a CLIA-approved facility. Local testing for KRAS and BRAF mutations for enrollment in the trial can occur any time prior to dosing. If KRAS and BRAF mutation status is unknown at screening, no biopsy for assessment of mutation status in association with this protocol should be taken prior to obtaining consent. Following consent, subjects should be screened for KRAS and BRAF mutation status (if not already performed) prior to any other study-related screening procedures. The BRAFV600E mutation status will be confirmed centrally using the GSK selected assay. For Part 1 and Part 2, a local test result for KRAS status is adequate for enrollment. Enrollment in Part 3 may only occur following confirmation of KRAS wild-type cancer, as determined by FDA-approved KRAS test for CRC (e.g., Qiagen test) and documented in source. For patients in Part 4 who have acquired secondary resistance to anti-EGFR therapy, repeat testing for RAS mutations is not required.

For subjects with known BRAFV600E mutations, confirmation of mutation must occur following registration in Parts 1, 2 and 4. Subjects will not be excluded if centralized testing is later found to be discordant or uninformative (e.g., inadequate sample), but additional subjects may be enrolled as replacement subjects at the discretion of the Sponsor and in consultation with the investigator.

RATIONALE: Addition of text describing population enrolling into Part 4 in the ongoing study

Section 3.6.2.1 Dose-Limiting Toxicity Definitions

PREVIOUS TEXT

Toxicity	DLT Definition
Hematologic	• Grade 4 absolute neutrophil count (ANC) for ≥5 days • Febrile neutropenia (defined as concurrent Grade 4 neutropenia and fever >38.5°C and lasting >24 hrs) • Grade 4 anemia of any duration • Grade 4 thrombocytopenia (platelets <25,000) of any duration
Non-hematologic	• Alanine aminotransferase (ALT) >5X upper limit of normal (ULN) OR, ALT >3X ULN AND bilirubin >2X ULN (after exclusion of disease progression and/or bile duct obstruction) • Grade ≥4 rash • Grade 4 Squamous Cell Carcinoma, keratoacanthoma or basal cell carcinoma • Grade 3 or greater clinically significant non-hematologic toxicity per NCI-CTCAE, v 4.0, other than those listed above, with the following exceptions: o Grade 3 or greater nausea, vomiting, diarrhea, or mucositis/esophagitis that responds to maximal supportive treatment(s) within 48 hours o Electrolyte disturbances that respond to correction within 24 hours o Grade 3 hypertension that is adequately controlled by the addition of up to 2 additional antihypertensive medications o Grade 3 pyrexia that does not result in study discontinuation
Cardiac	• Ejection fraction < lower limit of normal (LLN) with an absolute decrease of >20% from baseline
Other	• Inability to received >75% of scheduled doses in treatment period due to toxicity • Grade 2 or higher toxicity that occurs beyond 28 days which in the judgment of the investigator and GSK Medical Monitor is considered to be a DLT

REVISED TEXT

Toxicity	DLT Definition
Hematologic	• Grade 4 absolute neutrophil count (ANC) for ≥5 days • Febrile neutropenia (defined as concurrent Grade 4 neutropenia and fever >38.5°C and lasting >24 hrs) • Grade 4 anemia of any duration • Grade 4 thrombocytopenia (platelets <25,000) of any duration
Non-hematologic	• Alanine aminotransferase (ALT) >5X upper limit of normal (ULN) OR, ALT >3X ULN AND bilirubin >2X ULN (after exclusion of disease progression and/or bile duct obstruction) • Grade ≥4 rash • Grade 4 Squamous Cell Carcinoma, keratoacanthoma or basal cell carcinoma • Grade 3 or greater clinically significant non-hematologic toxicity per NCI-CTCAE, v 4.0, other than those listed above, with the following exceptions: o Grade 3 or greater nausea, vomiting, diarrhea, or mucositis/esophagitis that responds to maximal supportive treatment(s) within 48 hours o Electrolyte disturbances that respond to correction within 24 hours o Grade 3 hypertension that is adequately controlled by the addition of up to 2 additional antihypertensive medications o Grade 3 pyrexia that does not result in study discontinuation
Cardiac	• Ejection fraction < lower limit of normal (LLN) with an absolute decrease of >20% from baseline
Other	• Inability to ~~received >~~receive ≥75% of scheduled doses in treatment period due to toxicity • Grade 2 or higher toxicity that occurs beyond 28 days which in the judgment of the investigator and GSK Medical Monitor is considered to be a DLT

RATIONALE: Correction to clarify subjects must have received greater than or equal to 75% of scheduled doses during the DLT period

Section 3.6.2.2 Maximum Tolerated Dose and Recommended Phase 2 Dose

PREVIOUS TEXT

The maximum tolerated dose (MTD) is defined as the highest dose at which one or fewer of up to 6 subjects experience a DLT during the first 28 days of treatment in Part 1. Due to the heterogeneity of the rash caused by panitumumab, if any DLTs are due to rash, the cohort may be expanded to 12 subjects in order to more fully assess the true risk of intolerable rash, in which case DLTs in >3 of 12 subjects defines an intolerable dose. The recommended doses in Part 2 and Part 3 may include doses that are less than or equal to the MTD but demonstrate biological activity and adequate tolerability.

REVISED TEXT

The maximum tolerated dose (MTD) is defined as the highest dose at which one or fewer of up to 6 subjects experience a DLT during the first 28 days of treatment in Part 1. Due to the heterogeneity of the rash caused by panitumumab and/or trametinib, if any DLTs are due to rash, the cohort may be expanded to 12 subjects in order to more fully assess

the true risk of intolerable rash, in which case DLTs in >3 of 12 subjects defines an intolerable dose. The recommended doses in Part 2 and Part 3 may include doses that are less than or equal to the MTD but demonstrate biological activity and adequate tolerability.

RATIONALE: Addition of text describing management of rash for patients enrolling into Part 4 in the ongoing study

Section 3.6.5 Part 4A Dose Escalation: Added Section

RATIONALE: Addition of text describing dose escalation and DLT evaluation for patients enrolling into Part 4 in the ongoing study

A combination dose will be defined for combination of trametinib and panitumumab as shown in Section3.4). Once safety data has been collected for at least 3 patients in Cohort 1, preliminary data will be evaluated for dose-limiting toxicities (DLTs) during the first 28 days of treatment, per table in Section 3.6.5.1.

Table 5 3+3 Cohort Dose Escalation

Number of subjects in cohort with DLT	Action
0 out of 3 subjects	Escalate to next dose level.
1 out of 3 subjects	Accrue 3 additional evaluable subjects at current dose level for a total of 6 evaluable subjects
1 out of 6 subjects	Escalate to next dose level with an increase of ≤ 50% (this represents the sum of relative escalation for each of the drugs)
2 or more subjects in a dosing cohort (up to 6 subjects)	Maximum tolerated dose has been exceeded. Either evaluate an intermediate dose lower than current dose or expand a prior cohort up to 12 subjects.

Dose escalation decisions will take into consideration all available data, including the safety profile of prior cohorts throughout the time subjects are on study, which will be reviewed by the investigator(s), GSK medical monitor(s), pharmacokineticist and statistician. The dose escalation decision for the subsequent cohort and rationale will be documented in writing with copies maintained at each site and the Master Study Files.

Due to the heterogeneity of the rash caused by panitumumab and/or trametinib, if any DLTs are due to rash, the cohort may be expanded to 12 subjects in order to more fully assess the true risk of intolerable rash, in which case DLTs in >3 of 12 subjects defines an intolerable dose. If the preliminary MTD is below the full dose of both agents, re-escalation may be considered ONLY if fewer than 4 DLTs have been reported after enrolling at least 12 patients at the preliminary MTD (including patients enrolled in the dose escalation and expansion cohorts).

14.1.1.1. Dose-Limiting Toxicity Definitions

An event will be considered a dose limiting toxicity (DLT) if it occurs within the first 28 days of dosing, has a possible causal relationship to the study drug(s) based on investigator assessment, and meets at least one of the following criteria:

Toxicity	DLT Definition
Hematologic	• Grade 4 absolute neutrophil count (ANC) for ≥5 days • Febrile neutropenia (defined as concurrent Grade 4 neutropenia and fever >38.5°C and lasting >24 hrs) • Grade 4 anemia of any duration • Grade 4 thrombocytopenia (platelets <25,000) of any duration
Non-hematologic	• Alanine aminotransferase (ALT) >5X upper limit of normal (ULN) OR, ALT >3X ULN AND bilirubin >2X ULN (after exclusion of disease progression and/or bile duct obstruction) • Grade ≥4 rash • Grade 3 or greater clinically significant non-hematologic toxicity per NCI-CTCAE, v 4.0, other than those listed above, with the following exceptions: o Grade 3 or greater nausea, vomiting, diarrhea, or mucositis/esophagitis that responds to maximal supportive treatment(s) within 48 hours o Electrolyte disturbances that respond to correction within 24 hours o Grade 3 hypertension that is adequately controlled by the addition of up to 2 additional antihypertensive medications o Grade 3 pyrexia that does not result in study discontinuation
Cardiac	• Ejection fraction < lower limit of normal (LLN) with an absolute decrease of >20% from baseline
Other	• Inability to receive ≥75% of scheduled doses in treatment period due to toxicity • Grade 2 or higher toxicity that occurs beyond 28 days which in the judgment of the investigator and GSK Medical Monitor is considered to be a DLT

Section 3.6.6 Part 4B Cohort Expansion: Added Section

In Part 4B cohort expansion, the primary objectives will be to further assess the safety and preliminary clinical activity of given doses and regimen(s) in subjects with advanced/metastatic CRC with either a BRAF-mutation (Cohort 1E) or who developed secondary resistance to prior anti-EGFR therapy (Cohort 2E). Enrollment in expansion cohorts will be initiated once dose escalation for the trametinib /panitumumab combination has been completed.

The trial may also be stopped at any time if excessive toxicities with the study treatment are observed.

RATIONALE: Addition of text rationale for cohort expansion in Part 4 of the ongoing study

Section 3.8 Treatment Assignment

PREVIOUS TEXT

All subjects will be assigned to study treatment in accordance with the randomization schedule generated by Discovery Biometrics, prior to the start of the study, using validated internal software. In Part 1, subjects will be assigned to a cohort/ dose level based on evaluation of safety in subjects enrolled in prior cohorts. In Part 2, subjects will be assigned to expansion cohorts at a selected dose of dabrafenib in combination with panitumumab and a selected dose of trametinib plus dabrafenib in combination with panitumumab. In Part 3, subjects will be randomized to study treatment.

REVISED TEXT

All subjects will be assigned to study treatment in accordance with the randomization schedule generated by Discovery Biometrics, prior to the start of the study, using validated internal software. In Part 1, subjects will be assigned to a cohort/ dose level based on evaluation of safety in subjects enrolled in prior cohorts. In Part 2, subjects will be assigned to expansion cohorts at a selected dose of dabrafenib in combination with panitumumab and a selected dose of trametinib plus dabrafenib in combination with panitumumab. In Part 3, subjects will be randomized to study treatment. In Part 4A dose escalation, subjects will be assigned to a cohort/ dose level based on evaluation of safety in subjects enrolled in prior cohorts. In Part 4B cohort expansion, subjects will be assigned to expansion cohorts at a selected dose of trametinib in combination with panitumumab.

RATIONALE: Addition of text explaining dose assignment in Part 4 of the ongoing study

Section 3.9.3 Intra-Subject Doublet to Triplet Crossover and Dose Escalation: Part 1 ~~and Part 2~~, 2 or 4

PREVIOUS TEXT

For subjects enrolled in Part 1 or Part 2, intra-subject doublet to triplet crossover is allowed if a patient has not experienced intolerable toxicity that could not be managed, and has demonstrated radiographic progression on therapy by RECIST v1.1 criteria, and approval will be based on review by GSK Medical Monitor. Dose administered must be from among those for which cohorts have been completed and data has been reviewed for safety.

Subjects are allowed to crossover once during the study.

Additionally, for subjects who have remained on study for ≥ 6 months in the triplet combination, their dose level for the combination may be increased up to the highest combination dose level that has previously been confirmed as not exceeding the MTD for the combination. The intra-subject dose escalation must be agreed to by the investigator and the GSK Medical Monitor.

REVISED TEXT

For BRAF-mutation positive subjects enrolled in Part 1, 2 or ~~Part 2~~ 4 doublet dosing, intra-subject doublet to triplet crossover is allowed if a patient has not experienced intolerable toxicity that could not be managed, and has demonstrated radiographic progression on therapy by RECIST v1.1 criteria, and approval will be based on review by GSK Medical Monitor. Dose administered must be from among those for which cohorts have been completed and data has been reviewed for safety.

At the time of crossover, certain safety assessments will be repeated prior to start of triplet dosing (additional information describing assessments is available in Section 6):

- brief physical examination
- vital signs
- dermatological examination
- ECG (single; repeated with 2 additional ECGs if clinically significant abnormalities are observed in the first assessment)
- ECHO/ MUGA
- disease assessment demonstrating radiographic progression on therapy by RECIST v1.1 criteria
- ophthalmic examination, repeated at Week 4 after start of dosing with trametinib

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

All crossover assessments must be completed within 14 days prior to first dose on triplet except informed consent, ophthalmology exam, ECHO/MUGA and Disease Assessment, which can occur within 35 days prior to the first dose on triplet.

The source documents for these assessments should be provided to GSK at least 24 hours in advance to planned start of triplet dosing. The medical monitor will review and provide approval for crossover from doublet to triplet, and site will be notified via email with a signed crossover form (refer to SPM).

Once approved, patients will follow the time and events table for Part 2 Expansion Cohorts, in Section 3.10.3, starting at the column labelled "Continuation Phase" for continued monitoring of safety and efficacy.

Subjects are allowed to crossover once during the study.

Additionally, for subjects who have remained on study for ≥ 6 months in the triplet combination, their dose level for the combination may be increased up to the highest combination dose level that has previously been confirmed as not exceeding the MTD for the combination. The intra-subject dose escalation must be agreed to by the investigator and the GSK Medical Monitor.

RATIONALE: Addition of evaluations required at time of crossover to evaluate risk/benefit

Section 3.9.4.1 Guidelines for Treatment of Pyrexia

PREVIOUS TEXT

Episodes of pyrexia have been observed in subjects receiving dabrafenib monotherapy ~~or~~ in combination with trametinib (refer to the GSK2118436 IB [GlaxoSmithKline Document Number 2012N136095_00], the GSK1120212 IB [GlaxoSmithKline Document Number HM2009/00151/03] and the GSK1120212 + GSK2118436 Clinical IB [GlaxoSmithKline Document Number, 2011N126811_00]). In a minority of cases the pyrexia was accompanied by symptoms such as severe chills, dehydration, hypotension, dizziness or weakness.

Pyrexia accompanied by hypotension, or dehydration requiring IV fluids, or severe rigors/chills should be reported as a serious adverse event (SAE) per Section 11.2.

Subjects should be instructed on the importance of immediately reporting febrile episodes. In the event of a fever, the subject should be instructed to take ~~non-steroidal~~ anti-pyretics as appropriate to control fever. In subjects experiencing pyrexia associated with rigors, severe chills, dehydration, hypotension, etc., renal function should be monitored carefully (see Section 3.9.6).

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

Table 10 Management and Dose Modification Guidelines for Pyrexia

Pyrexia[a] Management	**Action and Dose Modification**
1st Event[b]: Clinical evaluation for infection and hypersensitivity[c] Laboratory work-up[c] Hydration as required[d] Blood sample for cytokine analysis[e] Administer anti-pyretic treatment if clinically indicated and continue prophylactic treatment[f]	1st Event: • Interrupt dabrafenib • Continue trametinib and/or panitumumab • Once pyrexia resolves to baseline, restart dabrafenib at the same dose level If fever was associated with dehydration or hypotension, **reduce dabrafenib by one dose level**
2nd Event[g]: Clinical evaluation for infection and hypersensitivity[c] Laboratory work-up[c] Hydration as required[d] Blood sample for cytokine analysis[e] • Within 3 days of onset of pyrexia:	2nd Event: • **Interrupt dabrafenib** • Continue trametinib and/or panitumumab • 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**

Pyrexia[a] Management	**Action and Dose Modification**
Optimize anti-pyretic therapy Consider oral cortiocosteroids (i.e., prednisone 10mg) for at least 5 days or as clinically indicated	
Subsequent Events: Clinical evaluation for infection and hypersensitivity[c] Laboratory work-up[c] Hydration as required[d] Blood sample for cytokine analysis[e] • Within 3 days of onset of pyrexia: Optimize oral corticosteroid dose as clinically indicated for recalcitrant pyrexia if corticosteroids have been tapered and pyrexia recurs, restart steroids if corticosteroids cannot be tapered consult medical monitor	**Subsequent Events:** • **Interrupt dabrafenib** • Continue trametinib and/or panitumumab Once pyrexia resolves to baseline, restart dabrafenib **reduced by one dose level[h]** If dabrafenib must be reduced to <75mg 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 subjects experiencing pyrexia complicated by rigors, severe chills, etc., a clinical evaluation and laboratory work-up is mandatory for each event; anti-pyretic treatment should be started immediately at the first occurrence and prophylactic anti-pyretic treatment is recommended
c. Thorough clinical examination for signs and symptoms of infection or hypersensitivity is required; laboratory workup 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 subjects without evidence of dehydration. Intravenous hydration is recommended in subjects experiencing pyrexia complicated by dehydration/hypotension.
e. Blood sample for cytokine analysis must be sent to the central laboratory
f. 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
g. In subject experiencing pyrexia complicated by rigors, severe chills, etc., which cannot be controlled with antipyretic medication, oral corticosteroids should be started at the 2nd event and doses should be gradually increased for subsequent events.
h. Dabrafenib should be reduced by one dose level after three episodes of pyrexia complicated by rigors, severe chills, etc., which cannot be managed by best supportive care and increasing doses of oral steroids. Escalation of dabrafenib is allowed if no episode of pyrexia is observed in the 4 weeks subsequent to dose reduction.

REVISED TEXT

Episodes of pyrexia have been observed in subjects receiving dabrafenib monotherapy ~~or~~ and is increased in incidence and severity in subjects receiving dabrafenib in combination with trametinib (refer to the GSK2118436 IB [GlaxoSmithKline Document Number 2012N136095_00], the GSK1120212 IB [GlaxoSmithKline Document Number HM2009/00151/03] and the GSK1120212 + GSK2118436 Clinical IB [GlaxoSmithKline Document Number, 2011N126811_00]). In a minority of cases the pyrexia was accompanied by symptoms such as severe chills, dehydration, hypotension, dizziness or weakness.

~~Pyrexia accompanied by hypotension, or dehydration requiring IV fluids, or severe rigors/chills should be reported as a serious adverse event (SAE) per Section .~~

Subjects should be instructed on the importance of immediately reporting febrile episodes. In the event of a fever, the subject should be instructed to take ~~non-steroidal~~ anti-pyretics (e.g., ibuprofen or acetaminophen/paracetamol) as appropriate to control fever. ~~In subjects experiencing pyrexia associated with rigors, severe chills, dehydration, hypotension, etc.,~~The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient. Monitor serum creatinine and other evidence of renal function ~~should be monitored carefully~~ during and following severe events of pyrexia (see Section 3.9.6).

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

Table 10 Management and Dose Modification Guidelines for Pyrexia

Pyrexia[a] Management	**Action and Dose Modification**
All Events: • Clinical evaluation for infection and hypersensitivity[c] • Laboratory work-up[c] • Hydration as required[d]	
1st Event[b]: ~~Clinical evaluation for infection and hypersensitivity[c]~~ ~~Laboratory work-up[c]~~ ~~Hydration as required[d]~~ ~~Blood sample for cytokine analysis[e]~~ Administer anti-pyretic treatment if clinically indicated and continue prophylactic treatment[f] if associated with rigors, renal failure, dehydration or hypotension[e]	1st Event: • Interrupt dabrafenib • Continue trametinib and/or panitumumab • Once pyrexia resolves to baseline, restart dabrafenib at the same dose level If fever was associated with dehydration or hypotension, **reduce dabrafenib by one dose level**
2nd Event[g]: ~~Clinical evaluation for infection and hypersensitivity[c]~~ ~~Laboratory work-up[c]~~ ~~Hydration as required[d]~~ ~~Blood sample for cytokine analysis[e]~~ • Within 3 days of onset of pyrexia: Optimize anti-pyretic therapy Consider oral cortiocosteroids (i.e.,	2nd Event: • **Interrupt dabrafenib** • Continue trametinib and/or panitumumab • Once pyrexia resolves to baseline, restart dabrafenib at the same dose level If fever was associated with rigors, renal failure, dehydration or hypotension, **reduce dabrafenib by one dose level**

Pyrexia[a] Management	Action and Dose Modification
prednisone 10mg) for at least 5 days or as clinically indicated	
Subsequent Events: ~~Clinical evaluation for infection and hypersensitivity[c]~~ ~~Laboratory work-up[c]~~ ~~Hydration as required[d]~~ ~~Blood sample for cytokine analysis[e]~~ • Within 3 days of onset of pyrexia: Optimize oral corticosteroid dose as clinically indicated for recalcitrant pyrexia if corticosteroids have been tapered and pyrexia recurs, restart steroids if corticosteroids cannot be tapered consult medical monitor	**Subsequent Events:** • **Interrupt dabrafenib** • Continue trametinib and/or panitumumab Once pyrexia resolves to baseline, restart dabrafenib **reduced by one dose level[h]** If dabrafenib must be reduced to <~~75mg~~ 50mg BID, permanently **discontinue dabrafenib. Trametinib may be continued.**

i. Pyrexia is defined as a body temperature equal to or above 38.5 °Celsius or 101.3° Fahrenheit.
j. For subjects experiencing pyrexia complicated by rigors, severe chills, etc., a clinical evaluation and laboratory work-up is mandatory for each event; anti-pyretic treatment should be started immediately at the first occurrence and prophylactic anti-pyretic treatment is recommended
k. Thorough clinical examination for signs and symptoms of infection or hypersensitivity is required; laboratory workup should include full-blood-count, electrolytes, creatinine, blood urea nitrogen (BUN), C-reactive protein (CRP), liver-function tests, blood culture, and urine culture.
l. Oral hydration should be encouraged in subjects without evidence of dehydration. Intravenous hydration is recommended in subjects experiencing pyrexia complicated by dehydration/hypotension.
~~m. Blood sample for cytokine analysis must be sent to the central laboratory~~
n. 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
~~o. In subject experiencing pyrexia complicated by rigors, severe chills, etc., which cannot be controlled with antipyretic medication, oral corticosteroids should be started at the 2nd event and doses should be gradually increased for subsequent events.~~
~~p. 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.~~

RATIONALE: Clarification of safety management guidelines based on revisions to accepted asset-specific text

Section 3.9.4.2.1 Rash Prophylaxis and Supportive Care

PREVIOUS TEXT

Acneiform rash. The need for oral or topical antibiotics (e.g., clindamycin cream, minocycline, doxycycline, etc) and higher strength topical steroids is a clinical decision of the investigator. Oral or topical retinoids are not recommended. Consider the algorithm provided in Table 11 for management of acneiform rash.

REVISED TEXT

Acneiform rash. The need for oral or topical antibiotics (e.g., clindamycin cream, minocycline, doxycycline, etc) and higher strength topical steroids is a clinical decision of the investigator. Prophylactic use of skin emollients, sunscreen, oral doxycycline and topical steroids was demonstrated to be more effective than reactive use of the same agents after rash developed [Lacouture 2010]. Oral or topical retinoids are not recommended. Consider the algorithm provided in Table 11 for management of acneiform rash.

Table 11 Acneiform Rash Management Guidelines

PREVIOUS TEXT

Step	Rash grading	Rash severity	Management of Rash	Dose Modification for Trametinib and Panitumumab[a]
1	Mild	Locallized Minimally symptomatic No impact on activities of daily living (ADL) No sign of superinfection	Initiate prophylactic regimen, including oral antibiotics, if not already started (see Section 3.9.4.2.1). Consider using moderate strength topical steroids[a]	Continue current doses. Reassess after 2 weeks; if rash worsens or does not improve, proceed to Step 2.
2	Moderate	Generalized Mild symptoms (e.g., pruritus, tenderness) Minimal impact on ADL No sign of superinfection	Initiate prophylactic regimen, including oral antibiotics, if not already started (see Section 3.9.4.2.1), using moderate strength topical steroids[a]	Reduce panitumumab dose by 50% or consider interrupting panitumumab until resolution of toxicity to Grade 1. If applicable, reduce trametinib by one dose level or consider interrupting trametinib until resolution of toxicity to Grade 1. If toxicity resolves, then can consider re-escalation to initial dose level. Reassess after 2 weeks; if rash worsens or does not improve, proceed to Step 3.
≥3	Severe	Generalized Severe symptoms (e.g., pruritus, tenderness) Significant impact on ADL Sign of or potential for superinfection	Initiate prophylactic regimen, including oral antibiotics, if not already started, using moderate strength topical steroids[b] plus methylprednisone dose pack (see Section 3.9.4.2.1). Consider obtaining dermatology consultation. Manage rash per	Interrupt panitumumab and trametinib until rash improves (moderate or mild), or resolves. If rash worsens or does not improve after 2 weeks, permanently discontinue panitumumab and trametinib. If rash does improve/resolve, restart panitumumab ONLY at full. 1. If panitumumab is tolerated for two weeks, consider

Step	Rash grading	Rash severity	Management of Rash	Dose Modification for Trametinib and Panitumumab[a]
			dermatologist's recommendation.	restarting trametinib at a lower dose level. 2. If it is not tolerated, hold panitumumab until resolution and restart at 50% of the previous dose. If the lower dose is tolerated, consider restarting trametinib at a lower dose level.

REVISED TEXT

Step	Rash grading	Rash severity	Management of Rash	Dose Modification for Trametinib and Panitumumab[a]
1	Mild	Localized Minimally symptomatic No impact on activities of daily living (ADL) No sign of superinfection	Initiate prophylactic regimen, including oral antibiotics, if not already started (see Section 3.9.4.2.1). Consider using moderate strength topical steroids[a]	Continue current doses. Reassess after 2 weeks; if rash worsens or does not improve, proceed to Step 2.
2	Moderate	Generalized Mild symptoms (e.g., pruritus, tenderness) Minimal impact on ADL No sign of superinfection	Initiate prophylactic regimen, including oral antibiotics, if not already started (see Section 3.9.4.2.1), using moderate strength topical steroids[a]	Reduce panitumumab dose by 50% or consider interrupting panitumumab until resolution of toxicity to Grade 1. If applicable, reduce trametinib by one dose level or consider interrupting trametinib until resolution of toxicity to Grade 1. If toxicity resolves, then can consider re-escalation to initial dose level. Reassess after 2 weeks; if rash worsens or does not improve, proceed to Step 3.
≥3	Severe	Generalized Severe symptoms (e.g., pruritus, tenderness) Significant impact on ADL Sign of or potential for superinfection	Initiate prophylactic regimen, including oral antibiotics, if not already started, using moderate strength topical steroids[b] plus methylprednisone dose pack (see Section 3.9.4.2.1). Consider obtaining	Interrupt panitumumab and trametinib until rash improves (moderate or mild), or resolves. If rash worsens or does not improve after 2 weeks, permanently discontinue panitumumab and trametinib. If rash does improve/resolve, restart trametinib and panitumumab ~~ONLY at full~~, each

Step	Rash grading	Rash severity	Management of Rash	Dose Modification for Trametinib and Panitumumab[a]
			dermatology consultation. Manage rash per dermatologist's recommendation.	reduced by a single dose level. 1. If ~~panitumumab~~ the combination is tolerated for two weeks, consider ~~restarting trametinib at a lower~~ dose escalating one or both agents to the prior dose level. 2. If it is not tolerated, hold ~~panitumumab~~ both agents until resolution to Gr1 and then restart ~~at 50% of the previous dose. If the lower dose is tolerated, consider restarting trametinib at a lower~~ both agents, each reduced by another dose level.

RATIONALE: Clarification of safety management guidelines based on revisions to accepted asset-specific text

Table 15 Management and Dose Modification Guidelines for Renal Insufficiency

PREVIOUS TEXT

Creatinine	Adverse Event Management	Action and Dose Modifcation
For subjects with serum creatinine increase >0.2 mg/dL (18 μmol/L) but ≤0.5 mg/dL (44 μmol/L) above baseline:	• Re-check serum creatinine within 1 week • If serum creatinine increases > 1 week, contact GSK Medical Monitor • If subject has fever (≥38.5°C), treat pyrexia as per guidelines[a]	Continue study treatment at the same dose level.
For subjects with serum creatinine rise>0.5 mg/dL (44 μmol/L) above baseline or serum creatinine >2 mg/dL (> 177	• Follow serum creatinine at least twice weekly • Consider hospitalization if serum creatinine cannot be monitored frequently • If subject has fever (≥38.5°C), treat pyrexia	• Interrupt study treatment(s)[c] until serum creatinine recovers to baseline. • Restart wtih study treatment[b] at either the same or a reduced dose

Creatinine	Adverse Event Management	Action and Dose Modifcation
μmol/L)	as per guidelines[a] • Consult nephrologist if clinically indicated • Perform renal biopsy if clinically indicated, for example: • Renal insufficiency persists despite volume repletion • Subject has new rash or signs of hypersensitivity (such as elevated eosinophil count)	level

REVISED TEXT

Creatinine	Adverse Event Management	Action and Dose Modifcation
For subjects with serum creatinine increase >0.2 mg/dL (18 μmol/L) but ≤0.5 mg/dL (44 μmol/L) above baseline:	• Re-check serum creatinine within 1 week • If serum creatinine increases > 1 week, contact GSK Medical Monitor • If ~~subject has fever (≥38.5°C)~~:pyrexia is present, treat pyrexia as per guidelines[a]	Continue study treatment at the same dose level.
For subjects with serum creatinine ~~rise~~ increase >0.5 mg/dL (44 μmol/L) above baseline or serum creatinine >2 mg/dL (> 177 μmol/L)	• Follow serum creatinine at least twice weekly • Consider hospitalization if serum creatinine cannot be monitored frequently • If ~~subject has fever (≥38.5°C)~~:pyrexia is present, treat pyrexia as per guidelines[a] • Consult nephrologist if clinically indicated • Perform renal biopsy if clinically indicated, for example: • Renal insufficiency persists despite volume repletion • Subject has new	• Interrupt study treatment(s)[c] until serum creatinine recovers to baseline. • Restart wtih study treatment[b] at either the same or a reduced dose level

Creatinine	Adverse Event Management	Action and Dose Modifcation
	rash or signs of hypersensitivity (such as elevated eosinophil count)	

RATIONALE: Clarification of safety management guidelines based on revisions to accepted asset-specific text

Section 3.9.7 Guidelines for Cardiovascular Adverse Events

PREVIOUS TEXT

Cardiovascular adverse events have been observed in subjects receiving either dabrafenib, trametinib, or the two drugs in combination. Additional information is available in the IBs: GSK2118436 IB [GlaxoSmithKline Document Number 2012N136095_00], the GSK1120212 IB [GlaxoSmithKline Document Number HM2009/00151/03] and the GSK1120212 + GSK2118436 Clinical IB [GlaxoSmithKline Document Number, 2011N126811_00].

REVISED TEXT

Cardiovascular adverse events have been observed in subjects receiving either dabrafenib, trametinib, or the two drugs in combination. Additional information is available in the IBs: GSK2118436 IB [GlaxoSmithKline Document Number 2012N136095_00], the GSK1120212 IB [GlaxoSmithKline Document Number HM2009/00151/03] and the GSK1120212 + GSK2118436 Clinical IB [GlaxoSmithKline Document Number, 2011N126811_00]. Guidelines for LVEF decreases, hypertension and prolonged QTc are provided in Section 3.9.7.1, Section 3.9.8 and Section 3.9.9, respectively.

Section 3.9.7.1 Left Ventricular Ejection Fraction (LVEF) Decreases

PREVIOUS TEXT

Section 3.9.7.1 Left Ventricular Ejection Fraction (LVEF) Decreases

Cardiac ejection fraction function assessments (ECHO or MUGA; ECHO is preferred) must be performed at Screening and at the post-treatment follow-up visit as outlined in the Time and Events Tables (Section 3.8). All assessments for an individual patient must be performed in the same modality (i.e., ECHO or MUGA), and preferably, by the same institution/operator, in order to reduce variability. Decreases of the left ventricular ejection fraction (LVEF) have been observed in subjects receiving trametinib monotherapy and in combination with dabrafenib. Therefore, cardiac ejection fraction must be assessed at regular intervals as outlined in the Time and Events Table (Section 3.8). Copies of all LVEF assessments and cardiology consultations performed on subjects who experience a >10% decrease in LVEF from baseline and whose cardiac ejection fraction is <institution's LLN will be required by GSK for review. Instructions

for submitting qualifying ECHOs/ MUGAs are provided in the Study Procedures Manual (SPM).

Dose modification guidance and stopping criteria for LVEF decrease are provided in Table 16. Additional guidelines for subjects enrolled at sites in France are provided in Appendix 5.

REVISED TEXT

Section 3.9.7.1 Left Ventricular Ejection Fraction (LVEF) ~~Decreases~~

~~Cardiac ejection fraction function assessments (ECHO or MUGA; ECHO is preferred) must be performed at Screening and at the post-treatment follow-up visit as outlined in the Time and Events Tables (Section~~ Decreases of the left-ventricular-ejection~~- Decreases of the left-ventricular ejection~~ fraction (LVEF) have been observed in subjects receiving trametinib monotherapy and in combination with dabrafenib. Therefore, ECHO/MUGAs must be performed to assess cardiac ejection fraction ~~must be assessed at~~ in regular intervals as outlined in the Time and Events Table (Section 3.10). All assessments for an individual patient must be peformed with the same modality (*i.e.,* ECHO or MUGA) and, preferably, by the same institution/operator, in order to reduce variability. Copies of all LVEF assessments and cardiology consultations performed on subjects who experience a >10% decrease in LVEF from baseline and whose cardiac ejection fraction is <institution's LLN will be required by GSK for review. Instructions for submitting qualifying ECHOs/ MUGAs are provided in the Study Procedures Manual (SPM).

Dose modification guidance and stopping criteria for LVEF decrease are provided in Table 16. Additional guidelines for subjects enrolled at sites in France are provided in Appendix 5.

Table 16 Dose Modification Guidelines and Stopping Criteria for LVEF Decrease

PREVIOUS TEXT

Clinic Presentation	LVEF decrease (%) or CTCAE grade	Action and Dose Modificationd
Asymptomatic	Absolute decrease of >10% in LVEF compared to baseline and ejection fraction below the institutional LLN	Interrupt study treatment with dabrafenib and trametinib and repeat ECHO/MUGA within 2 weeks[a] IF 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 trametinib reduced by one dose level • Restart dabrafenib at previous dose level • Repeat ECHO/MUGA at 2, 4, 8, and 12 weeks after re-start; continue in 12 week intervals thereafter

Clinic Presentation	LVEF decrease (%) or CTCAE grade	Action and Dose Modificationd
		If LVEF **does not recover** within 4 weeks: **e.** Consult with cardiologist **f.** **Permanently discontinue dabrafenib and trametinib** **g.** Repeat ECHO/MUGA after 2, 4, 8, 12 and 16 weeks or until resolution **h.** Consult with GSK Medical Monitor[d]
Symptomatic[c]	Grade 3: resting LVEF 39-20% or >20% absolute reduction from baseline	Permanently discontinue study treatment with dabrafenib and trametinib Consult with cardiologist Repeat ECHO/MUGA after 2, 4, 8, 12 and 16 weeks or until resolution.
	Grade 4: resting LVEF <20%	

a. If ECHO/MUGA does not show LVEF recovery after 2 weeks, repeat ECHO/MUGA 2 weeks later.
b. Symptoms may include: dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema.
c. Once LVEF recovers to baseline, restarting dabrafenib monotherapy may be considered in consultation with the GSK Medical Monitor.

REVISED TEXT

Clinic Presentation	LVEF decrease (%) or CTCAE grade	Action and Dose Modificationd
Asymptomatic	Absolute decrease of >10% in LVEF compared to baseline and ejection fraction below the institutional LLN	Interrupt study treatment with dabrafenib and trametinib and repeat ECHO/MUGA within 2 weeks[a] IF 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 trametinib reduced by one dose level[b] • Restart dabrafenib at previous dose level • Repeat ECHO/MUGA at 2, 4, 8, and 12 weeks after re-start; continue in 12 week intervals thereafter If LVEF **does not recover** within 4 weeks: **i.** Consult with cardiologist **j.** **Permanently discontinue dabrafenib and trametinib** **k.** **Report as SAE** **l.** Repeat ECHO/MUGA after 2, 4, 8, 12 and 16 weeks or until resolution **m.** Consult with GSK Medical Monitor[d]
Symptomatic[c]	Grade 3: resting LVEF 39-20% or >20% absolute reduction from baseline	Permanently discontinue study treatment with dabrafenib and trametinib **Report as SAE** Consult with cardiologist Repeat ECHO/MUGA 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/MUGA does not show LVEF recovery after 2 weeks, repeat ECHO/MUGA 2 weeks later.
b. Escalation of trametinib to previous dose level can be considered if LVEF remains stable for 4 weeks after restarting of trametinib. Approval from GSK Medical Monitor is required
c. Symptoms may include: dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema.
d. Once LVEF recovers to baseline, restarting dabrafenib monotherapy may be considered in consultation with the GSK Medical Monitor.

RATIONALE: Clarification of safety management guidelines based on revisions to accepted asset-specific text

Section 3.9.8.1 Monitoring of Hypertension

PREVIOUS TEXT

All blood pressure measurements should be performed under optimal conditions, ie after:

- subject has been seated with back support, ensuring that legs are uncrossed and both feet are flat on the floor,
- subject has relaxed comfortably for at least 5 minutes prior to measurements,
- preparatory steps, such as removal of restrictive clothing over the cuff area and selection of the appropriate cuff size has been ensured,
- the arm is supported so that the middle of the cuff is at heart level, and
- the subject remains quiet and still during the measurement.

In subjects with an initial blood pressure reading within the hypertensive range, a second reading should be taken at least 1 minute after the initial reading, with the average of the 2 readings averaged to obtain a final blood pressure measurement. The averaged value should be recorded in the electronic Case Report Form (eCRF).

Persistent hypertension is defined as an increase of systolic blood pressure (SBP) to >140mm Hg and / or diastolic blood pressure (DBP) to >90mm Hg in up to 3 subsequent visits with blood pressure assessments from 2 readings under the optimal conditions described above. Visits to monitor increased blood pressure should be scheduled independently from the per-protocol visits outlined in the Time and Events Table (Section 3.8). Ideally, subsequent blood pressure assessments should be performed within 1 week.

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

REVISED TEXT

All blood pressure measurements should be performed under the following optimal conditions~~, ie after~~:

- subject has been seated with back support, ensuring that legs are uncrossed and both feet are flat on the floor,
- subject has relaxed comfortably for at least 5 minutes prior to measurements,
- preparatory steps, such as removal of restrictive clothing over the cuff area and selection of the appropriate cuff size has been ensured,
- the arm is supported so that the middle of the cuff is at heart level, and
- the subject remains quiet and still during the measurement.

In subjects with an initial blood pressure reading within the hypertensive range, a second reading should be taken at least 1 minute after the initial reading, with the average of the 2 readings averaged to obtain a final blood pressure measurement. The averaged value should be recorded in the electronic Case Report Form (eCRF).

Persistent hypertension is defined as an increase of systolic blood pressure (SBP) to >140mm Hg and / or diastolic blood pressure (DBP) to >90mm Hg in up to 3 ~~subsequent~~consecutive visits with blood pressure assessments from 2 readings under the optimal conditions described above. Visits to monitor increased blood pressure ~~should~~can be scheduled independently from the per-protocol visits outlined in the Time and Events Table (Section 3.8). Ideally, subsequent blood pressure assessments should be performed within 1 week.

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

Table 17 Guidelines for Management of Hypertension

PREVIOUS TEXT

Hypertension	Action and Dose Modification
Scenario A: Asymptomatic and persistent[a] SBP ≥140mm Hg and <160mm Hg, or DBP ≥90mm Hg and <100mm Hg, or a clinically significant increase in DBP of 20mm Hg, with an overall reading <100mm Hg	Step 1: Continue study treatments at the current dose. Step 2: Adjust current or initiate new antihypertensive medication(s). Step 3: Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled[b] blood pressure. If BP is not well-controlled within 2 weeks, consider referral to a specialist and follow steps outlined for Scenario B.
Scenario B:	

Hypertension	Action and Dose Modification
Asymptomatic SPB ≥160mm Hg, or DBP ≥100mm Hg, or failure to achieve well-controlled BP within 2 weeks in Scenario A	Step 1: Interrupting study treatment(s)[d], if clinically indicated. Step 2: Adjust current or initiate new antihypertensive medication(s). Step 3: Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. Step 4: Once blood pressure (BP) is well-controlled, restart study treatment(s)[df] with **one dose level reduction**.
Scenario C: Symptomatic hypertension or recurring[c] SBP ≥160mm Hg, or DBP ≥100mm Hg, despite modification of antihypertensive medication(s)	Step 1: Interrupt study treatment(s)[df] Step 2: Adjust current or initiate new antihypertensive medication(s). Step 3: Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. Referral to a specialist for further evaluation and follow-up is also recommended. Step 4: Once BP is well-controlled, restart study treatment(s)[df] with **one dose level reduction**.
Scenario D: Refractory hypertension unresponsive to above interventions	Discontinue administration of study treatment(s)[d] and continue[f] follow-up per protocol.

a. Hypertension detected in two separate readings during up to three subsequent visits.
b. Blood pressure of SBP < 140 mm Hg and DBP < 90 mm Hg in two separate readings during up to three subsequent visits.
c. Persistent asymptomatic hypertension after initially successful anti-hypertensive intervention.
d. Modification to study treatment(s) should be discussed with the GSK Medical Monitor.

REVISED TEXT

Hypertension	Action and Dose Modification
Scenario A: Asymptomatic and ~~persistent~~ [a]persistent[a] SBP ≥140mm Hg and <160mm Hg, or DBP ≥90mm Hg and <100mm Hg, or a clinically significant increase in DBP of 20mm Hg~~, with an overall reading <100mm Hg~~(but DBP still <100 mmHg).	Step 1: Continue study treatments at the current dose. Step 2: Adjust current or initiate new antihypertensive medication(s). Step 3: Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled[b] blood pressure. If BP is not well-controlled within 2 weeks, consider referral to a specialist and follow steps outlined for Scenario B.
Scenario B: Asymptomatic SPB ≥160mm Hg, or DBP ≥100mm Hg, or failure to achieve well-controlled BP within 2 weeks in	Step 1: Interrupting study treatment(s)[d], if clinically indicated. Step 2: Adjust current or initiate new antihypertensive medication(s). Step 3: Titrate antihypertensive medication(s) during next

Hypertension	Action and Dose Modification
Scenario A	2 weeks as indicated to achieve well-controlled BP. Step 4: Once blood pressure (BP) is well-~~controlled~~controlled[b], restart study treatment(s)[df] with **one dose level reduction**.
Scenario C: Symptomatic hypertension or ~~recurring~~[c] Persistent[e] SBP ≥160mm Hg, or DBP ≥100mm Hg, despite modification of antihypertensive medication(s) and dose reduction of trametinib	Step 1: Interrupt study treatment(s)[df] Step 2: Adjust current or initiate new antihypertensive medication(s). Step 3: Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. Referral to a specialist for further evaluation and follow-up is also recommended. Step 4: Once BP is well-~~controlled~~controlled[b], restart study treatment(s)[df] with **one dose level reduction**.
Scenario D: Refractory hypertension unresponsive to above interventions, or having hypertensive crisis	Discontinue administration of study treatment(s)[d] ~~and continue~~[f] 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 subsequent visits.
b. Blood pressure of SBP ~~<~~ ≤140 mm Hg and DBP ~~<~~≤ 90 mm Hg in two separate readings during up to three ~~subsequent~~consecutive visits.
c. Escalation of trametinib to previous dose level can be considered if BPs remain well-controlled for 4 weeks after restarting of trametinib. Approval from GSK Medical Monitor is required.
d. 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
e. Persistent asymptomatic hypertension after initially successful anti-hypertensive intervention.
f. Modification to study treatment(s) should be discussed with the GSK Medical Monitor.

RATIONALE: Clarification of safety management guidelines based on revisions to accepted asset-specific text

Section 3.9.9 Guidelines for Prolonged QTc

PREVIOUS TEXT

Guidelines for dose modification and stopping criteria due to QTc prolongation are provided in Table 18.

Table 18 Withholding and Stopping Criteria for QTc Prolongation

QTc Prolongation[a]	Action and Dose Modification
QTcB≥501msec	• Interrupt study treatment until QTcB prolongation resolves to Grade 1 or baseline • Test serum potassium, calcium, phosphorus and magnesium. If <LLN, correct with supplements to within normal limits. • Review concomitant medication usage for a prolonged QTc. • If event resolves, restart study treatment at current dose level[b] • **If event does not resolve, permanently discontinue study treatments.** • **If event recurs, permanently discontinue study treatments**

REVISED TEXT

Guidelines for dose modification and stopping criteria due to QTc prolongation are provided in Table 18. For subjects enrolled in France, please refer to Appendix 5 for QTc prolongation withholding and stopping criteria.

Table 18 Withholding and Stopping Criteria for QTc Prolongation

QTc Prolongation[a]	Action and Dose Modification
QTcB≥501msec or uncorrected QT>600msec or QTcB>530msec for subjects with bundle branch block	• Interrupt study treatment until QTcB prolongation resolves to Grade 1 or baseline • Test serum potassium, calcium, phosphorus and magnesium. If ~~<LLN~~ abnormal, correct ~~with supplements~~ per routine clinical practice to within normal limits. • Review concomitant medication usage for a prolonged QTc. • ~~If event resolves, restart~~ Restart study treatment at current dose level[b] • **If event does not resolve, permanently discontinue study treatments. Consider evaluation with cardiologist.** • **If event recurs, permanently discontinue study treatments**

RATIONALE: Clarification of safety management guidelines based on revisions to accepted asset-specific text

Section 3.9.11 Guidelines for Visual Changes or Specified Ophthalmic Examination Findings

PREVIOUS TEXT

Section 3.9.11 Visual Changes Stopping Criteria

Episodes of visual changes have been observed in subjects 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 and an ophthalmologist should be consulted. Special attention should be given to retinal (e.g., RPED) 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 19.

Table 19 Management and Dose Modification Guidelines for Visual Changes

CTCAE Grade[a]	Adverse Event Management	Action and Dose Modification
Grade 1 Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.	• Consult ophthalmologist within 7 days of onset • Exclude RPED or RVO • Consult retinal specialist in case of RPED or RVO • Report RPED and RVO as SAE • Continue follow up examination(s) by retinal specialist for RPED and RVO	• Continue study treatment at the same dose level until ophthalmic examination can be conducted[b] • If ophthalmic 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 • <u>If RPED is diagnosed:</u> Interrupt study treatment until symptoms resolve and exam by retinal specialist shows resolution. • Restart with study treatment reduced by one dose level • <u>If RVO is diagnosed:</u> **Permanently discontinue study treatment**

CTCAE Grade[a]	Adverse Event Management	Action and Dose Modification
Grade 2 Moderate, minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL. and Grade 3 Severe or medically significant but not immediately sight-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL	• Consult ophthalmologist immediately • Exclude RPED and RVO • Consult retinal specialist in case of RVO or RPED for follow-up exam • Report RPED and RVO as SAE • Continue follow up examination(s) by retinal specialist for RPED and RVO	• Interrupt study treatment until signs and symptoms have resolved to baseline • Restart with study treatment reduced by one dose level • <u>If RPED is diagnosed:</u> Interrupt study treatment until symptoms resolve and exam by retinal specialist shows resolution. • Restart study treatment **reduced by one dose level** • <u>If RVO is diagnosed:</u> **Permanently discontinue study treatment**
Grade 4 Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye.	• Consult ophthalmologist immediately • Exclude RPED and RVO • Report RPED and RVO as SAE • Continue follow up examination(s) by retinal specialist for RPED and RVO	• **Permanently discontinue study treatment**

Abbreviations: RPED = Retinal pigment epithelium detachment; 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.

For all visual changes, regardless of grade, a blood sample for pharmacokinetic analysis must be drawn as close as possible to the time of onset of the event.

REVISED TEXT

Section 3.9.11 ~~Visual Changes Stopping Criteria~~ Guidelines for Visual Changes or Specified Ophthalmic Examination Findings

Episodes of visual changes have been observed in subjects receiving <u>trametinib,</u> dabrafenib~~, trametinib or the~~ <u>and</u> combination ~~of both therapies. The causal relationship between a change in vision and the study treatment should be carefully explored and an~~<u>therapy. An</u> ophthalmologist should be consulted <u>if changes in vision develop. However, if the visual changes are clearly unrelated to study treatment (e.g., allergic</u>

conjunctivitis), then monitor closely as it may be reasonable to defer ophthalmic examination.

Treatment with dabrafenib has been associated with the development of uveitis, including iritis. Monitor patients for visual signs and symptoms (such as, change in vision, photophobia and eye pain) during therapy. Special attention should be given to retinal ~~(e.g.,~~ findings (e.g., retinal pigment epithelial detachment (RPED) or ~~retinal vein~~ retinovascular abnormalities (~~e.g.,~~ i.e., branch or central retinal vein occlusions (RVO).

For events of visual changes (regardless of severity) for which an ophthalmic examination is conducted, a blood sample for PK analysis must be drawn as close as possible to the time of the event.

Guidelines regarding management and dose reduction for visual changes considered to be related to study treatment are provided in Table 19.

Table 19 Management and Dose Modification Guidelines for Visual Changes and/or Ophthalmic Examination Findings

CTCAE Grade[a]	Adverse Event Management	Action and Dose Modification
Grade 1 ~~Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated~~..	• Consult ophthalmologist within 7 days of onset • ~~Exclude RPED or RVO~~ • ~~Consult retinal specialist in case of RPED or RVO~~ • ~~Report RPED and RVO as SAE~~ • ~~Continue follow up examination(s) by retinal specialist for RPED and RVO~~	• ~~Continue study treatment at the same dose level until ophthalmic examination can be conducted[b]~~ • If ~~ophthalmic~~ dilated fundus examination cannot be performed within 7 days of onset, interrupt study treatment until ~~CSR~~ RPED and RVO can be excluded by retinal specialist / ophthalmologist • if RPED and ~~symptoms resolve.~~ • ~~Restart study treatment~~ RVO excluded, continue (or restart) trametinib at same dose level • If RPED is suspected or diagnosed: see RPED dose modification Table 20 ~~Interrupt study treatment until symptoms resolve and exam by retinal specialist shows resolution.~~ • ~~Restart with study treatment reduced by one dose level~~ • ~~If RVO is~~ below; **report as SAE if diagnosed.** • If RVO diagnosed, **Permanently discontinue ~~study treatment~~ trametinib and report as SAE.**

CTCAE Grade[a]	Adverse Event Management	Action and Dose Modification
Grade 2 ~~Moderate, minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.~~ and Grade 3 ~~Severe or medically significant but not immediately sight-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL~~	• Consult ophthalmologist immediately • Exclude RPED and RVO • Consult retinal specialist in case of RVO or RPED for follow-up exam • Report RPED and RVO as SAE Continue follow up examination(s) by retinal specialist for RPED and RVO • Interrupt trametinib. If subject is receiving trametinib/dabrafenib combination therapy, dabrafenib may be discontinued.	• ~~Interrupt study treatment until signs~~ If RPED and ~~symptoms have resolved to baseline~~ • ~~Restart with study treatment reduced by one~~ RVO excluded, restart trametinib at same dose level • If RPED diagnosed: see RPED dose modification Table 20 ~~is diagnosed: Interrupt study treatment until symptoms resolve and exam by retinal specialist shows resolution~~ below; **report as SAE**. • ~~Restart study treatment **reduced by one dose level**~~ • If RVO is diagnosed: **Permanently discontinue ~~study treatment~~ trametinib and report as SAE**
Grade 4 ~~Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye.~~	• Consult ophthalmologist immediately • ~~Exclude RPED and RVO~~ • ~~Report RPED and RVO as SAE~~ • ~~Continue follow up examination(s) by retinal specialist for RPED and RVO~~ Interrupt trametinib. . If subject is receiving trametinib/dabrafenib combination therapy, dabrafenib may be discontinued.	• **~~Permanently~~** If RPED and RVO excluded, may consider restarting trametinib at same or reduced dose after discussion with study medical monitor • **If RVO or RPED diagnosed, permanently discontinue study treatment**

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

c. Refers to CTCAE Version 4.0 'Eye disorders – Other, specify
d. If visual changes are clearly unrelated to study treatment (e.g., allergic conjunctivitis), monitor closely but ophthalmic examination is not required.

~~For all visual changes, regardless of grade, a blood sample for pharmacokinetic analysis must be drawn as close as possible to the time of onset of the event~~.

Table 20 Recommended dose modifications for trametinib for retinal pigment epithelial detachments (RPED)[a]

CTCAE Grade	Action and Dose Modification
Grade 1 RPED (Asymptomatic; clinical or diagnostic observations only)	• Continue treatment with retinal evaluation monthly until resolution. If RPED worsens follow instructions below
Grade 2-3 RPED (Symptomatic with mild to moderate decrease in visual acuity; limiting instrumental ADL)	• Interrupt trametinib • Retinal evaluation monthly • If improved to ≤ Grade 1, restart trametinib at lower dose (reduced by 0.5 mg) or discontinue in patients taking trametinib 1 mg daily

a. Refers to CTCAE Version 4.0 'Retinopathy'

RATIONALE: Clarification of safety management guidelines based on revisions to accepted asset-specific text

Table 21 Management and Dose Modification Guidelines for Pneumonitis/ILD

PREVIOUS TEXT

CTCAE Grade	Adverse Event Management	Action and Dose Modification
Grade 1	CT scan (high-resolution with lung windows) is recommended. Clinical evaluation and laboratory work-up for infection should be performed. Monitoring of oxygenation via pulse-oximetry is recommended. Consultation by a pulmonologist is recommended.	Continue dabrafenib and trametinib at current dose. Permanently discontinue panitumumab.
Grade 2	CT scan (high-resolution with lung windows) is recommended. Clinical evaluation and laboratory work-up for infection should be performed. Consult a pulmonologist. Pulmonary function testing should be performed; if < normal, repeat every 8 weeks until results are normal. Bronchoscopy with biopsy and/or	Interrupt dabrafenib and trametinib until recovery to ≤Grade 1. Permanently discontinue panitumumab. Restart dabrafenib and trametinib, **reduced by one dose level**. Escalation to previous dose level after 4 weeks and after consultation with the GSK Medical Monitor If symptoms do not recover to ≤Grade 1

CTCAE Grade	Adverse Event Management	Action and Dose Modification
	bronchalveolar lavage (BAL) is recommended. Symptomatic therapy including corticosteroids is recommended if clinically indicated.	within 4 weeks, **permanently discontinue dabrafenib and trametinib**.
Grade 3	CT scan (high-resolution with lung windows) should be performed. Clinical evaluation and laboratory work-up for infection should be performed. Consult a pulmonologist. Pulmonary function testing should be performed; if < normal, repeat every 8 weeks until results are normal. Bronchoscopy with biopsy and/or BAL if possible. Symptomatic therapy including corticosteroids is recommended if clinically indicated.	Interrupt dabrafenib and trametinib until recovery to ≤Grade 1. Permanently discontinue panitumumab. After consultation with GSK Medical Monitor, dabrafenib and trametinib may be restarted with a one dose level reduction. If symptoms do not recover to ≤Grade 1 within 4 weeks, **permanently discontinue dabrafenibtrametinib**
Grade 4	CT scan (high-resolution with lung windows) should be performed. Clinical evaluation and laboratory work-up for infection should be performed. Consult a pulmonologist. Pulmonary function testing should be performed; if < normal, repeat every 8 weeks until results are normal. Bronchoscopy with biopsy and/or BAL if possible. Symptomatic therapy including corticosteroids is recommended if clinically indicated.	Permanently discontinue dabrafenib, panitumumab and trametinib

REVISED TEXT

CTCAE Grade	Adverse Event Management	Action and Dose Modification
Grade 1	CT scan (high-resolution with lung windows) is recommended. Clinical evaluation and laboratory work-up for infection should be performed. Monitoring of oxygenation via pulse-oximetry is recommended. Consultation by a pulmonologist is recommended.	Continue dabrafenib and trametinib at current dose. Permanently discontinue panitumumab.
Grade 2	CT scan (high-resolution with lung windows) is recommended. Clinical evaluation and laboratory work-up for infection should be performed. Consult a pulmonologist. Pulmonary function testing should be performed; if < normal, repeat every 8 weeks until results are normal. Bronchoscopy with biopsy and/or bronchalveolar lavage (BAL) is recommended. Symptomatic therapy including corticosteroids is recommended if clinically indicated.	Interrupt dabrafenib and trametinib until recovery to ≤Grade 1. Permanently discontinue panitumumab. Restart dabrafenib and trametinib, **reduced by one dose level**. Escalation to previous dose level after 4 weeks and after consultation with the GSK Medical Monitor If symptoms do not recover to ≤Grade 1 within 4 weeks, **permanently discontinue dabrafenib and trametinib**.
Grade 3	CT scan (high-resolution with lung windows) should be performed. Clinical evaluation and laboratory work-up for infection should be performed. Consult a pulmonologist. Pulmonary function testing should be performed; if < normal, repeat every 8 weeks until results are normal. Bronchoscopy with biopsy and/or BAL if possible. Symptomatic therapy including corticosteroids is recommended if clinically indicated.	Interrupt dabrafenib and trametinib until recovery to ≤Grade 1. Permanently discontinue panitumumab. After consultation with GSK Medical Monitor, dabrafenib and trametinib may be restarted with a one dose level reduction. If symptoms do not recover to ≤Grade 1 within 4 weeks, **permanently discontinue dabrafenibtrametinib**
Grade 4	~~CT scan (high-resolution with lung windows) should be performed.~~ ~~Clinical evaluation and laboratory work-up for infection should be performed.~~	Permanently discontinue dabrafenib, panitumumab and trametinib

CTCAE Grade	Adverse Event Management	Action and Dose Modification
	~~Consult a pulmonologist.~~ ~~Pulmonary function testing should be performed; if < normal, repeat every 8 weeks until results are normal.~~ ~~Bronchoscopy with biopsy and/or BAL if possible.~~ ~~Symptomatic therapy including corticosteroids is recommended if clinically indicated.~~Same as Grade 3.	

RATIONALE: Clarification of safety management guidelines based on revisions to accepted asset-specific text

Section 3.10.1 Part 1 Dose Escalation Time and Events Table

PREVIOUS TEXT

Hematology/Clinical Chemistry (including Screening assessment of adequate baseline organ function as noted in Table 18)

Footnote 1: All screening assessments must be completed within 14 days prior to first dose except informed consent, ophthalmology exam, ECHO/MUGA and Disease Assessment, which can occur within 35 days prior to the first dose. Note: Procedures conducted as part of the subject's routine clinical management (e.g., blood counts, imaging study) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures meet the protocol requirements.

Footnote 14: Vital signs and temperature should be measured within 30 minutes prior to initiation and upon completion of the panitumumab infusion

REVISED TEXT

Hematology/Clinical Chemistry ~~(including Screening assessment of adequate baseline organ function as noted in Table 18)~~

Coagulation; Repeat as clinically indicated: at Screening

CEA: at Screening, Day 1, Day 15, Day 21, in Continuation Phase: At Week 4, then every 4 weeks until Week 24, then every 8 weeks, at Initial Follow-up and at Secondary Follow-up Visits

Footnote 1: All screening assessments must be completed within 14 days prior to first dose except informed consent, ophthalmology exam, dermatology exam, ECHO/MUGA and Disease Assessment, which can occur within 35 days prior to the first dose. Note: Procedures conducted as part of the subject's routine clinical management (e.g., blood

counts, imaging study) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures meet the protocol requirements.

Footnote 14: Vital signs and temperature should be measured within 30 minutes prior to initiation and upon completion of the panitumumab infusion (up to 15 minutes after the end of infusion).

RATIONALE: Clarification of previous assessments, addition of CEA collection timepoints

Section 3.10.2 Part 2 Expansion Cohorts Time and Events Table

PREVIOUS TEXT

Hematology/Clinical Chemistry (including Screening assessment of adequate baseline organ function as noted in Table 18)

Footnote 1: All screening assessments must be completed within 14 days prior to first dose except informed consent, ophthalmology exam, ECHO/MUGA and Disease Assessment, which can occur within 35 days prior to the first dose. Note: Procedures conducted as part of the subject's routine clinical management (e.g., blood counts, imaging study) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures meet the protocol requirements.

Footnote 14: Vital signs and temperature should be measured within 30 minutes prior to initiation and upon completion of the panitumumab infusion

REVISED TEXT

Hematology/Clinical Chemistry ~~(including Screening assessment of adequate baseline organ function as noted in Table 18)~~

Coagulation; Repeat as clinically indicated: at Screening

CEA: at Screening, Day 1, Day 15, in Continuation Phase: At Week 4, then every 4 weeks until Week 24, then every 8 weeks, at Initial Follow-up and at Secondary Follow-up Visits

[redacted]

Footnote 1: All screening assessments must be completed within 14 days prior to first dose except informed consent, ophthalmology exam, dermatology exam, ECHO/MUGA and Disease Assessment, which can occur within 35 days prior to the first dose. Note: Procedures conducted as part of the subject's routine clinical management (e.g., blood

counts, imaging study) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures meet the protocol requirements.

Footnote 14: Vital signs and temperature should be measured within 30 minutes prior to initiation and upon completion of the panitumumab infusion (up to 15 minutes after the end of infusion).

RATIONALE: Clarification of previous assessments, addition of CEA collection timepoints and collection of blood sample [redacted]

Section 3.10.3 Part 3 Randomized Phase 2 Time and Events Table

PREVIOUS TEXT

Hematology/Clinical Chemistry (including Screening assessment of adequate baseline organ function as noted in Table 18)

Footnote 1: All screening assessments must be completed within 14 days prior to first dose except informed consent, ophthalmology exam, ECHO/MUGA and Disease Assessment, which can occur within 35 days prior to the first dose. Note: Procedures conducted as part of the subject's routine clinical management (e.g., blood counts, imaging study) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures meet the protocol requirements.

Footnote 10: Vital signs and temperature should be measured within 30 minutes prior to initiation and upon completion of the panitumumab infusion

REVISED TEXT

Hematology/Clinical Chemistry ~~(including Screening assessment of adequate baseline organ function as noted in Table 18)~~

Coagulation; Repeat as clinically indicated: at Screening

CEA: at Screening, Day 1, Day 15, every 4 weeks, every 8 weeks, every 12 weeks and at Follow-up visit

[redacted]

Footnote 10: Vital signs and temperature should be measured within 30 minutes prior to initiation and upon completion of the panitumumab infusion (up to 15 minutes after the end of infusion).

RATIONALE: Clarification of previous assessments, addition of CEA collection timepoints and collection of blood sample for [redacted]

Section 3.10.4 Part 4 Dose Escalation and Cohort Expansion Time and Events Table, Added Section

Day:	Screening[1]	Screening[1]	First treatment period, Day 1 thru Day 28/end of Week 4			Continuation phase ≥ Day 29/start of Week 5[2]	Initial follow-up[3]	Secondary follow-up[3]	Tertiary follow-up[3]
Visit Window (relative to Day 1)	-35 to -1 days	-14 to -1 days	on Day 1	on Day 15 (± 2 days)	on Day 21 (± 2 days)		14 (±7) days from last dose of trametinib	4 weeks (±7 days) after the last dose of panitumumab	8 weeks (±7 days) after the last dose of panitumumab
Informed Consent	X								
Demographics		X							
Collection of archival tissue[12]	X								
Complete physical[5]	X						X		
Brief physical[5]			X	X		At Week 4, then every 4 wks			
Medical/medication/ drug/alcohol history		X	X[6]			X	X		
12-lead ECG[7]		X	X[6]	X	X	At Week 4, then every 4 weeks until Week 24, then every 8 weeks	X		
Vital signs[13] (including weight)		X	X	X	X	X	X		
Height		X							
Ophthalmic examination	X					At Week 4, then as symptomatically warranted			
ECOG		X	X[6]			At Week 4, then every 4 wks	X		
ECHO/MUGA[17]	X					At Week 4, then at Week 12, then every 12 weeks	X		

Day:	Screening[1]	Screening[1]	First treatment period, Day 1 thru Day 28/end of Week 4			Continuation phase ≥ Day 29/start of Week 5[2]	Initial follow-up[3]	Secondary follow-up[3]	Tertiary follow-up[3]
Visit Window (relative to Day 1)	-35 to -1 days	-14 to -1 days	on Day 1	on Day 15 (± 2 days)	on Day 21 (± 2 days)		14 (±7) days from last dose of trametinib	4 weeks (±7 days) after the last dose of panitumumab	8 weeks (±7 days) after the last dose of panitumumab
Serum or urine pregnancy test (β-hCG;women)[4]			X			Every 8 to 12 weeks [4]			
Hema/Chem/Urinalysis tests		X	X[6]			At Week 4, then every 4 weeks until Week 24, then every 8 weeks		X	X
Coagulation Repeat as clinically indicated	X								
CEA		X	X			At Week 4, then every 4 weeks until Week 24, then every 8 weeks		X	X
Tumor biopsy[15]	X (pre-dose)[15]			X[9] (to be collected from Day 15 to Day 18)			X[10] (at progression)		
[redacted]									

Day:	**Screening[1]**	**Screening[1]**	**First treatment period, Day 1 thru Day 28/end of Week 4**			**Continuation phase ≥ Day 29/start of Week 5[2]**	**Initial follow-up[3]**	**Secondary follow-up[3]**	**Tertiary follow-up[3]**
Visit Window (relative to Day 1)	**-35 to -1 days**	**-14 to -1 days**	**on Day 1**	**on Day 15 (± 2 days)**	**on Day 21 (± 2 days)**		**14 (±7) days from last dose of trametinib**	**4 weeks (±7 days) after the last dose of panitumumab**	**8 weeks (±7 days) after the last dose of panitumumab**
[redacted]									
Collection of blood sample for immunogenicity analysis			X (pre-dose)			Predose at Week 8		X[14]	X[14]
AE assessment									
PK blood sample[8]			X	X	X				
Panitumumab Dosing			X	X		X every 2 weeks from Day 1			
Trametinib dosing			X	X	X	X			
Disease assessments[11]	x					Every 6 weeks until Week 24, then every 8 weeks.[16]			
[redacted]									

19. All screening assessments must be completed within 14 days prior to first dose except informed consent, ophthalmology exam, dermatological exam, ECHO/MUGA and Disease Assessment, which can occur within 35 days prior to the first dose. Note: Procedures conducted as part of the subject's routine clinical management (e.g., blood counts, imaging study) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures meet the protocol requirements.
20. Assessments throughout the study are calendar-based starting from the first day of dosing (Day 1) in the first treatment period. Dose interruptions should not alter the assessment schedule for any subsequent treatment period. The continuation phase starts with Day 29; events in the continuation phase are allowed ± 7 days from projected date. Safety lab tests (chemistry/hematology/UA) may be done the day before the visit so that results are available on the day of the visit, but all assessments should be done within the ± 7 day window.
21. Initial follow-up visit should be 14 days (± 7 days) from last dose of trametinib. If a subject is unable to return to the clinic due to hospitalization, site staff are encouraged to telephone the subject for assessment of AEs. Secondary follow-up visits should occur at 4 weeks and 8 weeks after the last dose of panitumumab.
22. Serum pregnancy test should be performed at screening; all subsequent pregnancy tests may be either serum or urine, and performed every 8 to 12 weeks.
23. Complete physical examination must include integument and genitalia. Note: pelvic exam in female subjects may be completed up to 24 weeks prior to date of first dose. Complete and brief physical examinations are defined in Section 6.2.
24. If within 72 hours of Screening, this assessment does not need to be repeated on Day 1.
25. Single ECGs will be collected prior to dosing.
26. Blood samples (2 mL) for PK analysis of trametinib will be collected on Day 1 and on Day 15 predose (within 30 minutes of dosing) and at 1, 2 and 4 hours after administration. Blood samples (4 mL) for PK analysis of panitumumab will be collected on Day 1 and on Day 15 predose (within 30 minutes of dosing with panitumumab) and at 1 hour (at the end of infusion of panitumumab). A single 4 mL blood sample for analysis of panitumumab will be collected pre-dose on Day 21 during the clinic visit. During the continuation phase, PK samples (for trametinib and panitumumab) will be collected pre-dose at Week 8, Week 12, Week 16, and Week 20. PK blood samples for trametinib, and panitumumab analysis should be collected along with the tumor biopsy taken at progression. On days when serial PK samples are collected, subjects should be instructed to hold doses of trametinib, report to the clinic for the predose PK blood draw, then dose with trametinib. Collect PK samples at the time indicated ± 5 minutes up to 2 hour sample, ± 20 minutes up to the 4 hour sample.
27. Collection of on-treatment tumor biopsy for subjects with accessible tumors. On-treatment biopsy may be collected 2 to 4 hours after dosing with oral study medication from Day 15 to Day 18. Biopsies should be performed on non-target lesions when possible. PK samples for trametinib and panitumumab analysis will be collected at the time of the post-dose tumor biopsy (± 24 hours) (unless the post-dose biopsy occurs on the same day that the Day 15 serial PK samples are collected).
28. Tumor biopsy at tumor progression in subjects who have had a response is highly encouraged. PK blood samples for trametinib, and panitumumab analysis should be collected along with the tumor biopsy taken at progression.
29. CT is the preferred method to measure lesions selected for response assessment. Refer to Appendix 4 for additional information regarding Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 methodology and criteria. Even if study treatment is withdrawn, radiographic disease assessments (computed tomography [CT] or magnetic resonance imaging [MRI], as appropriate according to the method used at baseline) should continue every 8 weeks until documented disease progression, the start of new anti-cancer therapy, withdrawal of consent or death.
30. Collection of archived tumor tissue or fresh tumor biopsies is required for enrollment; if a fresh tumor biopsy is collected at screening, this tissue may be used for the day 1/ predose tumor biopsy. [redacted] The Day 1/predose tumor biopsy may be collected at any point after signing consent, up to 14 days prior to first dose.
31. Vital signs and temperature should be measured within 30 minutes prior to initiation and upon completion of the panitumumab infusion (up to 15 minutes after the end of infusion).

[redacted]

33. Collection of archived tumor tissue or fresh tumor biopsies and determination of the subject's tumor BRAF mutation status is required for enrollment; if a fresh tumor biopsy is collected during screening and up to prior to dosing on Day1 for BRAF mutation confirmation, this tissue may be used for the day 1/ predose tumor biopsy. [redacted] The Day 1/predose tumor biopsy may be collected at any point after signing consent, after completing wash-out from

prior therapies (either 5 half-lives or 14 days from last dose of prior therapy). Pre- and post-dose tumor biopsies are mandatory. If the patient's tumors are inaccessible for biopsy, permission to enroll must be granted by the GSK Medical Monitor

17. After study treatment is withdrawn, disease assessments (the method used at baseline) should continue every 8 weeks until documented disease progression, the start of new anti-cancer therapy, withdrawal of consent, or death.

~~1.~~ ECHO is preferred. MUGA may be used only if ECHO is not available. The same method must be used consistently from screening throughout the study.

[redacted]

RATIONALE: Time and events table describing assessments associated with addition of Part 4

Section 4.1 Number of Subjects, Paragraph 2

PREVIOUS TEXT

To complete Part 1, it is estimated that 24 evaluable subjects (~4 per cohort) will be enrolled. Part 2 will enroll approximately 30 subjects in total. Approximately 40 subjects will be evaluated at the end of Part 2, including those enrolled in Part 1 at the same dose levels. For Part 3, approximately 47 subjects per arm will be enrolled. .

REVISED TEXT

To complete Part 1, it is estimated that 24 evaluable subjects (~4 per cohort) will be enrolled. Part 2 will enroll approximately 30 subjects in total. In order to confirm safety in Japanese patients, up to three additional Japanese patients may be enrolled in Japan in each expansion cohort. Approximately ~~40~~ 20 subjects will be evaluated at the RP2D/R for each combination tested by the end of Part 2, including those subjects enrolled ~~in Part 1~~ at the ~~same dose levels~~ RP2D/R in Part 1. For Part 3, approximately 47 subjects per arm will be enrolled. For Part 4A (dose escalation), it is estimated that up to 18 evaluable subjects (~6 per cohort) will be enrolled. Part 4B (expansion cohorts 1E and 2E) will enroll approximately 17 additional subjects in each of two expansion cohorts (n=34). This will be a total of approximately 20 patients at the RP2D/R for each patient population, including the subjects enrolled in Part 4A.

RATIONALE: Addition of number of subjects to be enrolled with addition of Part 4

PREVIOUS TEXT

Section 4.2.1 Part 1 and Part 2 Inclusion Criteria

REVISED TEXT

Section 4.2.1 Part 1, 2 and ~~Part 2~~4 Inclusion and Exclusion Criteria

Section 4.2.1.1 Part 1, 2 and Part 4 Inclusion Criteria

PREVIOUS TEXT

Inclusion criterion 3:

Histologically- or cytologically-confirmed diagnosis of advanced or metastatic BRAF V600E mutation positive colorectal cancer (CRC), as determined by relevant genetic testing and documented in source. For subjects enrolled based on local mutation testing, confirmation of mutation will occur following registration in Part 1 and Part 2.

Note: Subjects will not be excluded if centralized testing is later found to be discordant or uninformative (e.g., inadequate sample), but additional subjects may be enrolled as replacement subjects at the discretion of the Sponsor and in consultation with the investigator

Table 22 Definitions for Adequate Baseline Organ Function

System	Laboratory Values
Hematologic	
Absolute neutrophil count	≥1.2 × 10^9/L
Hemoglobin	≥9 g/dL or 5.6 mmol/L
Platelets	≥75 × 10^9/L
Prothrombin Time / International Normalized Ratio (PT/INR) and Partial Thromboplastin Time (PTT)	≤1.5 x ULN
Chemistry	
Mg++	≥ LLN
Hepatic	
Albumin	≥2.5 g/dL or 25 g/L
Total bilirubin	≤1.5 x ULN
AST and ALT	≤ 2.5× ULN
Renal	
Creatinine **or**	≤ 1.5 ULN
Calculated creatinine clearance[a] **or** 24-hour urine creatinine clearance	≥ 50 mL/min
Cardiac	
Left Ventricular Ejection fraction (LVEF)	≥ LLN by ECHO or multigated acquisition scan (MUGA)[b]

d. Calculated by the Cockcroft-Gault formula.
e. Same method as used at baseline must be use throughout the study, ECHO is the preferred method

Inclusion criterion 12:

Subjects enrolled in France: In France, a subject will be eligible for inclusion in this study only if either affiliated to, or a beneficiary of, a social security category

REVISED TEXT

Inclusion criterion 3:

Part 1 and Part 2: Histologically- or cytologically-confirmed diagnosis of advanced or metastatic BRAF V600E mutation positive colorectal cancer (CRC), as determined by relevant genetic testing and documented in source. For subjects enrolled based on local mutation testing, confirmation of mutation will occur following registration in Part 1 and Part 2.

Note: Subjects will not be excluded if centralized testing is later found to be discordant or uninformative (e.g., inadequate sample), but additional subjects may be enrolled as replacement subjects at the discretion of the Sponsor and in consultation with the investigator

Inclusion criterion 4:

Part 4A and 4B ONLY: Histologically- or cytologically-confirmed diagnosis of advanced or metastatic colorectal cancer (CRC) that either:

- harbours the BRAF V600E –mutation, as determined by relevant genetic testing and documented in source, OR
- has developed secondary resistance to anti-EGFR therapy, defined as patients that derived benefit (disease control based on investigator assessment for > 6 months OR partial response [confirmed or unconfirmed] based on RECIST 1.1) from prior anti-EGFR-containing therapy (as defined below) and then subsequently progressed on therapy. The anti-EGFR therapy must have been the most recent therapy and the patient must have progressed based on investigator assessment within 3 months of screening. Acceptable prior anti-EGFR-containing therapies include:
    a. Monotherapy anti-EGFR, including cetuximab or panitumumab OR
    b. irinotecan/anti-EGFR combo after previously having disease progression (based on investigator assessment) on an irinotecan-containing regimen

System	Laboratory Values
Hematologic	
Absolute neutrophil count	≥1.2 × 10^9/L
Hemoglobin	≥9 g/dL or 5.6 mmol/L
Platelets	≥75 × 10^9/L
Coagulation parameters Prothrombin Time / International Normalized Ratio (PT/INR) and Partial Thromboplastin Time (PTT)[a]	≤1.5 x ULN
Chemistry	
Mg++	≥ LLN
Hepatic	
Albumin	≥2.5 g/dL or 25 g/L
Total bilirubin	≤1.5 x ULN
AST and ALT	≤ 2.5× ULN

Renal	
Creatinine **or**	≤ 1.5 ULN
Calculated creatinine clearance[ab] **or** 24-hour urine creatinine clearance	≥ 50 mL/min
Cardiac	
Left Ventricular Ejection fraction (LVEF)	≥ LLN by ECHO or multigated acquisition scan (MUGA)[bc]

a. Subjects receiving anticoagulant therapy are eligibile if their INR is stable and within the recommended range for the desired level of anticoagulation
b. Calculated by the Cockcroft-Gault formula.
c. Same method as used at baseline must be use throughout the study, ECHO is the preferred method.

Inclusion criterion 12:

Subjects enrolled in France or Italy: In France or Italy, a subject will be eligible for inclusion in this study only if either affiliated to, or a beneficiary of, a social security category

RATIONALE: Addition inclusion criteria to define eligibility for subjects to be enrolled with addition of Part 4

Section 4.2.1.2 Part 1, 2 and Part 4 Exclusion Criteria

PREVIOUS TEXT

Exclusion criterion 6:

Prior exposure to BRAF or MEK inhibitors.

Exclusion criterion 7:

Prior exposure to EGFR inhibitors, including anti-EGFR antibodies (Part 2 ONLY)

Exclusion criterion 8:

Known presence of KRAS-mutation based on previous KRAS-testing.

Note: Propsective KRAS testing is not required. However, if the results of previous KRAS testing are known, they must be used in assessing eligibility. KRAS testing will be performed retrospectively for all patients.

Exclusion criterion 11:

Known Human Immunodeficiency Virus (HIV), Hepatitis B, or Hepatitis C infection.

Exclusion criteria 15 & 16:

History of retinal vein occlusion (RVO) or Retinal pigment epithelium detachment (RPED), predisposing factors to RVO or RPED (e.g., uncontrolled glaucoma or ocular

hypertension, uncontrolled systemic disease such as hypertension, diabetes mellitus, or a history of hyperviscosity or hypercoagulability syndromes).

Visible retinal pathology as assessed by ophthalmic examination that is considered a risk for RVO or RPED, such as:

- Evidence of new optic disc cupping.
- Evidence of new visual field defects.

Intraocular pressure >21mm Hg as measured by tonography

REVISED TEXT

Exclusion criterion 6:

Prior exposure to ~~BRAF or~~ a MEK ~~inhibitors~~ inhibitor.

Exclusion criterion 7:

Part 1, Part 2 and BRAF-mutant patients in Part 4 ONLY: Prior exposure to ~~EGFR inhibitors, including anti-EGFR antibodies (Part 2 ONLY)~~a BRAF inhibitor.

Exclusion criterion 8:

Part 1, Part 2 and BRAF-mutant patients in Part 4 ONLY: Known presence of KRAS-mutation based on previous KRAS-testing.

Note: Propsective KRAS testing is not required. However, if the results of previous KRAS testing are known, they must be used in assessing eligibility. KRAS testing will be performed retrospectively for all patients.

Exclusion criterion 11:

Known ~~Human Immunodeficiency Virus (HIV),~~ Hepatitis B, or Hepatitis C infection.

Exclusion criteria 17:

~~History of retinal vein occlusion (RVO) or Retinal pigment epithelium detachment (RPED), predisposing factors to RVO or RPED (e.g., uncontrolled glaucoma or ocular hypertension, uncontrolled systemic disease such as hypertension, diabetes mellitus, or a history of hyperviscosity or hypercoagulability syndromes).~~

~~Visible retinal pathology as assessed by ophthalmic examination that is considered a risk for RVO or RPED, such as:~~

- ~~Evidence of new optic disc cupping.~~
- ~~Evidence of new visual field defects.~~
- ~~Intraocular pressure >21mm Hg as measured by tonography~~.

History of retinal vein occlusion (RVO).

RATIONALE: Revision of eligibility criteria to reflect revised safety

management guidelines based on accepted asset-specific text

Section 4.2.2.2 Part 3 Exclusion Criteria

PREVIOUS TEXT

Exclusion criteria 14 & 15:

History of retinal vein occlusion (RVO) or Retinal pigment epithelium detachment (RPED), predisposing factors to RVO or RPED (e.g., uncontrolled glaucoma or ocular hypertension, uncontrolled systemic disease such as hypertension, diabetes mellitus, or a history of hyperviscosity or hypercoagulability syndromes).

Visible retinal pathology as assessed by ophthalmic examination that is considered a risk for RVO or RPED, such as:

- Evidence of new optic disc cupping.
- Evidence of new visual field defects.

Intraocular pressure >21mm Hg as measured by tonography.

REVISED TEXT

Exclusion criterion 14:

~~History of retinal vein occlusion (RVO) or Retinal pigment epithelium detachment (RPED), predisposing factors to RVO or RPED (e.g., uncontrolled glaucoma or ocular hypertension, uncontrolled systemic disease such as hypertension, diabetes mellitus, or a history of hyperviscosity or hypercoagulability syndromes).~~

~~Visible retinal pathology as assessed by ophthalmic examination that is considered a risk for RVO or RPED, such as:~~

- ~~Evidence of new optic disc cupping.~~
- ~~Evidence of new visual field defects.~~
- ~~Intraocular pressure >21mm Hg as measured by tonography~~.

<u>History of retinal vein occlusion (RVO).</u>

RATIONALE: Revision of eligibility criteria to reflect revised safety management guidelines based on accepted asset-specific text

Section 5.1 Hypotheses and Treatment Comparisons

PREVIOUS TEXT

Section 5.1.1 Part 1

The primary goals in Part 1 of this study are to determine safety and the recommended dose(s) for Part 2 based on available safety, PK and any clinical activity data of trametinib when administered in combination with dabrafenib and panitumumab; thus, no

formal statistical hypotheses will be tested. Analysis will be descriptive [redacted]

Section 5.1.2 Part 2, Paragraphs 1 and 2

For Part 2, efficacy will be evaluated to decide whether to proceed with further development based on the clinical activity seen in Part 1 and Part 2. Futility analysis criteria at the end of Part 2 will be based on 2-stage Green-Dahlberg design's [Green, 1992] interim analysis criteria. The criteria will be based on a historically unimportant response rate of 15% versus a response rate of interest of 30%. The Part 2 portion of the study will employ a Bayesian design that allows the trial to be monitored more frequently at multiple stages. Bayesian statistics will be employed to calculate the predictive probability that the response rate ≥30% and ≥15% at interim assuming a Beta prior for the Binomial distributed data. Predictive probability calculates the probability that the response rate ≥30% or ≥15% at the end of Part 2 (after 20 subjects) given the responses have already been observed. It predicts what is likely to happen at the end of Part 2 so is more meaningful and straightforward than posterior probability. A weak prior Beta (0.003, 0.007) is used, which is equivalent to the information present in 0.01 subject.

An initial total of 10 subjects will be recruited at a dose level based on the recommended dose for each treatment (including the subjects treated in Part 1 at the same dose). The number of subjects will be increased up to a total of 20 depending on the results observed. The tables below show the decision rules for the 10^{th} to 19^{th} evaluable subjects, specifying the number of subjects with a confirmed response needed for continuing enrolment or stopping for futility. The methodology is based on the predictive probability of success if enrolment continues to 20 subjects [Lee, 2008]. These rules are intended as a guideline. Actual decisions will depend on the totality of the data.

REVISED TEXT

Section 5.1.1 Part 1 and Part 4 Dose Escalation

The primary goals in Part 1 of this study are to determine safety and the recommended dose(s) for Part 2 and Part 4 based on available safety, PK and any clinical activity data of trametinib when administered in combination with dabrafenib and panitumumab; thus, no formal statistical hypotheses will be tested. Analysis will be descriptive [redacted]

Section 5.1.2 Part 2 and Part 4 Cohort Expansion, Paragraphs 1 and 2

For Part 2 and Part 4 cohort expansion, efficacy will be evaluated for each cohort to decide whether to proceed with further development based on the clinical activity seen in Part 1 ~~and Part 2~~. Futility analysis criteria at the end of Part 2 and Part 4 will be based on 2-stage Green-Dahlberg design's [Green, 1992] interim analysis criteria. The criteria will be based on a historically unimportant response rate of 15% versus a response rate of interest of 30%. The Part 2 and Part 4B portion of the study will employ a Bayesian design that allows the trial to be monitored more frequently at multiple stages. Bayesian statistics will be employed to calculate the predictive probability that the response rate ≥30% and ≥15% at interim assuming a Beta prior for the Binomial distributed data. Predictive probability calculates the probability that the response rate ≥30% or ≥15% at

the end of Part 2 (after 20 subjects) given the responses have already been observed. It predicts what is likely to happen at the end of Part 2 and Part 4 so is more meaningful and straightforward than posterior probability. A weak prior Beta (0.003, 0.007) is used, which is equivalent to the information present in 0.01 subject. Futility analysis criteria based on 2-stage Green-Dahlberg design's are only used at the end of Part 2 and Part 4B when all subjects are enrolled. Bayesian design based criteria are only used for interim data monitoring before the end of Part 2 or Part 4B data analysis allowing early stop for futility. An initial total of 10 subjects will be recruited at a dose level based on the recommended dose for each treatment/cohort (including the subjects treated in Part 1 or Part 4A at the same dose). with the same mutation status). The number of subjects will be increased up to a total of 20 per treatment cohort depending on the results observed. The tables below show the decision rules for the 10th to 19th evaluable subjects, specifying the number of subjects with a confirmed response needed for continuing enrolment or stopping for futility. The methodology is based on the predictive probability of success if enrolment continues to 20 subjects [Lee, 2008]. These rules are intended as a guideline. Actual decisions will depend on the totality of the data.

RATIONALE: Revisions to incorporate analysis of Part 4 data

Section 5.2.1 Sample Size Assumptions

PREVIOUS TEXT

Section 5.2.1.1 Part 1

The total number of subjects in Part 1 will depend on the number of dose escalations needed. However, the maximum anticipated number of subjects will be approximately 24.

Table 21 Statistical Basis for Phase 1 Dose Escalation

True incidence of dose-limiting toxicity	10%	20%	30%	40%	50%	60%
Probability of escalating the dose	0.91	0.71	0.49	0.31	0.17	0.08

REVISED TEXT

Section 5.2.1.1 Part 1 and Part 4 Dose Escalation

The total number of subjects in Part 1 and Part 4 dose escalation will depend on the number of dose escalations needed. However, the maximum anticipated number of subjects will be approximately 24 in Part 1 and approximately 12 in Part 4 dose escalation.

Table 25 Statistical Basis for Phase 1 Dose Escalation

True incidence of dose-limiting toxicity	10%	20%	30%	40%	50%	60%
Probability of escalating the dose	0.91	0.71	0.49	0.31	0.17	0.08

RATIONALE: Revisions to incorporate analysis of Part 4 data.

PREVIOUS TEXT

Section 5.2.1.2 Part 2, Paragraph 1

Part 2 will enroll approximately 30 subjects in total. Approximately 40 subjects will be evaluated at the end of Part 2, including those enrolled in Part 1 at the same dose levels.

REVISED TEXT

Part 2 will enroll approximately 30 subjects in total. Approximately 40 subjects will be evaluated at the end of Part 2, including those enrolled in Part 1 at the same dose levels. Part 4 cohort expansion will enroll approximately 40 subjects in total (20 subjects in Cohort 1E and 20 subjects in Cohort 2E). For each cohort, approximately 20 subjects will be evaluated separately at the end of Part 4, including those enrolled in dose escalation at the same dose levels and the same mutation status.

RATIONALE: Revisions to incorporate enrolment of subjects into Part 4.

Section 5.2.3 Analysis Populations, Paragraph 4

PREVIOUS TEXT

The **Crossover Population** will comprise the subset of subjects in Part 1 and Part 2 who had intra-subject dose escalation. It will be the primary population when summarizing data in Part 1 and Part 2 crossover phase.

REVISED TEXT

The **Crossover Population** will comprise the subset of subjects in Part 1, Part 2 and Part ~~2~~4 who had intra-subject dose escalation or intra-subject doublet to triplet crossover. It will be the primary population when summarizing data in Part 1, Part 2 and Part ~~2~~4 crossover phase.

RATIONALE: Revisions to incorporate analysis of subjects who crossover from doublet to triplet dosing

Section 5.3.7 Interim Analysis

PREVIOUS TEXT

Section 5.3.7.1 Part 1

Section 5.3.7.2 Part 2

REVISED TEXT

Section 5.3.7.1 Part 1 and Part 4 Dose Escalation

Section 5.3.7.2 Part 2 and Part 4 Cohort Expansion

Section 5.3.8.7 Efficacy Analyses

PREVIOUS TEXT

Section 5.3.8.7.1 Part 1 and Part 2

The ORR endpoint will be tabulated based on number and percentage of subjects attaining either a confirmed or unconfirmed overall best response of CR or PR in the ITT population. Per RECIST, version 1.1, confirmation of response is not required. Subjects 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.

PFS will be estimated using the Kaplan Meier method. PFS will be defined as the time from randomization until the first date of either disease progression or death due to any cause. The date of objective disease progression will be defined as the earliest date of disease progression as assessed by the investigator using RECIST, version 1.1. For subjects who have not progressed or died at the time of the PFS analysis, censoring will be performed using the date of the last adequate disease assessment. In addition, subjects with an extended loss to follow-up or who start a new anti-cancer therapy prior to a PFS event will be censored at the date of the last adequate disease assessment prior to the extended loss to follow-up or start of new anti-cancer therapy, respectively. Further details on censoring rules will be outlined in the RAP.

For Part 1 and Part 2, anti-tumor activities will be evaluated based on clinical evidence and response criteria. If the data warrant, the response data from both parts will be combined and summarized by dose level. Subjects who crossover from dabrafenib/panitumumab combination to dabrafenib/trametinib/panitumumab combination will not be included in the main efficacy analysis for dabrafenib/trametinib/panitumumab combinations. The efficacy for these subjects will be summarized separately.

REVISED TEXT

Section 5.3.8.7.1 Part 1, Part 2 and Part ~~2~~4

The ORR endpoint will be tabulated based on number and percentage of subjects attaining either a confirmed or unconfirmed overall best response of CR or PR in the ITT population. Per RECIST, version 1.1, confirmation of response is not required. Subjects 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.

PFS will be estimated using the Kaplan Meier method. PFS will be defined as the time from randomization until the first date of either disease progression or death due to any cause. The date of objective disease progression will be defined as the earliest date of disease progression as assessed by the investigator using RECIST, version 1.1. For subjects who have not progressed or died at the time of the PFS analysis, censoring will be performed using the date of the last adequate disease assessment. In addition, subjects with an extended loss to follow-up or who start a new anti-cancer therapy prior to a PFS event will be censored at the date of the last adequate disease assessment prior to the extended loss to follow-up or start of new anti-cancer therapy, respectively. Further details on censoring rules will be outlined in the RAP.

For Part 1 and Part 2, anti-tumor activities will be evaluated based on clinical evidence and response criteria. If the data warrant, the response data from both parts will be combined and summarized by dose level. Subjects who crossover from dabrafenib/panitumumab combination or trametinib/panitumumab to dabrafenib/trametinib/panitumumab combination will not be included in the main efficacy analysis for dabrafenib/trametinib/panitumumab combinations. The efficacy for these subjects will be summarized separately.

RATIONALE: Revisions to incorporate analysis of Part 4 data

Section 6.2 Safety

PREVIOUS TEXT

Vital Signs

Vital sign measurements will include systolic and diastolic blood pressure, pulse rate and temperature. Vital signs should be assessed under optimal conditions as described in Section 3.9.8.1.

Vital signs should be measured within 30 minutes prior to initiation and upon completion of panitumumab infusion. On other study days where vital signs are measured multiple times, temperature does not need to be repeated, unless clinically indicated.

Ophthalmic Exam

Subjects are required to have a standard ophthalmic exam performed by an ophthalmologist at baseline and as clinically warranted per protocol's guidance (refer to Visual Changes Stopping Criteria, Section 3.9.11). The exam will include indirect fundoscopic examination, visual acuity (corrected), visual field examination, tonometry, and direct fundoscopy, with special attention to retinal abnormalities that are predisposing factors for RVO or RPED.

In addition, it is recommended that subjects have baseline color fundus photographs taken at screening to document baseline appearance. In subjects with clinical suspicion of RVO or RPED, additional color fundus photographs are recommended, and fluorescein angiography and/or optical coherence tomography are recommended.

Clinical Laboratory Assessments

Clinical Chemistry

Albumin	Sodium	AST (SGOT)	Magnesium
BUN	Potassium	ALT (SGPT)	Total and direct bilirubin
Creatinine	Chloride	Gamma glutamyl transferase (GGT)	Uric Acid
Glucose fasting glucose at screening only	Total carbon dioxide (CO_2)	Alkaline phosphatase	Inorganic phosphorus
Lactacte dehydrogenase (LDH)	Calcium		Total Protein

REVISED TEXT

Vital Signs

Vital sign measurements will include systolic and diastolic blood pressure, pulse rate and temperature. Vital signs should be assessed under optimal conditions as described in Section 3.9.8.1.

Vital signs should be measured within 30 minutes prior to initiation and upon completion of panitumumab infusion (up to 15 minutes after the end of infusion). On other study days where vital signs are measured multiple times, temperature does not need to be repeated, unless clinically indicated.

Ophthalmic Exam

~~Subjects are required to have a standard ophthalmic~~ At certain time points in the trial and if visual changes develop, an eye exam ~~performed by an ophthalmologist at baseline and as clinically warranted per protocol's guidance~~ is indicated (refer to Visual Changes Stopping Criteria, Section 3.9.11). The exam will include ~~indirect fundoscopic~~ best corrected visual acuity, tonometry, slit lamp biomicroscopic examination, visual ~~acuity (corrected), visual~~ field examination, ~~tonometry,~~ and ~~direct~~ dilated indirect fundoscopy~~,~~ with special attention to retinal abnormalities ~~that~~. Optical coherence tomography is strongly recommended at scheduled visits, and if retinal abnormalities are suspected. Other types of ancillary testing including color fundus photography and fluorescein angiography are ~~predisposing factors for RVO or RPED~~. also recommended if clinically indicated.

In addition, it is recommended that subjects have baseline color fundus photographs taken at screening to document baseline appearance. ~~In subjects with clinical suspicion of RVO or RPED, additional color fundus photographs are recommended, and fluorescein angiography and/or optical coherence tomography are recommended~~.

Clinical Laboratory Assessments

Clinical Chemistry

Albumin	Sodium	AST (SGOT)	Magnesium
BUN	Potassium	ALT (SGPT)	Total and direct bilirubin
Creatinine	Chloride	Gamma glutamyl transferase (GGT)	Uric Acid
Glucose fasting glucose at screening only; all other glucose measurements may be non-fasting	Total carbon dioxide (CO_2)	Alkaline phosphatase	Inorganic phosphorus
Lactacte dehydrogenase (LDH)	Calcium		Total Protein

RATIONALE: Revision of safety assessment text to reflect revised asset-specific text

Section 6.7.1 Fresh Pre- and Post- dose Tumor Tissues

PREVIOUS TEXT

Tumor specimens that are accessible and can be sampled easily will be requested in Part 1 and Part 2. These biopsies will be taken during the screening period, e.g., within 14 days before treatment, and within 2 to 4 hrs after dosing on Day 15 (+3 days) in those subjects who have signed the corresponding section of the informed consent. Details of the tumor biopsy collection including processing, storage and shipping procedures will be provided in the SPM.

REVISED TEXT

Tumor specimens that are accessible and can be sampled easily will be requested in Part 1 and Part 2. These biopsies will be taken during the screening period, e.g., within 14 days before treatment, and within 2 to 4 hrs after dosing on Day 15 (+3 days) in those subjects who have signed the corresponding section of the informed consent. Details of the tumor biopsy collection including processing, storage and shipping procedures will be provided in the SPM.

RATIONALE: Clarification

Section 6.7.2 Fresh Tumor Tissue at Progression, Paragraph 1

PREVIOUS TEXT

Tumor specimens that are accessible and can be sampled easily will be requested from some subjects at time of demonstrated progression on therapy, as determined by RECIST v1.1 criteria. Subjects of interest will be those who have had meaningful clinical response in target lesions (≥20% reduction, or stable disease for ≥6 months) and then progressed on existing target lesions or if a new lesion emerged. The guidance on the lesion selection for the progression biopsy are:

REVISED TEXT

Tumor specimens that are accessible and can be sampled easily will be requested from ~~some~~ subjects at time of demonstrated progression on therapy <u>from all parts of the study</u>, as determined by RECIST v1.1 criteria. Subjects of interest will be those who have had meaningful clinical response in target lesions (≥20% reduction, or stable disease for ≥6 months) and then progressed on existing target lesions or if a new lesion emerged. The guidance on the lesion selection for the progression biopsy are:

RATIONALE: Clarification

Section 6.7.4 Archival Tumor Tissue, Paragraph 1

PREVIOUS TEXT

Collection of archival primary tumor tissue is required when it is available. These samples will be used to confirm or determine the BRAF mutation status of subjects for study enrolment.

REVISED TEXT

Collection of archival primary tumor tissue is required ~~when it is available~~. These samples will be used to confirm or determine the BRAF <u>or KRAS</u> mutation status of

subjects ~~for study enrolment~~. [redacted]

[redacted]

Section 7.1.1 Female Subjects

PREVIOUS TEXT

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 subject must have a follicular stimulating hormone (FSH) value >40 mIU/mL and an estradiol value < 40pg/mL (<140 pmol/L).

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

Female subjects of childbearing potential must not become pregnant and so must be sexually inactive by abstinence or use contraceptive methods with a failure rate of < 1% from start of dosing and.

- for 6 months after the last dose of panitumumab (Vectibix)
- for 4 months after the last dose oftrametinib in combination with dabrafenib
- for 4 weeks after the last dose of dabrafenib.

<u>Abstinence</u>

Sexual inactivity by abstinence must be consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are <u>not</u> acceptable methods of contraception.

Complete abstinence from sexual intercourse for 14 days prior to first dose of study treatment, through the dosing period, and from the first dose of study drug(s) until 60 days after the last dose of any study drug.

Contraceptive Methods with a Failure Rate of ≤ 1%

- Intrauterine device (IUD) or intrauterine system (IUS) that meets the <1% failure rate as stated in the product label
- Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into the study, and this male is the sole partner for that subject. For this definition, "documented" refers to the outcome of the investigator's/designee's medical examination of the subject or review of the subject's medical history for study eligibility, as obtained via a verbal interview with the subject or from the subject's medical records.
- Double-barrier method: condom and occlusive cap (diaphragm or cervical/vault caps) plus vaginal spermicidal agent (foam/gel/film/cream/suppository)

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring subjects understand how to properly use these methods of contraception.

REVISED TEXT

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

A female of non-childbearing potential (i.e., physiologically incapable of becoming pregnant) is defined as any female who has had a hysterectomy, bilateral oophorectomy (ovariectomy) 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 subject must have a follicular stimulating hormone (FSH) value >40 mIU/mL and an estradiol value < 40pg/mL (<140 pmol/L).

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

Female subjects of childbearing potential must not become pregnant and so must be sexually inactive by abstinence or use contraceptive methods with a failure rate of < 1% from start of dosing and.

- for 6 months after the last dose of panitumumab (Vectibix)
- for 4 months after the last dose of trametinib in combination with dabrafenib
- for 4 weeks after the last dose of dabrafenib
- for 4 months after the last dose of trametinib.

Abstinence

Sexual inactivity by abstinence must be consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Complete abstinence from sexual intercourse for 14 days prior to first dose of study treatment, through the dosing period, and from the first dose of study drug(s) until 60 days after the last dose of any study drug.

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

Contraceptive Methods with a Failure Rate of ≤ 1%

- Intrauterine device (IUD) or intrauterine system (IUS) that meets the <1% failure rate as stated in the product label
- Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into the study, and this male is the sole partner for that subject. For this definition, "documented" refers to the outcome of the investigator's/designee's medical examination of the subject or review of the subject's medical history for study eligibility, as obtained via a verbal interview with the subject or from the subject's medical records.
- Double-barrier method: condom and occlusive cap (diaphragm or cervical/vault caps) plus vaginal spermicidal agent (foam/gel/film/cream/suppository)

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

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring subjects understand how to properly use these methods of contraception.

RATIONALE: Clarification of requirements for female contraception

Section 8.1 Permitted Medications

PREVIOUS TEXT

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. Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the eCRF. The minimum requirement is that drug name, dose, and the dates of administration are to be recorded. Additionally, a complete list of all prior cancer therapies will be recorded in the eCRF.

Subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines. Growth factors and bisphosphonates are allowed but must not be initiated durof ing the first 4 weeks of treatment.

REVISED TEXT

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. Any concomitant medication(s), including ~~herbal preparations~~,dietary supplements,) taken during the study will be recorded in the eCRF. The minimum requirement is that drug name, dose, and the dates of administration are to be recorded. Additionally, a complete list of all prior cancer therapies will be recorded in the eCRF.

Subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines. Growth factors and bisphosphonates are allowed but must not be initiated during the first 4 weeks of treatment. Use of anticoagulants such as warfarin is permitted however, caution should be exercised and additional International Normalized Ratio (INR) monitoring is recommended when dabrafenib is used concomitantly with warfarin.

While patients are on study treatment, palliative radiation therapy is permitted for non-target lesions that are either new or present at baseline.

Radiation skin injury has been reported with concurrent use of dabrafenib and radiation. It is recommended that dabrafenib be held for seven days before and two days after XRT in subjects receiving dabrafenib monotherapy or in combination with trametinib. These recommendations can be modified based on the physician's assessment of the risk of radiation skin injury.

RATIONALE: Clarification of permitted medications, and additional information regarding use of anti-coagulants and palliative radiation therapy

Section 8.2 Prohibited Medications

PREVIOUS TEXT

The use of certain medications, and illicit drugs within 5 half-lives or 28 days, whichever is shorter prior to the first dose of study drug and for the duration of the trial will not be allowed. If a prohibited medication is required for single use (such as for a procedure) while study drug is held, the GSK medical monitor can approve such use.

The following medications or non-drug therapies are prohibited:

- Other anti-cancer therapy while on treatment in this study.

- Antiretroviral drugs (subjects with known HIV are ineligible for study participation).
- Herbal remedies (e.g., St. John's wort).
- Dabrafenib is metabolized primarily by Cytochrome P450 (CYP) 2C8 and CYP3A4. Co-administration of dabrafenib with ketoconazole, a CYP3A4 inhibition, or with gemfibrozil, a CYP2C8 inhibitor, resulted in increases in dabrafenib AUC of 71% and 47%, respectively. Drugs that are strong inhibitors or inducers of CYP3A and CYP2C8 (see list in Table 26) may only be used under special circumstances (e.g. as a single use for a procedure) while treatment with study drug is interrupted as they may alter dabrafenib concentrations; consider therapeutic substitutions for these medications. Approval of the GSK medical monitor is required in these situations. The list may be modified based on emerging data.
- Oral contraceptives (either combined or progesterone only), estrogenic vaginal ring/percutaneous contraceptive patches, or implants of levonorgestrel/Injectable progesterone is prohibited in this study as it is not known if there is the potential of inhibition/induction of enzymes that affect the metabolism of estrogens and/or progestins.

REVISED TEXT

The use of certain medications, and illicit drugs within 5 half-lives or 28 days, whichever is shorter prior to the first dose of study drug and for the duration of the trial will not be allowed. If a prohibited medication is required for single use (such as for a procedure) while study drug is held, the GSK medical monitor can approve such use.

The following medications or non-drug therapies are prohibited:

- Other anti-cancer therapy while on treatment in this study.
- Antiretroviral drugs ~~(subjects with known HIV are ineligible for study participation).~~.
- Herbal remedies (e.g., St. John's wort).
- Dabrafenib is metabolized primarily by Cytochrome P450 (CYP) 2C8 and CYP3A4. Co-administration of dabrafenib with ketoconazole, a CYP3A4 inhibition, or with gemfibrozil, a CYP2C8 inhibitor, resulted in increases in dabrafenib AUC of 71% and 47%, respectively. Drugs that are strong inhibitors or inducers of CYP3A and CYP2C8 (see list in Table 30) may only be used under special circumstances (e.g. as a single use for a procedure) while treatment with study drug is interrupted as they may alter dabrafenib concentrations; consider therapeutic substitutions for these medications. Approval of the GSK medical monitor is required in these situations. The list may be modified based on emerging data.
- Oral contraceptives (either combined or progesterone only), estrogenic vaginal ring/percutaneous contraceptive patches, or implants of levonorgestrel/Injectable progesterone is prohibited in this study as it is not

known if there is the potential of inhibition/induction of enzymes that affect the metabolism of estrogens and/or progestins.

RATIONALE: Clarification of prohibited medications

Section 10.3.1 Preparation

PREVIOUS TEXT

No special preparation of dabrafenib and trametinib is required. Refer to the GSK2118436 IB [GlaxoSmithKline Document Number 2012N136095_00], the GSK1120212 IB [GlaxoSmithKline Document Number HM2009/00151/03] and the GSK1120212 + GSK2118436 Clinical IB [GlaxoSmithKline Document Number, 2011N126811_00] for detailed information regarding dabrafenib and trametinib.

Please refer to the FDA approved label and/or EU SmPC for panitumumab for updated detailed information. The following text is summarized from the approved FDA label [VECTIBIX (panitumumab) Injection for Intravenous Use, Revised August 2012].

Prepare the solution for infusion, using aseptic technique, as follows:

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Although panitumumab should be colorless, the solution may contain a small amount of visible translucent-to-white, amorphous, proteinaceous, panitumumab particulates (which will be removed by filtration; see below). Do not shake. Do not administer if discoloration is observed.

- Withdraw the necessary amount of panitumumab for the study- prescribed dose.

- Dilute to a total volume of 100 mL with 0.9% sodium chloride injection, USP. Doses higher than 1000 mg should be diluted to 150 mL with 0.9% sodium chloride injection, USP. Do not exceed a final concentration of 10 mg/mL.

- Mix diluted solution by gentle inversion. Do not shake.

REVISED TEXT

No special preparation of dabrafenib and trametinib is required. Refer to the GSK2118436 IB [GlaxoSmithKline Document Number 2012N136095_00], the GSK1120212 IB [GlaxoSmithKline Document Number HM2009/00151/03] and the GSK1120212 + GSK2118436 Clinical IB [GlaxoSmithKline Document Number, 2011N126811_00] for detailed information regarding dabrafenib and trametinib.

Please refer to the FDA approved label and/or EU SmPC for panitumumab for updated detailed information. The following text is summarized from the approved FDA label [VECTIBIX (panitumumab) Injection for Intravenous Use, Revised August 2012].

Prepare the solution for infusion, using aseptic technique, as follows:

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Although panitumumab should be colorless, the solution may contain a small amount of visible translucent-to-white, amorphous, proteinaceous, panitumumab particulates (which will be removed by filtration; see below). Do not shake. Do not administer if discoloration is observed.

- Withdraw the necessary amount of panitumumab for the study- prescribed dose.

- Dilute to a total volume of 100 mL with 0.9% sodium chloride injection, USP. Doses higher than 1000 mg should be diluted to 150 mL with 0.9% sodium chloride injection, USP. Do not exceed a final concentration of 10 mg/mL.

- Mix diluted solution by gentle inversion. Do not shake.

- Administer using a low-protein-binding 0.2µm or 0.22µm in-line filter.

- Vectibix must be administered via infusion pump.

    - Flush line before and after Vectibix administration with 0.9% sodium chloride injection, USP, to avoid mixing with other drug products or intravenous solutions. Do not mix Vectibix with, or administer as an infusion with, other medicinal products. Do not add other medications to solutions containing panitumumab.

    - Infuse over 60 minutes through a peripheral intravenous line or indwelling intravenous catheter. Doses higher than 1000mg should be infused over 90 minutes.

RATIONALE: Additional text on preparation of Vectibix as noted in the approved product label

Section 10.3.2 Handling

Section 10.3.3 Storage

PREVIOUS TEXT

Section 10.3.2 Handling

Precaution will be taken to avoid direct contact with the investigational product. Material Safety Data Sheets (MSDS) for dabrafenib and trametinib describing occupational hazards and recommended handling precautions will be provided to the investigator.

Please refer to the FDA approved label and/or EU SmPC for panitumumab for updated detailed information [VECTIBIX (panitumumab) Injection for Intravenous Use, Revised August 2012].

However, precautions are to be taken to avoid direct skin contact, eye contact, and generating aerosols or mists. In the case of unintentional occupational exposure notify the monitor, medical monitor and/or study manager.

Precaution will be taken to avoid direct contact with the investigational product. A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions will be provided to the investigator.

Section 10.3.3 Storage

All investigational products must be stored in original bottles supplied by GSK and in a secure area with access limited to the investigator and authorized site staff. Dabrafenib is to be stored up to 30°C (86°F) in an opaque bottle, as supplied by GSK. Trametinib is to be stored at 2 to 8°C (36 to 46°F), protected from moisture and light, and stored and dispensed in the original cartons supplied by GSK. Please ensure that the bottles have equilibrated back to room temperature before opening them to avoid moisture condensation on the tablets. Whole bottles of investigational products are dispensed at each 4 week visit. Maintenance of a temperature log (manual or automated) is required.

Please refer to the FDA approved label and/or EU SmPC for panitumumab for updated detailed information. The following text is summarized from the approved FDA label [VECTIBIX (panitumumab) Injection for Intravenous Use, Revised August 2012]. Store vials in the original carton under refrigeration at 2° to 8°C (36° to 46°F) until time of use. Protect from direct sunlight. DO NOT FREEZE. Since panitumumab does not contain preservatives, any unused portion remaining in the vial must be discarded.

REVISED TEXT

Section 10.3.2 Handling and Storage of Study Treatments

Precaution will be taken to avoid direct contact with the investigational product. Material Safety Data Sheets (MSDS) for dabrafenib and trametinib describing occupational hazards and recommended handling precautions will be provided to the investigator.

Please refer to the FDA approved label and/or EU SmPC for panitumumab for updated detailed information [VECTIBIX (panitumumab) Injection for Intravenous Use, Revised March 2013].

However, precautions are to be taken to avoid direct skin contact, eye contact, and generating aerosols or mists. In the case of unintentional occupational exposure notify the monitor, medical monitor and/or study manager.

Precaution will be taken to avoid direct contact with the investigational product. A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions will be provided to the investigator.

Section 10.3.3 Storage

~~All investigational products~~ Dabrafenib and trametinib must be dispensed and administered in accordance with the protocol, and only to subjects enrolled in the study. Dabrafenib and trametinib must be stored in ~~original bottles supplied by GSK and in~~ a secure area ~~with access limited to the investigator and authorized site staff. Dabrafenib is to be stored up to 30°C (86°F) in an opaque bottle, as supplied by GSK. Trametinib~~ under the appropriate physical conditions for the product. Study medication is to be stored at ~~2 to 8°C (36 to 46°F), protected from moisture and light, and stored and dispensed in the original cartons supplied by GSK. Please ensure that the bottles have equilibrated back to room~~the temperature ~~before opening them to avoid moisture condensation~~specified on the tablets. ~~Whole bottles of investigational products are dispensed at each 4 week visit~~.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.

Please refer to the FDA approved label and/or EU SmPC for panitumumab for updated detailed information. The following text is summarized from the approved FDA label [VECTIBIX (panitumumab) Injection for Intravenous Use, Revised March 2013; VECTIBIX (panitumumab) Injection for Intravenous Use, Revised August 2012]. Store vials in the original carton under refrigeration at 2° to 8°C (36° to 46°F) until time of use. Protect from direct sunlight. DO NOT FREEZE. Since panitumumab does not contain preservatives, any unused portion remaining in the vial must be discarded.

Procedures for final disposition of unused study treatments will be provided in the Study Procedures Manual (SPM).

RATIONALE: Updated text concerning handling and storage requirements for study treatments

Section 10.5 Treatment of Study Treatment Overdose

PREVIOUS TEXT

In the event of a dabrafenib overdose, defined as administration of more than 300mg as a single dose or 600mg daily (the highest dose tested in clinical studies to date), or in the event of a trametinib overdose (defined as administration of more than the prescribed dose), the investigator should contact the GSK Medical Monitor immediately and closely monitor the subject for AEs/SAEs and laboratory abnormalities. In the event of an overdose of panitumumab, refer to the package insert [VECTIBIX, 2012].

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

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.

REVISED TEXT

In the event of a dabrafenib overdose, defined as administration of more than 300mg as a single dose or 600mg daily (the highest dose tested in clinical studies to date), or in the event of a trametinib overdose ~~(~~defined as administration of more than 3.0 mg once daily (the ~~prescribed~~ maximum tolerated dose defined in the MEK111054 Study), the investigator should contact the GSK Medical Monitor immediately and closely monitor the subject for AEs/SAEs and laboratory abnormalities. ~~In the event of an overdose of panitumumab, refer to the package insert [, 2012]~~. GSK does not recommend specific treatment. The investigator will use clinical judgment to treat any overdose. Haemodialysis is not expected to enhance the elimination of either dabrafenib or trametinib as both are highly bound to plasma proteins.

In the event of an overdose of panitumumab, refer to the package insert [VECTIBIX, 2013; VECTIBIX, 2012].

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

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, but within 10 days from the date of the last dose of on-study dosing.

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

RATIONALE: Clarification of treatment of overdose with study drugs

Section 11.2 Definition of Serious Adverse Events, Item I

PREVIOUS TEXT

j. 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 subjects receiving anticoagulants).

  Note: Bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥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 tumor, including cutaneous squamous cell carcinoma, basal cell carcinoma, and secondary melanoma
- Laboratory abnormalities as referenced in Section 1111.
- LVEF that meets stopping criteria Section 3.7.7.1.
- RPED or RVO.
- Pyrexia accompanied by hypotension, or dehydration requiring IV fluids, or severe rigors/chills.

REVISED TEXT

k. 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 subjects receiving anticoagulants).

  Note: Bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥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 tumor, including cutaneous squamous cell carcinoma, basal cell carcinoma, and secondary melanoma
- ~~Laboratory abnormalities as referenced in Section 11~~.
- Symptomatic LVEF decrease that meets stopping criteria or asymptomatic LVEF decrease that does not recover, as outlined as LVEF guidance Section 3.9.7.1.
- RPED or RVO.
- ~~Pyrexia accompanied by hypotension, or dehydration requiring IV fluids, or severe rigors/chills~~.

RATIONALE: Revisions to text reflect updated asset-specific safety guidelines

Section 13.2 Regulatory and Ethical Considerations, Including the Informed Consent Process, Paragraph 6

PREVIOUS TEXT

In approving the clinical protocol the IEC/IRB and, where required, the applicable regulatory agency are also approving the optional assessments. Where permitted by regulatory authorities, approval of the optional assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the optional assessments is being deferred and the study, except for the optional assessments, can be initiated. When the optional assessments are not approved, then the approval for the rest of the study will clearly indicate this and therefore, the optional assessments will not be conducted.

REVISED TEXT

In approving the clinical protocol the IEC/IRB and, where required, the applicable regulatory agency are also approving the optional assessments, [redacted] Where permitted by regulatory authorities, approval of the optional assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the optional assessments is being deferred and the study, except for the optional assessments, can be initiated. When the optional assessments are not approved, then the approval for the rest of the study will clearly indicate this and therefore, the optional assessments will not be conducted.

[redacted]

Section 14 References

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Misale S, Arena S, Lamba S et al. Blockade of EGFR and MEK intercepts heterogenous mechanisms of acquired resistance to anti-EGFR therapies in colorectal cancer. Sci Transl Med 2014; 6 (224):224-226.

Misale S, Yaeger R, Hobor S et al. Emergence of KRAS mutations and acquired resistance to anti-EGFR therapy in colorectal cancer. *Nature* 2012; 486 (7404):532-536.

Schwartzberg LS, Rivera F, Karthaus M et al. PEAK: a randomized, multicenter Phase II study of panitumumab plus modified fluorouracil, leucovorin, an oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated,

unresectable, wild-type KRAS exon 2 metastatic colorectal cancer. *J Clin Oncol* Published online JCO.2013.53.2473; March 31, 2014.

TAFINLAR (dabrafenib) prescribing information. January 2014.

VECTIBIX (panitumumab) Product Information. March 2013.

Appendix 1: Liver Safety Algorithms

PREVIOUS TEXT

Part 1 and Part 2

REVISED TEXT

Part 1, Part 2 and Part ~~2~~4

Appendix 2: Blood Requirements

PREVIOUS TEXT

Part 1: Dose Escalation Cohorts

Test	Sample Volume	Total Volume for Screening, One 4-wk treatment period and Follow-up
Hematology/Clin Chem	5 mL	25
Coagulation	5 mL	5
PK Analysis (panitumumab)	4 mL	20
PK & Metabolite Analysis (dabrafenib, trametinib)	4 mL	48
[redacted]		
Serum Pregnancy Test	1 mL	1
Total		**155mL/subject plus any wasteage associated with collection**

Part 2: Expansion Cohorts

Test	Sample Volume	Total Volume for Screening, One 4-wk treatment period and Follow-up
Hematology/Clin Chem	5 mL	20
Coagulation	5 mL	5
PK Analysis (panitumumab)	4 mL	16
PK & Metabolite Analysis (dabrafenib, trametinib)	4 mL	48
[redacted]		
Serum Pregnancy Test	1 mL	1
Total		**146mL/subject plus any wasteage associated with collection**

Part 3: Randomized Phase II Study

Test	Sample Volume	Total Volume for Screening, One 4-wk treatment period and Follow-up
Hematology/Clin Chem	5 mL	20
Coagulation	5 mL	5
[redacted]		
Serum Pregnancy Test	1 mL	1
Total		**82/subject plus any wasteage associated with collection**

REVISED TEXT

Part 1: Dose Escalation Cohorts

Test	Sample Volume	Total Volume for Screening, One 4-wk treatment period and Follow-up
Hematology/Clin Chem	5 mL	30
Coagulation	5 mL	5
PK Analysis (panitumumab)	4 mL	20
PK & Metabolite Analysis (dabrafenib, trametinib)	4 mL	48
[redacted]		
Serum Pregnancy Test	1 mL	1
CEA	2 mL	12
Total		**167mL/subject plus any wasteage associated with collection**

Part 2: Expansion Cohorts

Test	Sample Volume	Total Volume for Screening, One 4-wk treatment period and Follow-up
Hematology/Clin Chem	5 mL	25
Coagulation	5 mL	5
PK Analysis (panitumumab)	4 mL	16
PK & Metabolite Analysis (dabrafenib, trametinib)	4 mL	48
[redacted]		
Serum Pregnancy Test	1 mL	1
[redacted]		
CEA	2	10
Total		**187mL/subject plus any wasteage associated with collection**

Part 3: Randomized Phase II Study

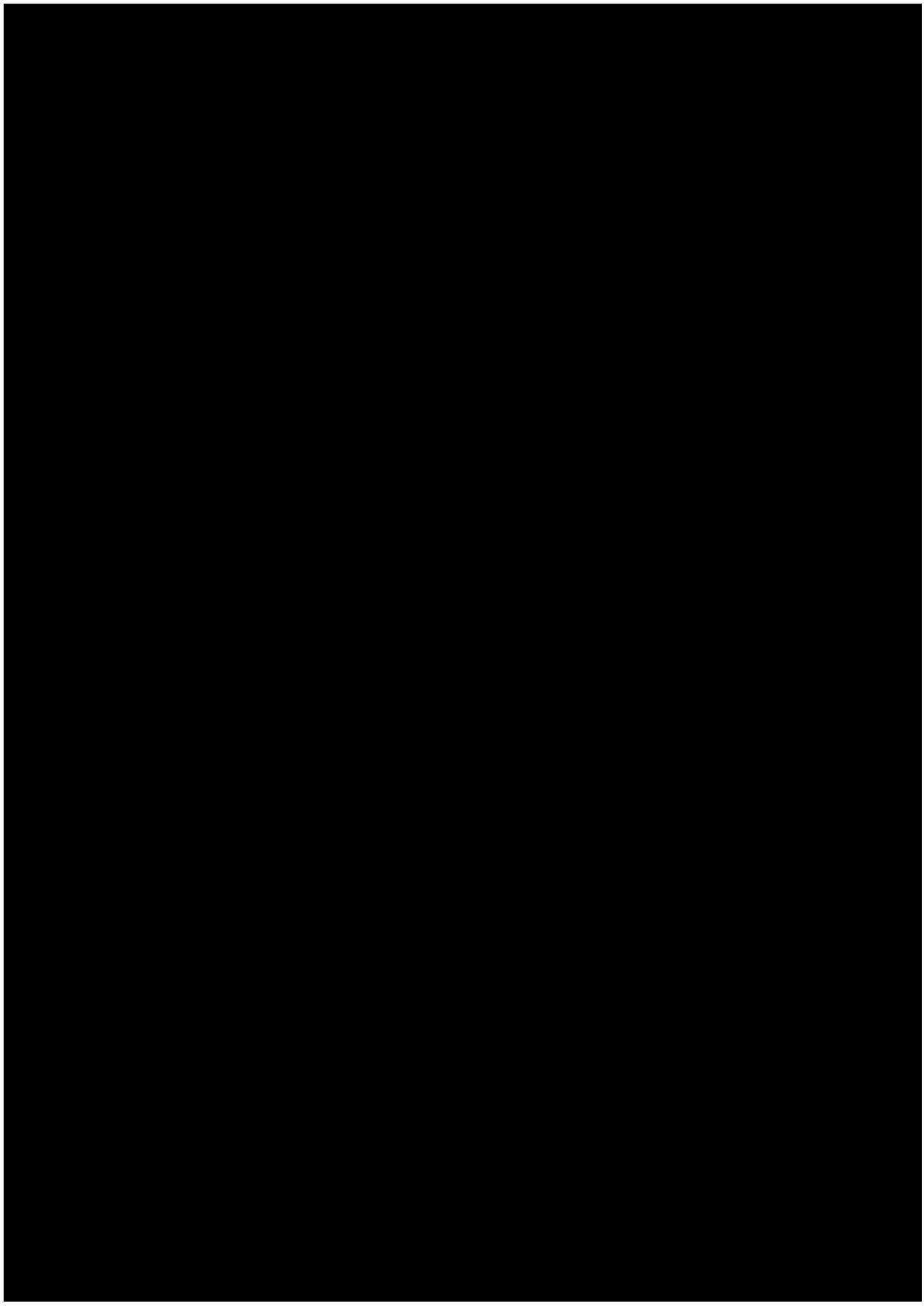
Test	Sample Volume	Total Volume for Screening, One 4-wk treatment period and Follow-up
Hematology/Clin Chem	5 mL	20
Coagulation	5 mL	5
[redacted]		
Serum Pregnancy Test	1 mL	1
Total		**82/subject plus any wasteage associated with collection**

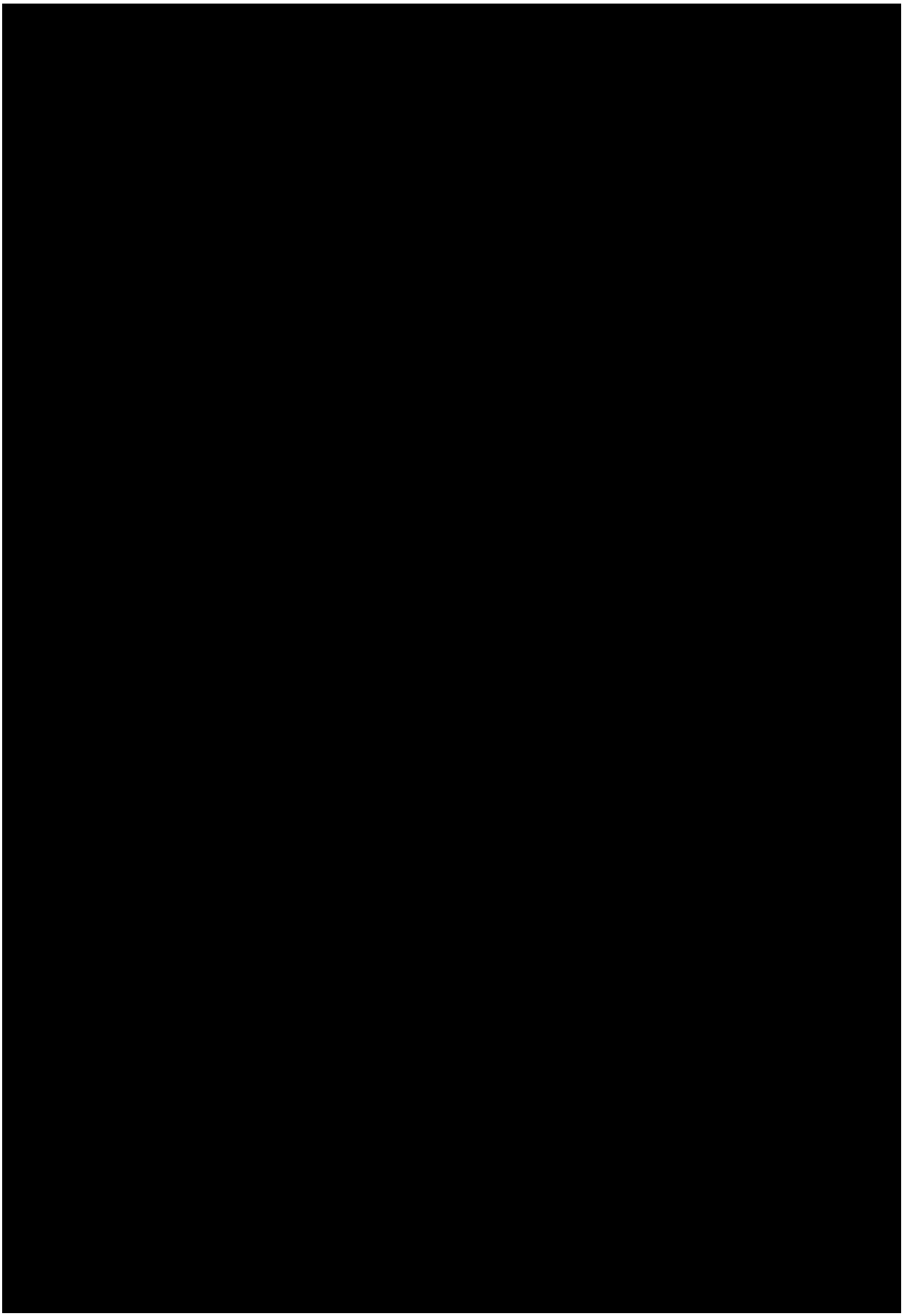
Part 4A and 4B: Dose Escalation and Expansion Cohorts

Test	Sample Volume	Total Volume for Screening, One 4-wk treatment period and Follow-up
Hematology/Clin Chem	5 mL	20
Coagulation	5 mL	5
PK Analysis (panitumumab)	4 mL	16
PK & Metabolite Analysis (dabrafenib, trametinib)	4 mL	48
[redacted]		
Serum Pregnancy Test	1 mL	1
[redacted]		
CEA	2	10
Total		**182mL/subject plus any wasteage associated with collection**

RATIONALE: Blood draw requirements updated based on updated time and events tables and addition of Part 4

[redacted]





[redacted]

AMENDMENT 2

Where the amendment applies

- French sites will follow revised schedule for dermatological examinations and assessment for non-cutaneous secondary/recurrent malignancy as noted below, per request of Agence Nationale de Securite du Medicament et des Produits de Sante (ANSM).

Cutaneous Squamous Cell Carcinoma (cuSCC) and New Primary Melanoma

Dermatological examinations should be performed prior to initiation of therapy with dabrafenib, monthly throughout treatment, and monthly 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. Subjects should be instructed to immediately inform their physician if new lesions develop.

Non-cutaneous Secondary/Recurrent Malignancy

Prior to initiation of dabrafenib treatment subjects 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. During treatment subjects 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 before and at the end of treatment or when considered clinically indicated. Complete blood cell counts should be performed as clinically indicated. Following discontinuation of dabrafenib 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. Abnormal findings should be reported as protocol-specific SAEs and managed according to clinical practices.

Amendment applies to all sites and all countries with changes to:

Throughout the protocol, central serous retinopathy (CSR) was changed to retinal pigment epithelium detachment (RPED.

Sponsor/Medical Monitor Information Page

PREVIOUS TEXT:

SPONSOR/MEDICAL MONITOR INFORMATION PAGE

Medical Monitor and Sponsor Contact Information:

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	Fax Number	GSK Address
[redacted] Monitor	[redacted] MD, PhD	[redacted]	[redacted]	[redacted]	GlaxoSmithKline 1250 Collegeville Road Mailstop UP4310 Collegeville, PA USA [redacted]
[redacted] Medical Monitor	[redacted] MD	[redacted]	[redacted]	[redacted]	GlaxoSmithKline 1250 Collegeville Road Mailstop UP4410 Collegeville, PA USA [redacted]
[redacted] Medical Monitor	[redacted] MD, PhD	[redacted]	[redacted]	[redacted]	GlaxoSmithKline 1250 Collegeville Road Mailstop UP4340 Collegeville, PA USA [redacted]
SAE fax number					

REVISED TEXT

SPONSOR/MEDICAL MONITOR INFORMATION PAGE

Medical Monitor and Sponsor Contact Information:

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	Fax Number	GSK Address
[redacted] Medical Monitor	[redacted] MD, PhD	[redacted]	[redacted]	[redacted]	GlaxoSmithKline 1250 Collegeville Road Mailstop UP4310 Collegeville, PA USA [redacted]
~~[redacted] Medical Monitor~~	~~[redacted] MD~~	[redacted]	[redacted]	[redacted]	~~GlaxoSmithKline 1250 Collegeville Road Mailstop UP4410 Collegeville, PA USA~~ [redacted]
[redacted] Medical Monitor	[redacted] MD, PhD	[redacted]	[redacted]	[redacted]	GlaxoSmithKline 1250 Collegeville Road Mailstop UP4340 Collegeville, PA USA [redacted]
SAE fax number					

Section 3.4.2, Table 1

PREVIOUS TEXT

Table 1 Part 1 Dosing Cohorts

	COHORTS							
	-1A	**-1B**	**-1C**	**1 STARTING DOSE**	**2**	**3A[a]**	**3B[a]**	**4**
dabrafenib[b]	100mg BID	150mg BID	100mg BID	150mg BID	RP2R* from Cohort 1 [b]	RP2R from Cohort 1 [b]	RP2R from Cohort 1 [b]	RP2R from Cohort 1 [b]
trametinib		-		-	1.5mg once daily	2mg once daily	1.5mg once daily	2mg once daily
panitumumab [c, d]	6mg/kg Q2W	4.8mg/kg Q2W	4.8mg/kg Q2W	6mg/kg Q2W	one dose level below RP2R from Cohort 1 [c]	one dose level below RP2R from Cohort 1 [c]	RP2R from Cohort 1 [d]	RP2R from Cohort 1 [d]

REVISED TEXT

Table 1 Part 1 Dosing Cohorts

	COHORTS							
	De-escalation cohorts			Dose escalation cohorts				
	-1A	-1B	-1C	1 STARTING DOSE	2	3A[a]	3B[a]	4
dabrafenib[b]	100mg BID	150mg BID	100mg BID	150mg BID	RP2R* from Cohort 1 [b]	RP2R from Cohort 1 [b]	RP2R from Cohort 1 [b]	RP2R from Cohort 1 [b]
trametinib		-		-	1.5mg once daily	2mg once daily	1.5mg once daily	2mg once daily
panitumumab [c, d]	6mg/kg Q2W	4.8mg/kg Q2W	4.8mg/kg Q2W	6mg/kg Q2W	one dose level below RP2R from Cohort 1 [c]	one dose level below RP2R from Cohort 1 [c]	RP2R from Cohort 1 [d]	RP2R from Cohort 1 [d]

Rationale: to distinguish between de-escalation and dose escalation cohorts.

Section 3.4.2, paragraph following Table 1

PREVIOUS TEXT

If the initial combination dose of dabrafenib and panitumumab in Cohort 1 (starting dose) is not tolerable, lower dose combination(s) defined in Cohort -1A, -1B and/or -1C may be evaluated. The actual Cohort -1 combination(s) that are opened will be based on the agent(s) that are most likely causing the intolerance. Once the dabrafenib/panitumumab combination dose is defined, subsequent cohorts in which trametinib is added will be based on the dabrafenib/panitumumab dose defined in Cohort 1 or -1 (e.g., if the maximally tolerated panitumumab dose in the dabrafenib/panitumumab combination is 4.8mg/kg, the panitumumab dose in Cohort 2 will be one dose level lower, or 3.6mg/kg. Cohorts that are designated as "3A" and "3B" may be opened simultaneously once the prior dosing cohort has completed the 28-day DLT window and met dose escalation criteria as specified in Table 2. If the combination doses in both Cohort 3A and Cohort 3B are well-tolerated, available safety and response data will be evaluated to determine the appropriate dose to evaluate in Part 2.

REVISED TEXT

If the initial combination dose of dabrafenib and panitumumab in Cohort 1 (starting dose) is not tolerable, lower dose combination(s) defined in de-escalation cohorts (Cohort -1A, -1B and/or -1C may be evaluated. The actual ~~Cohort -1 combination(s)~~ de-escalation cohorts that are opened will be based on the agent(s) that are most likely causing the intolerance. Once the dabrafenib/panitumumab combination dose is defined, subsequent

cohorts in which trametinib is added will be based on the dabrafenib/panitumumab dose defined in Cohort 1 or -1 (e.g., if the maximally tolerated panitumumab dose in the dabrafenib/panitumumab combination is 4.8mg/kg, the panitumumab dose in Cohort 2 will be one dose level lower, or 3.6mg/kg. Cohorts that are designated as "3A" and "3B" may be opened simultaneously once the prior dosing cohort has completed the 28-day DLT window and met dose escalation criteria as specified in Table 2. If the combination doses in both Cohort 3A and Cohort 3B are well-tolerated, available safety and response data will be evaluated to determine the appropriate dose to evaluate in Part 2.

Rationale: to distinguish between de-escalation and dose escalation cohorts.

Section 3.4.3 Part 2, paragraph 1

PREVIOUS TEXT:

In Part 2, the primary objectives will be to further assess the safety and preliminary clinical activity of given doses and regimen(s) in subjects with BRAF-V600E mutation-positive CRC. Enrollment in Part 2 will be initiated once dose escalation for both dabrafenib in combination with panitumumab and a trametinib plus dabrafenib in combination with panitumumab has been completed.

REVISED TEXT:

In Part 2, the primary objectives will be to further assess the safety and preliminary clinical activity of given doses and regimen(s) in subjects with BRAF-V600E mutation-positive CRC. Enrollment in Part 2 doublet will be initiated once dose escalation for the doublet ~~both~~ (dabrafenib in combination with panitumumab) ~~and a trametinib plus dabrafenib in combination with panitumumab~~ has been completed. Enrollment in Part 2 triplet (trametinib plus dabrafenib in combination with panitumumab) will open once dose escalation for the triplet has been completed.

Rationale: to clarify timing of opening Part 2 doublet and Part 2 triplet cohorts.

Section 3.7.3 Intra-subject Dose Escalations

PREVIOUS TEXT

In Part 1, intra-subject dose escalation will be allowed for patients enrolling in the triplet cohorts provided that the subject has completed at least two 28-day periods on treatment. A subject's dose level for the combination may be increased up to the highest combination dose level that has previously been confirmed as not exceeding the MTD for the combination. The intra-subject dose escalation must be agreed to by the investigator and the GSK Medical Monitor.

REVISED TEXT

Section 3.7.3 Intra-subject Doublet to Triplet Crossover and Dose Escalation: Part 1 and Part 2

~~In Part 1, intra-subject dose escalation will be allowed for patients enrolling in the triplet cohorts provided that the subject has completed at least two 28-day periods on treatment. A subject's dose level for the combination may be increased up to the highest combination dose level that has previously been confirmed as not exceeding the MTD for the combination. The intra-subject dose escalation must be agreed to by the investigator and the GSK Medical Monitor.~~

For subjects enrolled in Part 1 or Part 2, intra-subject doublet to triplet crossover is allowed if a patient has not experienced intolerable toxicity that could not be managed, and has demonstrated radiographic progression on therapy by RECIST v1.1 criteria, and approval will be based on review by GSK Medical Monitor. Dose administered must be from among those for which cohorts have been completed and data has been reviewed for safety.

Subjects are allowed to crossover once during the study.

Additionally, for subjects who have remained on study for ≥ 6 months in the triplet combination, their dose level for the combination may be increased up to the highest combination dose level that has previously been confirmed as not exceeding the MTD for the combination. The intra-subject dose escalation must be agreed to by the investigator and the GSK Medical Monitor.

Rationale: To include text allowing subjects who enrolled in Part 1 or Part 2 doublet cohort to crossover to a triplet cohort, or to allow those enrolled at a lower than MTD cohort to dose-escalate.

Section 3.7.9, Table 15 Withholding and Stopping Criteria for QTc Prolongation

PREVIOUS TEXT

QTc Prolongation[a]	**Action and Dose Modification**
QTcB≥501msec	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

REVISED TEXT

QTc Prolongation[a]	Action and Dose Modification
QTcB≥501msec	• Interrupt study treatment until QTcB prolongation resolves to Grade 1 or baseline • Test serum potassium, calcium, phosphorus and magnesium. If <LLN correct with supplements to within normal limits. • Review concomitant medication usage for a prolonged QTc. • If event resolves, restart study treatment at current dose level[b] • **If event does not resolve, permanently discontinue study treatments** • **If event recurs, permanently discontinue study treatments**

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

Rationale: to clarify text based on updated standardized safety text for dabrafenib and trametinib assets.

Section 3.8.1, Time and Events Table, Part 1 Dose Escalation

Added text:

Hematology/Clinical Chemistry (including Screening assessment of adequate baseline organ function as noted in Table 18)

Footnote 7: French sites will perform dermatological exams monthly while on-therapy, and monthly for 6 months following discontinuation of dabrafenib or until initiation of another anti-neoplastic therapy, whichever comes first. Refer to Appendix 7 for full information.

Footnote 11: Tumor biopsy at tumor progression in subjects who have had a radiologic response (20% or more) or had stable disease for 6 months is highly encouraged.

Footnote 13: Collection of archived tumor tissue or fresh tumor biopsies and determination of the subject's tumor BRAF mutation status is required for enrollment; if a fresh tumor biopsy is collected ~~at~~ during screening and up to prior to dosing on Day 1 for BRAF mutation confirmation, this tissue may be used for the day 1/ predose tumor biopsy. [redacted] The Day 1/predose tumor biopsy may be collected at any point after signing consent, after completing washout from prior therapies (either 5 half-lives or 14 days from last dose of prior therapy) ~~up to 14 days prior to first dose.~~

Rationale: to indicate that subjects should have all assessments performed to meet inclusion/exclusion requirements at screening; to point out requirements for French sites

in timing of dermatological exams; and to clarify which subjects should have tumor biopsy at progression.

Section 3.8.2, Time and Events Table, Part 2 Cohort Expansion

Added text:

Hematology/Clinical Chemistry (including Screening assessment of adequate baseline organ function as noted in Table 18)

Footnote 7: French sites will perform dermatological exams monthly while on-therapy, and monthly for 6 months following discontinuation of dabrafenib or until initiation of another anti-neoplastic therapy, whichever comes first. Refer to Appendix 7 for full information.

Footnote 11: Tumor biopsy at tumor progression in subjects who have had a radiologic response (20% or more) or had stable disease for 6 months is highly encouraged.

Footnote 12: Optional biopsy for subjects who had a radiologic response (20% or more decrease) or had a stable disease for 6 months at disease progression (if feasible). ~~Mandatory tumor biopsy at tumor progression.~~ A single PK sample will be collected at the time of tumor progression. Refer to Section 6.7.2.

Footnote 13: Collection of archived tumor tissue or fresh tumor biopsies and determination of the subject's tumor BRAF mutation status is required for enrollment; if a fresh tumor biopsy is collected ~~at~~ during screening and up to prior to dosing on Day 1 for BRAF mutation confirmation, this tissue may be used for the day 1/ predose tumor biopsy. [redacted] The Day 1/predose tumor biopsy may be collected at any point after signing consent, after completing washout from prior therapies (either 5 half-lives or 14 days from last dose of prior therapy) ~~up to 14 days prior to first dose~~.

Rationale: to indicate that subjects should have all assessments performed to meet inclusion/exclusion requirements at screening; to point out requirements for French sites in timing of dermatological exams; and to clarify which subjects should have tumor biopsy at progression.

Section 3.8.3, Time and Events Table, Part 3 Randomized Phase II

Added text:

Hematology/Clinical Chemistry (including Screening assessment of adequate baseline organ function as noted in Table 19)

Tumor tissue biopsy (optional) at progression

Footnote 7: French sites will perform dermatological exams monthly while on-therapy, and monthly for 6 months following discontinuation of dabrafenib or until

initiation of another anti-neoplastic therapy, whichever comes first. Refer to Appendix 7 for full information.

Footnote 16: Optional biopsy for subjects who had a radiologic response (20% or more decrease) or had a stable disease for 6 months at disease progression. The biopsy at progression is highly encouraged.

Rationale: to indicate that subjects should have all assessments performed to meet inclusion/exclusion requirements at screening; to add an optional tumor biopsy at progression; to point out requirements for French sites in timing of dermatological exams; and to clarify which subjects should have tumor biopsy at progression.

Section 4.2.1.1 Part 1 and Part 2 Inclusion Criteria

PREVIOUS TEXT

7. Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use one of the contraception methods listed in Section 7.1.2 from the time of the first dose of study drug(s) and until 6 months after the last dose of panitumumab, or 16 weeks following the last dose of dabrafenib or trametinib, whichever is later to allow for clearance of any altered sperm.

9. Female subjects must agree to use contraception from the time of the first dose of study drug(s) until 60 days after the last dose of any study drug. *Note: oral contraceptives are not reliable due to potential drug-drug interactions.* Additionally, women of childbearing potential must have had a negative serum pregnancy test within 7 days prior to the first dose of study drug(s).

REVISED TEXT

7. Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use one of the contraception methods listed in Section 7.1.2 from ~~the time of~~ 7 days prior to the first dose of study drug(s) and until 6 months after the last dose of panitumumab, or 16 weeks following the last dose of dabrafenib or trametinib, whichever is later to allow for clearance of any altered sperm.

9. Female subjects must agree to use contraception from ~~the time of~~ 7 days prior to the first dose of study drug(s) until ~~60 days after the last dose of any study drug~~ 6 months after the last dose of panitumumab, until 4 months after the last dose of trametinib, or 4 weeks after the last dose of dabrafenib, whichever is longer. *Note: oral contraceptives are not reliable due to potential drug-drug interactions.* Additionally, women of childbearing potential must have had a negative serum pregnancy test within 7 days prior to the first dose of study drug(s).

Rationale: update to contraception requirements per updated standardized safety text for dabrafenib and trametinib assets.

Section 4.2.2.1 Part 3 Inclusion Criteria

PREVIOUS TEXT

9. Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use one of the contraception methods listed in Section 7.1.2 from the time of the first dose of study drug(s) and until 6 months after the last dose of panitumumab, or 16 weeks following the last dose of dabrafenib or trametinib, whichever is later to allow for clearance of any altered sperm.

11. Female subjects must agree to use contraception from the time of the first dose of study drug(s) until 60 days after the last dose of any study drug. *Note: oral contraceptives are not reliable due to potential drug-drug interactions.* Additionally, women of childbearing potential must have had a negative serum pregnancy test within 7 days prior to the first dose of study drug(s).

REVISED TEXT

9. Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use one of the contraception methods listed in Section 7.1.2 from ~~the time of~~ 7 days prior to the first dose of study drug(s) and until 6 months after the last dose of panitumumab, or 16 weeks following the last dose of dabrafenib or trametinib, whichever is later to allow for clearance of any altered sperm.

11. Female subjects must agree to use contraception from ~~the time of~~ 7 days prior to the first dose of study drug(s) until ~~60 days after the last dose of any study drug~~ 6 months after the last dose of panitumumab, until 4 months after the last dose of trametinib, or 4 weeks after the last dose of dabrafenib, whichever is longer. *Note: oral contraceptives are not reliable due to potential drug-drug interactions.* Additionally, women of childbearing potential must have had a negative serum pregnancy test within 7 days prior to the first dose of study drug(s).

Rationale: update to contraception requirements per updated standardized safety text for dabrafenib and trametinib assets.

Section 5.2.3 Analysis Populations, added paragraph

The **Crossover Population** will comprise the subset of subjects in Part 1 and Part 2 who had intra-subject dose escalation. It will be the primary population when summarizing data in Part 1 and Part 2 crossover phase.

Rationale: to address how subjects who crossover from doublet to triplet dosing will be analysed.

Section 5.3.7.8.1 Efficacy Analyses, Part 1 and Part 2, added text to last paragraph

For Part 1 and Part 2, anti-tumor activities will be evaluated based on clinical evidence and response criteria. If the data warrant, the response data from both parts will be combined and summarized by dose level. Subjects who crossover from

dabrafenib/panitumumab combination to dabrafenib/trametinib/panitumumab combination will not be included in the main efficacy analysis for dabrafenib/trametinib/panitumumab combinations. The efficacy for these subjects will be summarized separately.

Rationale: to address how subjects who crossover from doublet to triplet dosing will be analysed.

Section 6.7.2 Fresh Tumor Tissue at Progression, added section

Tumor specimens that are accessible and can be sampled easily will be requested from some subjects at time of demonstrated progression on therapy, as determined by RECIST v1.1 criteria. Subjects of interest will be those who have had meaningful clinical response in target lesions (≥20% reduction, or stable disease for ≥6 months) and then progressed on existing target lesions or if a new lesion emerged. The guidance on the lesion selection for the progression biopsy are:

- if subject has new lesions only, preferably biopsy a new lesion if feasible
- if a subject has growth of existing lesions only, biopsy a growing lesion if feasible if a subject has both emergence of new lesions and growth of existing lesions, then biopsy both a new lesion and existing lesions, if feasible.
- If above criteria based lesions are not feasible to be biopsied, selection of lesion will be at the discretion of the interventional radiologist.

[redacted]

Details of the tumor biopsy collection including processing, storage and shipping procedures will be provided in the SPM.

Rationale: to provide clarity on collection of tumor biopsy at progression

Section 7.1.1 Contraception Requirements, Female Subjects

PREVIOUS TEXT

Female subjects of childbearing potential must not become pregnant and so must be sexually inactive by abstinence or use contraceptive methods with a failure rate of < 1% from start of dosing and until 60 days after the last dose of any study drug.

REVISED TEXT

Female subjects of childbearing potential must not become pregnant and so must be sexually inactive by abstinence or use contraceptive methods with a failure rate of < 1% from start of dosing and ~~until 60 days after the last dose of any study drug~~.

- for 6 months after the last dose of panitumumab (Vectibix)
- for 4 months after the last dose oftrametinib in combination with dabrafenib
- for 4 weeks after the last dose of dabrafenib.

Rationale: update to contraception requirements per updated standardized safety text for dabrafenib and trametinib assets.

Section 7.1.2 Contraception Requirements, Male Subjects

PREVIOUS TEXT

To prevent pregnancy in a female partner or to prevent exposure of any partner to the study treatment from a male subject's semen, male subjects must use one of the following contraceptive methods after the start of dosing and until 6 months after the last dose of panitumumab, or 16 weeks following the last dose of dabrafenib or trametinib, whichever is later to allow for clearance of any altered sperm:

REVISED TEXT

To prevent pregnancy in a female partner or to prevent exposure of any partner to the study treatment from a male subject's semen, male subjects must use one of the following contraceptive methods ~~after the start of dosing~~ from 7 days prior to the first dose and until 6 months after the last dose of panitumumab, or 16 weeks following the last dose of dabrafenib or trametinib, whichever is later to allow for clearance of any altered sperm:

Rationale: update to contraception requirements per updated standardized safety text for dabrafenib and trametinib assets.

Section 7.2 Meals and Dietary Restrictions

PREVIOUS TEXT

Dabrafenib and trametinib should be administered under fasting conditions, either one hour before or 2 hours after a meal. If a subject vomits within 4 hours after taking study medication, the subject should be instructed not to retake the dose and should take the next scheduled dose. These subjects will be excluded from PK analysis, but not replaced.

REVISED TEXT

Dabrafenib and trametinib should be administered **in the morning** at approximately the same time every day. The second dose of dabrafenib (150 mg) should be administered approximately 12 hours after the morning dose. 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.

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

Rationale: to provide clarity on timing of dosing

Section 10.3.3 Storage

PREVIOUS TEXT

All investigational products must be stored in original bottles supplied by GSK and in a secure area with access limited to the investigator and authorized site staff. Dabrafenib is to be stored up to 30°C (86°F) in an opaque bottle, as supplied by GSK. Trametinib is to be stored at 25°C (77°F), protected from moisture and light, and stored and dispensed in the original cartons supplied by GSK. Whole bottles of investigational products are dispensed at each 4 week visit. Maintenance of a temperature log (manual or automated) is required.

REVISED TEXT

All investigational products must be stored in original bottles supplied by GSK and in a secure area with access limited to the investigator and authorized site staff. Dabrafenib is to be stored up to 30°C (86°F) in an opaque bottle, as supplied by GSK. Trametinib is to be stored at 2 to 8°C (36 to 46°F) ~~25°C (77°F)~~, protected from moisture and light, and stored and dispensed in the original cartons supplied by GSK. Please ensure that the bottles have equilibrated back to room temperature before opening them to avoid moisture condensation on the tablets. Whole bottles of investigational products are dispensed at each 4 week visit. Maintenance of a temperature log (manual or automated) is required.

Rationale: new storage specifications for trametinib have been provided.

AMENDMENT 1

Where the amendment applies

This amendment applies to all sites in all countries.

Summary of Amendment Changes with Rationale

Major revisions in this amendment restricts enrollment to V600E mutation positive CRC; formerly allowed V600E or V600K mutations; allows use of MUGA to evaluate LVEF if ECHO is not available; allows use of therapeutic warfarin (previously exclusionary); adds text on Bayesian design for Part 2; clarifies follow-up (PFS, OS) for subjects who discontinue study treatment for any reason other than disease progression; addresses cardiac monitoring assessments as requested by the ANSM.

Throughout the protocol, minor edits have been made to clarify text, including removal of references to V600K mutation specific to enrollment in this study, clarification of supporting documents (Investigator Brochures, supplements to the Investigator Brochures) and reformatting of the study schematic for Part 1 to be more easily understood.

Title

Previous text: An Open-Label, Three-Part, Phase I/II Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of the MEK Inhibitor GSK1120212, BRAF Inhibitor GSK2118436 and the anti-EGFR Antibody Panitumumab in Combination in Subjects with BRAF-mutation V600E or V600K Positive Colorectal Cancer

Revised text: An Open-Label, Three-Part, Phase I/II Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of the MEK Inhibitor GSK1120212, BRAF Inhibitor GSK2118436 and the anti-EGFR Antibody Panitumumab in Combination in Subjects with BRAF-mutation V600E ~~or V600K~~ Positive Colorectal Cancer

Rationale: The studypopulation was revised to clearly reflect the majority of patients with BRAF-mutation positive colorectal cancer will have the BRAF V600E mutation.

Synopsis

Previous text:

Part 2 of the study will consist of expansion cohorts to enroll subjects with BRAF-mutation V600E or V600K positive CRC, and investigate safety and clinical activity of dabrafenib in combination with panitumumab and trametinib plus dabrafenib in combination with panitumumab

Revised text:

Part 2 of the study will consist of expansion cohorts to ~~enroll subjects with BRAF-mutation V600E or V600K positive CRC, and~~ investigate safety and clinical activity of dabrafenib in combination with panitumumab and trametinib plus dabrafenib in combination with panitumumab.

Rationale: Clarification of text; the population enrolled for all parts of the study will be subjects with BRAF-mutation-positive CRC.

SPONSOR/MEDICAL MONITOR INFORMATION PAGE

Medical Monitor and Sponsor Contact Information:

Previous text:

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	Fax Number	GSK Address
[redacted] Medical Monitor	[redacted], MD	[redacted]	[redacted]	[redacted]	GlaxoSmithKline 1250 Collegeville Road Mailstop UP4210 Collegeville, PA USA [redacted]

Revised text:

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	Fax Number	GSK Address
[redacted] Medical Monitor	[redacted] MD	[redacted]	[redacted]	[redacted]	GlaxoSmithKline 1250 Collegeville Road Mailstop UP4410 Collegeville, PA USA [redacted]

Rationale: Revision to Secondary Medical Monitor contact information to reflect changes in staffing.

Previous text:

Regulatory Agency Identifying Number(s); IND#113557

Revised text:

Regulatory Agency Identifying Number(s): IND# 113557, EUDRACT# 2012-004802-81, NCT# 01750918

Rationale: Addition of EUDRACT # and NCT# once available.

Abbreviations:

Added text:

CuSCC	Cutaneous squamous cell carcinoma

Rationale: Addition of abbreviation used in added text in body of protocol.

Section 1.4.2 GSK1120212: Trametinib, paragraph 4:

Previous text:

Cardiac function: A reduction in cardiac function in a fraction of subjects (specifically, left ventricular ejection fraction) is a known class effect of MEK inhibitors and have been seen with trametinib. Subjects with pre-existing heart failure will be excluded from this study. To monitor cardiac function, echocardiogram (ECHO) exams will be performed. In addition, withholding criteria for left ventricular ejection fraction decreases will be implemented.

Revised text:

Cardiac function: A reduction in cardiac function in a fraction of subjects (specifically, left ventricular ejection fraction) is a known class effect of MEK inhibitors and have been seen with trametinib. Subjects with pre-existing heart failure will be excluded from this study. ~~To monitor~~ Cardiac function~~, echocardiogram (ECHO) exams~~ will be performed. assessed prior to enrollment, and will be monitored on study. In addition, withholding criteria for left ventricular ejection fraction decreases will be implemented.

Rationale: Revised text to allow either ECHO or MUGA for evaluation of cardiac function prior to start of study and allow for ECHO or MUGA for on study evaluation of changes. ECHO is the preferred method; MUGA will be allowed only at sites which cannot perform ECHO.

Section 2.1 Part 1: Phase I Dose Escalation

Previous text:

Secondary	To describe the pharmacokinetics of dabrafenib, trametinib and panitumumab after combination therapy To determine preliminary clinical activity of dabrafenib dosed orally in combination with panitumumab To determine clinical activity of trametinib dosed orally in combination with dabrafenib and	Maximum observed concentration (Cmax), time of occurrence of Cmax (tmax), and area under the concentration-time curve from zero (pre-dose) 8 hours (AUC(0-8)), pre-dose (trough) concentration at the end of the dosing interval ($C\tau$) of trametinib and dabrafenib. Predose ($C\tau$) and Cmax concentrations of panitumumab. Response rate (complete response [CR] + partial response [PR])

	panitumumab	Progression free survival Duration of response Response rate (CR +PR) Progression free survival Duration of response
[redacted]		

Revised text:

Secondary	To describe the pharmacokinetics of dabrafenib, trametinib and panitumumab after combination therapy To determine preliminary clinical activity of dabrafenib dosed orally in combination with panitumumab To determine clinical activity of trametinib dosed orally in combination with dabrafenib and panitumumab	Maximum observed concentration (Cmax), time of occurrence of Cmax (tmax), and area under the concentration-time curve from zero (pre-dose) 8 hours (AUC(0-8)), pre-dose (trough) concentration at the end of the dosing interval ($C\tau$) of trametinib and dabrafenib. Predose ($C\tau$) and Cmax concentrations of panitumumab. Response rate (complete response [CR] + partial response [PR]) Progression free survival Duration of response

		Response rate (CR +PR) Progression free survival Duration of response
	To evaluate the pharmacodynamic response in colorectal tumors following combination treatment	Change in levels of proteins/RNA implicated in MAPK/PI3K/EGFR pathways in pre- and post-dose tumor tissue.
[redacted]		

Section 2.2 Part 2: Cohort Expansions

Previous text:

Secondary	To characterize the population PK parameters of dabrafenib and trametinib dosed orally in combination with anti-EGFR antibody (panitumumab)	Population PK parameters, oral clearance (CL/F), oral volume of distribution (V/F), and absorption rate constant (Ka)
	To characterize the durability of response with dabrafenib dosed orally in combination with panitumumab	Duration of response Progression-free survival Overall survival
	To characterize the durability of response with trametinib dosed orally	Duration of response Progression-free survival

	in combination with dabrafenib and panitumumab	Overall Survival
[redacted]		

Revised text:

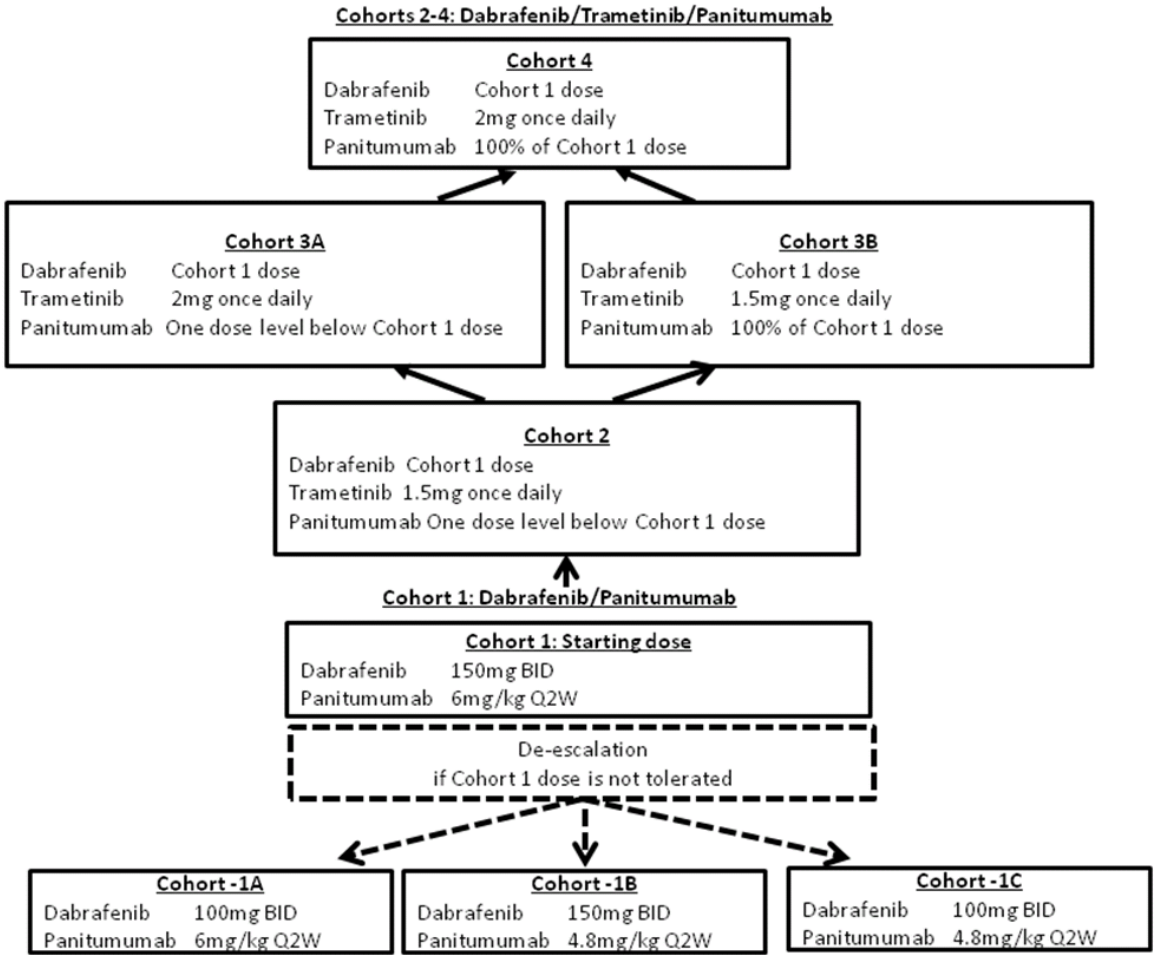
Secondary	To characterize the population PK parameters of dabrafenib and trametinib dosed orally in combination with anti-EGFR antibody (panitumumab)	Population PK parameters, oral clearance (CL/F), oral volume of distribution (V/F), and absorption rate constant (Ka)
	To characterize the durability of response with dabrafenib dosed orally in combination with panitumumab	Duration of response Progression-free survival Overall survival
	To characterize the durability of response with trametinib dosed orally in combination with dabrafenib and panitumumab	Duration of response Progression-free survival Overall Survival

	To evaluate the pharmacodynamic response in colorectal tumors following combination treatment	Change in levels of proteins/RNA implicated in MAPK/PI3K/EGFR pathways in pre- and post-dose tumor tissue
[redacted]		

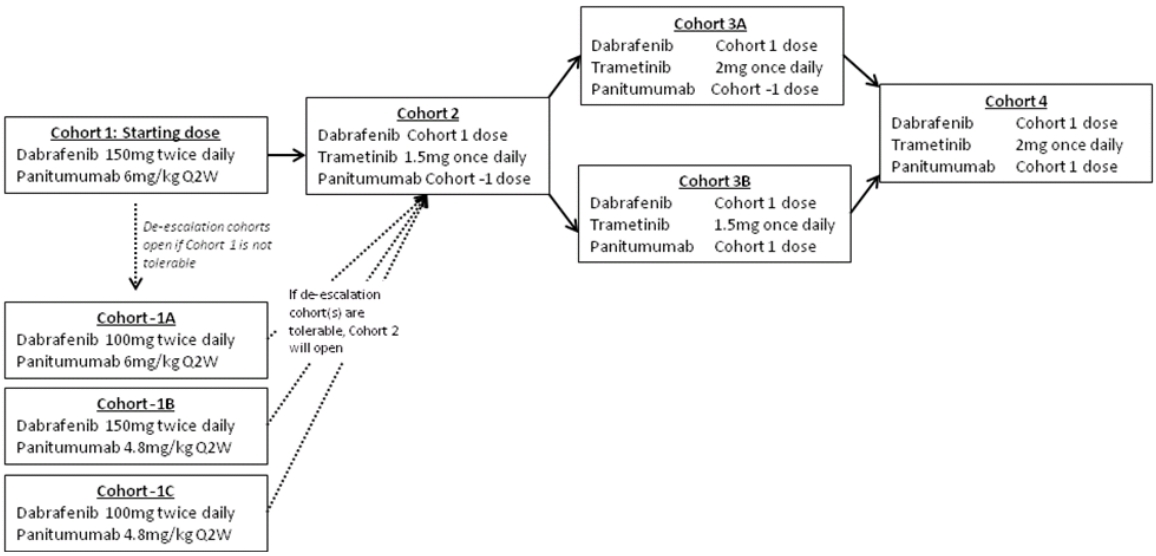
Rationale: Given that pharmacodynamics will be investigated during the course of the study, the pharmacodynamics objective and endpoint was moved from [redacted] secondary for both Part 1 (Section 2.1) and Part 2 (Section 2.2).

Section 3.1 Part 1 Dose Escalation Study Design/Schematic

Previous schematic:



Revised schematic:



Rationale: Clarification of schematic; no revision to study design.

Section 3.4.1 Prescreening for KRAS and BRAF Mutation Status, paragraphs 4 and 5

Previous text:

Enrollment in Part 3 will only occur following centralized determination of BRAFV600E or V600K mutation.

Archived tumor tissue sample must be collected from all subjects enrolled in this study at screening. If this has not been done and an archived tumor tissue sample is not available, the subject should undergo a biopsy to obtain a tumor tissue sample. [redacted]

Revised text:

Enrollment in Part 3 will only occur following centralized determination of BRAFV600E ~~or V600K~~ mutation. Testing must be performed in a CLIA certified central laboratory. The testing will be preferably conducted on metastatic tumor tissue or on recently obtained tumor tissue.

Archived tumor tissue sample must be collected from all subjects enrolled in this study at screening. If this has not been done and an archived tumor tissue sample is not available, the subject should undergo a biopsy prior to dosing to obtain a tumor tissue sample. [redacted]

Rationale: Addition of specific requirements for central laboratory testing, and type of tissue to be tested.

Section 3.4.2 Part 1, paragraph 2 (following Table 1)

Previous text:

If the initial combination dose of dabrafenib and panitumumab in Cohort 1 is not tolerable, lower dose combination(s) defined in Cohort -1 will be evaluated.

Revised text:

If the initial combination dose of dabrafenib and panitumumab in Cohort 1 (starting dose) is not tolerable, lower dose combination(s) defined in Cohort ~~-1 will~~ 1A, -1B and/or -1C may be evaluated.

Rationale: Clarification regarding inclusion of Cohort -1A, -1B and/or -1C. These cohorts will be opened only if toxicity emerges in Cohort 1.

Section 3.4.2 Part 1, paragraph 5 (following Table 2)

Previous text:

Any cohort may be expanded beyond the 3 to 6 subjects enrolled during dose escalation, to a maximum of 12 subjects, to facilitate additional collection of safety data.

Revised text:

Any cohort may be expanded beyond the initial 3 to 6 subjects enrolled during dose escalation, to a maximum of 12 subjects, to facilitate additional collection of safety data.

Rationale: Clarification of the number of subjects that may be enrolled.

Section 3.4.2.1 Dose-Limiting Toxicity Definitions

Previous text:

Toxicity	DLT Definition
Hematologic	• Grade 4 absolute neutrophil count (ANC) for ≥5 days • Febrile neutropenia (defined as concurrent Grade 4 neutropenia and fever >38.5°C and lasting >24 hrs) • Grade 4 anemia of any duration • Grade 4 thrombocytopenia (platelets <25,000) of any duration
Non-hematologic	Alanine aminotransferase (ALT) >5X upper limit of normal (ULN) OR, ALT >3X ULN AND bilirubin >2X ULN (after exclusion of disease progression and/or bile duct obstruction) • Grade ≥4 rash • Grade 4 Squamous Cell Carcinoma, keratoacanthoma or basal cell carcinoma Grade 3 or greater clinically significant non-hematologic toxicity per NCI-CTCAE, v 4.0, other than those listed above, with the following exceptions: o Grade 3 or greater nausea, vomiting, diarrhea, or mucositis/esophagitis that responds to maximal supportive treatment(s) within 48 hours o Electrolyte disturbances that respond to correction within 24 hours o Grade 3 hypertension that is adequately controlled by the addition of up to 2 additional antihypertensive medications • Grade 3 pyrexia that does not result in study discontinuation
Cardiac	• Ejection fraction < lower limit of normal (LLN) with an absolute decrease of >10% from baseline with confirming assessment within 7 days.
Other	• Inability to received >75% of scheduled doses in treatment period due to toxicity • Grade 2 or higher toxicity that occurs beyond 21 days which in the judgment of the investigator and GSK Medical Monitor is considered to be a DLT

Revised text:

Toxicity	DLT Definition
Hematologic	• Grade 4 absolute neutrophil count (ANC) for ≥5 days • Febrile neutropenia (defined as concurrent Grade 4 neutropenia and fever >38.5°C and lasting >24 hrs) • Grade 4 anemia of any duration • Grade 4 thrombocytopenia (platelets <25,000) of any duration
Non-hematologic	Alanine aminotransferase (ALT) >5X upper limit of normal (ULN) OR, ALT >3X ULN AND bilirubin >2X ULN (after exclusion of disease progression and/or bile duct obstruction) • Grade ≥4 rash • Grade 4 Squamous Cell Carcinoma, keratoacanthoma or basal cell carcinoma Grade 3 or greater clinically significant non-hematologic toxicity per NCI-CTCAE, v 4.0, other than those listed above, with the following exceptions: o Grade 3 or greater nausea, vomiting, diarrhea, or mucositis/esophagitis that responds to maximal supportive treatment(s) within 48 hours o Electrolyte disturbances that respond to correction within 24 hours o Grade 3 hypertension that is adequately controlled by the addition of up to 2 additional antihypertensive medications o Grade 3 pyrexia that does not result in study discontinuation
Cardiac	• Ejection fraction < lower limit of normal (LLN) with an absolute decrease of >~~10~~ 20% from baseline ~~with confirming assessment within 7 days.~~
Other	• Inability to received >75% of scheduled doses in treatment period due to toxicity • Grade 2 or higher toxicity that occurs beyond ~~21~~ 28 days which in the judgment of the investigator and GSK Medical Monitor is considered to be a DLT

Rationale: Clarification that: Grade 3 pyrexia that does not result in study discontinuation" is a sub-bullet to "Grade 3 or greater clinically significant non-hematologic toxicity per NCI-CTCAE, v 4.0, other than those listed above, with the following exceptions:'. Revising the ejection fraction criteria per safety data. Correcting the period of time for DLT evaluation from 21 to 28 days.

Section 3.4.3 Part 2, paragraph 4

Previous text:

The responses will be assessed and decisions to continue to Part 3 will be made based on response data are available for up to 20 subjects for each cohort. **In order to proceed to Part 3, sufficient evidence of clinical activity (e.g. observing 4 responses out of up to 20 subjects) should be observed to warrant further development.**

Revised text:

The responses will be assessed and decisions to continue to Part 3 will be made based on response data are available for up to 20 subjects for each cohort. **In order to proceed to Part 3, sufficient evidence of clinical activity (e.g. observing 4 responses out of up to 20 subjects) should be observed to warrant further development.** Meanwhile**,** the Part 2 portion of the study will employ a Bayesian design that allows the trial to be monitored more frequently at multiple stages.

Rationale: Additional text to define use of Bayesian design in Part 2/Cohort Expansion.

Section 3.6 Investigational Products and Other Study Treatment Dosage/Administration

Previous text:

Trametinib: GSK1120212
Each tablet contains 0.5mg or 2.0 mg GSK1120212 [redacted]

Revised text:

Trametinib: GSK1120212
Each tablet contains 0.5mg or 2.0 mg GSK1120212 [redacted]

Rationale: Correction to indicate that the film coating will contain yellow or pink, not both yellow and pink.

Section 3.7.1, Table 3 Categories of Dose Modification Guidelines

Added table:

Adverse Event	Dabrafenib	Trametinib	Section
General Guidelines for Clinically Significant Toxicities	X	X	Section 3.7.4
Guidelines for Specific Adverse Events Cardiovascular Adverse Events[a]			
LVEF		X	Section 3.7.7.1
Hypertension	X	X	Section 3.7.8
Prolonged QTc	X	X	Section 3.7.9
Skin –Related Adverse Events (Except cuSCC)[b]			
Rash	X	X	Section 3.7.4.2
Hand-Foot Skin Reaction	X	X	Section 3.7.4.2.4
Other Adverse Events			
Pyrexia	X		Section 3.7.4.1
Diarrhea	X	X	Section 3.7.5
Renal Insufficiency	X	X	Section 3.7.6
Visual Changes	X	X	Section 3.7.11
Pneumonitis	X	X	Section 3.7.13
Liver Chemistry Stopping Criteria	X	X	Section 3.7.10

a. For subjects enrolled in France, please see Appendix 5 for additional dose modification guidelines.
b. Refer to Section 3.7.4.3 for management of cuSCC

Rationale: Table was added to summarize dose modification guidelines and to ease navigation through the text.

Section 3.7.2 Dose Adjustment, paragraphs 4 and 5

Previous text:

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 with approval from the GSK Medical Monitor.

A dose reduction below 75mg BID for dabrafenib, 1mg once daily for trametinib and 3mg/kg every 14 days for panitumumab is not allowed. If a dose reduction below 75 mg BID for dabrafenib is required, dabrafenib will be permanently discontinued, but the subjects will be allowed to continue trametinib and panitumumab. If a dose reduction below1.0 mg once daily for trametinib is required, then trametinib will be permanently discontinued, but these subjects will be allowed to continue dabrafenib and panitumumab. If a dose reduction below 3mg/kg every 14 days for panitumumab is required, panitumumab will be permanently discontinued, but the subjects will be allowed to continue dabrafenib and trametinib.

Revised text:

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 with approval from the GSK Medical Monitor.

A dose reduction below 75mg BID for dabrafenib, 1mg once daily for trametinib and 3mg/kg every 14 days for panitumumab is not allowed (per the panitumumab label [VECTIBIX, 2012]. If a dose reduction below 75 mg BID for dabrafenib is required, dabrafenib will be permanently discontinued, but the subjects will be allowed to continue trametinib and panitumumab. If a dose reduction below1.0 mg once daily for trametinib is required, then trametinib will be permanently discontinued, but these subjects will be allowed to continue dabrafenib and panitumumab. If a dose reduction below 3mg/kg every 14 days for panitumumab is required, panitumumab will be permanently discontinued, but the subjects will be allowed to continue dabrafenib and trametinib.

Rationale: Dose re-escalation may occur only after discussion between the investigator and the GSK medical monitor. Panitumumab dosing may not be decreased below label parameters.

Section 3.7.3 Intra-subject Dose Escalations

Previous text:

In Part 1, intra-subject dose escalation will be allowed provided that the subject has completed at least two 28-day periods on treatment.

Revised text:

In Part 1, intra-subject dose escalation will be allowed for patients enrolling in the triplet cohorts provided that the subject has completed at least two 28-day periods on treatment.

Rationale: Patients enrolling in the doublet cohort, dosing with dabrafenib plus panitumumab, are receiving the maximum approved dose.

Section 3.7.4 Dose Adjustment/Stopping Safety Criteria

Revised section title to: General Guidelines for Clinically Significant Toxicities

Added text: 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.

Revised Table 5:

Non-hematologic and hematologic toxicity (except neutropenia and fever), CTCAE Grade	Dose modification algorithms [a, b, c, d]
Grade 1	Continue dabrafenib, trametinib and panitumumab at full dose~~; monitor as clinically indicated~~ • Monitor closely Provide supportive care according to institutional standards

Rationale: Clarification that text in this section refers to toxicities not specifically addressed elsewhere in the protocol.

Section 3.7.4.3 Guidelines for cuSCC, added section

Cutaneous squamous cell carcinomas have been observed in subjects treated with dabrafenib and the combination of dabrafenib and trametinib (see the GSK1120212 + GSK2118436 Clinical IB and Supplements [GlaxoSmithKline Document Number, 2011N126811_00, GlaxoSmithKline Document Number 2012N1523310_00. GlaxoSmithKline Document Number 2012N152310_01]). 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. Submit cuSCC tumor tissue for analysis as directed in the SPM.

Rationale: New section added to address toxicity specific to dabrafenib and the combination of dabrafenib and trametinib.

Section 3.7.7.1 Left Ventricular Ejection Fraction (LVEF) Decreases

Previous text:

Echocardiography must be performed at Screening and at the post-treatment follow-up visit as outlined in the Time and Events Tables (Section 3.8). . Decreases of the left ventricular ejection fraction (LVEF) have been observed in subjects 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 (Section 3.8). Copies of all ECHOs and cardiology consultations performed on subjects who experience a >10% decrease in LVEF from baseline and whose cardiac ejection fraction is <institution's LLN will be required by GSK for review. Instructions for submitting qualifying ECHOs are provided in the Study Procedures Manual (SPM).

Dose modification guidance and stopping criteria for LVEF decrease are provided in Table 13.

Revised text:

~~Echocardiography~~ Cardiac ejection fraction function assessments (ECHO or MUGA; ECHO is preferred) must be performed at Screening and at the post-treatment follow-up visit as outlined in the Time and Events Tables (Section 3.8). All assessments for an individual patient must be peformed with the same modality (*i.e.,* ECHO or MUGA) and, preferably, by the same institution/operator, in order to reduce variability. Decreases of the left ventricular ejection fraction (LVEF) have been observed in subjects receiving trametinib monotherapy and in combination with dabrafenib. Therefore, ~~ECHOs must be performed to assess~~ cardiac ejection fraction must be assessed at regular intervals as outlined in the Time and Events Table (Section 3.8). Copies of all ~~ECHOs~~ LVEF assessments and cardiology consultations performed on subjects who experience a >10% decrease in LVEF from baseline and whose cardiac ejection fraction is <institution's LLN will be required by GSK for review. Instructions for submitting qualifying ECHOs/ MUGAs are provided in the Study Procedures Manual (SPM).

Dose modification guidance and stopping criteria for LVEF decrease are provided in Table 13. Additional guidelines for subjects enrolled at sites in France are provided in Appendix 5.

Rationale: Text was revised to allow use of MUGA for institutions that cannot perform ECHOs.

Table 13: Dose Modification Guidelines and Stopping Criteria for LVEF Decrease

Previous table:

Clinic Presentation	LVEF decrease (%) or CTCAE grade	Action and Dose Modification
Asymptomatic	Absolute decrease of >10% in LVEF compared to baseline and ejection fraction below the institutional LLN	Interrupt study treatment with dabrafenib and trametinib and repeat ECHO within 2 weeks[a] IF 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 dabrafenib and trametinib at previous dose level • Repeat ECHO at 2, 4, 8, and 12 weeks after re-start; continue in 12 week intervals thereafter If LVEF does not recover within 4 weeks: n. Consult with cardiologist **o. Permanently discontinue dabrafenib and trametinib** p. Repeat ECHO after 2, 4, 8, 12 and 16 weeks or until resolution q. Consult with GSK Medical Monitor[c]
Symptomatic[b]	Grade 3: resting LVEF 39-20% or >20% absolute reduction from baseline Grade 4: resting LVEF <20%	Permanently discontinue study treatment with dabrafenib and trametinib Consult with cardiologist Repeat ECHO after 2, 4, 8, 12 and 16 weeks or until resolution.

a. If ECHO does not show LVEF recovery after 2 weeks, repeat ECHO 2 weeks later.
b. Symptoms may include: dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema.
c. Once LVEF recovers to baseline, restarting dabrafenib monotherapy may be considered in consultation with the GSK Medical Monitor.

Revised table:

Clinic Presentation	LVEF decrease (%) or CTCAE grade	Action and Dose Modification
Asymptomatic	Absolute decrease of >10% in LVEF compared to baseline and ejection fraction below the institutional LLN	Interrupt study treatment with dabrafenib and trametinib and repeat ECHO/MUGA within 2 weeks[a] IF 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 reduced by one dose level • Restart dabrafenib ~~and trametinib~~ at previous dose level • Repeat ECHO/MUGA at 2, 4, 8, and 12 weeks after re-start; continue in 12 week intervals thereafter If LVEF does not recover within 4 weeks: r. Consult with cardiologist **s. Permanently discontinue dabrafenib and trametinib** t. Repeat ECHO/MUGA after 2, 4, 8, 12 and 16 weeks or until resolution u. Consult with GSK Medical Monitor[c]
Symptomatic[b]	Grade 3: resting LVEF 39-20% or >20% absolute reduction from baseline Grade 4: resting LVEF <20%	Permanently discontinue study treatment with dabrafenib and trametinib Consult with cardiologist Repeat ECHO/MUGA after 2, 4, 8, 12 and 16 weeks or until resolution.

a. If ECHO/MUGA does not show LVEF recovery after 2 weeks, repeat ECHO/MUGA 2 weeks later.
b. Symptoms may include: dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema.
c. Once LVEF recovers to baseline, restarting dabrafenib monotherapy may be considered in consultation with the GSK Medical Monitor.

Rationale: Revisions incorporate safety text for restarting trametinib at a dose reduction, and allow for use of MUGA at institutions that cannot perform ECHO.

Table 15: Withholding and Stopping Criteria for QTc Prolongation

Previous table:

QTc Prolongation[a]	**Action and Dose Modification**
QTcB≥501msec Uncorrected QT >600msec QTcB >530msec for subjects with bundle branch block (BBB)	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

Revised table:

QTc Prolongation[a]	**Action and Dose Modification**
QTcB≥501msec ~~Uncorrected QT >600msec~~ QTcB >530msec for subjects with bundle branch block (BBB)	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

Rationale: Revisions to stopping criteria for clarification.

Section 3.7.11 Visual Changes Stopping Criteria

Added introductory paragraph:

Episodes of visual changes have been observed in subjects 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 16.

*Note, the remaining text in this section was reformatted from bullets to a tabular presentation for ease of understanding.

Section 3.8.1 Part 1 Dose Escalation (Time and Events Table)

Revisions with rationale:

- in column header "First Treatment Period", added "(Day 1 through Day 28)" to clarify duration of the first treatment period.
- added columns, "Initial follow-up", "Secondary follow-up": separation of follow-up into initial follow-up and secondary follow-up to clarify procedures that were needed within 14 ± 7 days of last dose of study drugs, within 4 weeks ± 7 days of last dose of panitumumab, and within 8 weeks ± 7 days of last dose of panitumumab.
- revised timing to allow the complete physical examination to be completed in screening, then a brief physical examination to be performed on Day 1.
- Tumor tissue biopsy (mandatory): added note "to be collected from Day 15 to Day 18" to clarify window of collection.

- added "At Week 4, then" to indicate that medical history/interim medical history, concurrent medication review, brief physical examination, weight and ECOG were to be performed at Week 4, then every 4 weeks in Continuation Phase.

- added "At Week 4, then" to clarify timing of ECGs and hematology/ clinical chemistry in Continuation Phase.

- added "or MUGA", with corresponding footnote 18 ("ECHO is preferred. MUGA may be used only if ECHO is not available. The same method must be used consistently from screening throughout the study"), to allow use of MUGA for institutions that cannot perform ECHO.

- revised formatting to clarify that dosing of dabrafenib and trametinib does not continue into follow-up.

- Day 1 visit: revised to allow for brief physical examination instead of complete physical examination.

- Day 15 visit: eliminated requirement for repeated measurement of height.

- Initial follow-up visit: added urinalysis (post-treatment)

- revised footnote 1 to allow informed consent to be completed within 35 days prior to first dose (previously, 14 days prior)

- added text to footnote 2: "The Continuation Phase starts with Day 29; …. Safety lab tests (chemistry/hematology/coag/UA) may be done the day before the visit so that results are ready on the day of the visit, but all assessments should be done within the ± 7 day window." to indicate start of the Continuation Phase and to allow a window for completion of assessments in continuation.

- revised footnote 3 to clarify initial follow-up visit and secondary follow-up visit timings and to allow a visit window for completion of assessments.

- added text to footnote 5: "Note: pelvic exam in female subjects may be completed up to 24 weeks prior to date of first dose*."* to allow an appropriate window for completion of pelvic examination.

- added text to footnote 9: "During the continuation phase, PK samples will be collected pre-dose at Week 8, Week 12, Week 16, and Week 20." to indicate a stopping point for collection of PK samples in continuation.

- added and revised text in footnote 10 to allow patients with few lesions to enroll:

    - **Added text:** "Collection of on-treatment biopsy for subjects with accessible tumors."

    - **Previous text**: "Biopsy should not be done on target lesions."

- **Revised text**: "Biopsies should be performed on non-target lesions when possible."

- added text to footnote 13: "The Day 1/predose tumor biopsy may be collected at any point after signing consent, up to 14 days prior to first dose." to indicate allowable window for collection of the predose tumor biopsy.

- added footnote 16: "Pre- and post-dose tumor biopsies are mandatory. If the patient's tumors are inaccessible for biopsy, permission to enroll must be granted by the GSK Medical Monitor." to ensure clarity of requirements for enrolment

- added footnote 17: "After study treatment is withdrawn, disease assessments (the method used at baseline) should continue every 8 weeks until documented disease progression, the start of new anti-cancer therapy, withdrawal of consent, or death." to define follow-up after discontinuation of study treatment.

- added footnote 18: "ECHO is preferred. MUGA may be used only if ECHO is not available. The same method must be used consistently from screening throughout the study." to allow for use of MUGA at institutions that cannot perform ECHO

Section 3.8.2 Part 2 Expansion Cohorts (Time and Events Table)

Revisions with rationale:

- in column header "First Treatment Period", added "(Day 1 through Day 28)" to clarify duration of the first treatment period.

- added columns, "Initial follow-up", "Secondary follow-up": separation of follow-up into initial follow-up and secondary follow-up to clarify procedures that were needed within 14 ± 7 days of last dose of study drugs, within 4 weeks ± 7 days of last dose of panitumumab, and within 8 weeks ± 7 days of last dose of panitumumab.

- revised timing to allow the complete physical examination to be completed in screening, then a brief physical examination to be performed on Day 1.

- added "At Week 4, then" to indicate that medical history/interim medical history, concurrent medication review, brief physical examination, weight and ECOG were to be performed at Week 4, then every 4 weeks in Continuation Phase.

- added "or MUGA", with corresponding footnote 18 ("ECHO is preferred. MUGA may be used only if ECHO is not available. The same method must be used consistently from screening throughout the study"), to allow use of MUGA for institutions that cannot perform ECHO.

- Day 1 visit: revised to allow for brief physical examination instead of complete physical examination.

- Day 1 visit: [redacted] (predose); previously collected during Screening visit

- revised timing of ECG collection for consistency of assessments (in comparison to Part 1):

    - **previous text**: At Week 4 then at Week 12, Week 24 and every 12 weeks thereafter

    - **revised text**: At Week 4, then every 4 weeks until Week 24, then every 8 weeks

- added "At Week 4, then" to clarify timing of hematology/ clinical chemistry in Continuation Phase.

- revised footnote 1 to allow informed consent to be completed within 35 days prior to first dose (previously, 14 days prior)

- added text to footnote 2: "The Continuation Phase starts with Day 29; …. Safety lab tests (chemistry/hematology/coag/UA) may be done the day before the visit so that results are ready on the day of the visit, but all assessments should be done within the ± 7 day window." to indicate start of the Continuation Phase and to allow a window for completion of assessments in continuation.

- revised footnote 3 to clarify initial follow-up visit and secondary follow-up visit timings and to allow a visit window for completion of assessments.

- added text to footnote 6: "Note: pelvic exam in female subjects may be completed up to 24 weeks prior to date of first dose*."* to allow an appropriate window for completion of pelvic examination.

- added and revised text in footnote 9 to allow patients with few lesions to enroll:

    - **Added text:** "Collection of on-treatment biopsy for subjects with accessible tumors."

    - **Previous text**: "Biopsy should not be done on target lesions."

    - **Revised text**: "Biopsies should be performed on non-target lesions when possible."

- added text to footnote 11: "The Day 1/predose tumor biopsy may be collected at any point after signing consent, up to 14 days prior to first dose." to indicate allowable window for collection of the predose tumor biopsy.

- Tumor tissue biopsy (mandatory): added note "to be collected from Day 15 to Day 18" to clarify window of collection.

- Initial follow-up visit: added urinalysis (post-treatment)

- added footnote 16: "Pre- and post-dose tumor biopsies are mandatory. If the patient's tumors are inaccessible for biopsy, permission to enroll must be granted by the GSK Medical Monitor." to ensure clarity of requirements for enrolment

- added footnote 17: "After study treatment is withdrawn, disease assessments (the method used at baseline) should continue every 8 weeks until documented disease progression, the start of new anti-cancer therapy, withdrawal of consent, or death." to define follow-up after discontinuation of study treatment.

- added footnote 18: "ECHO is preferred. MUGA may be used only if ECHO is not available. The same method must be used consistently from screening throughout the study." to allow for use of MUGA at institutions that cannot perform ECHO

Section 4.2.1.1 Part 1 and Part 2 Inclusion Criteria

Previous text, inclusion criterion 3:

3. Histologically- or cytologically-confirmed diagnosis of advanced or metastatic BRAF V600E or V600K mutation positive colorectal cancer (CRC), as determined by relevant genetic testing and documented in source. For subjects enrolled based on local mutation testing, confirmation of mutation will occur following registration in Part 1 and Part 2.

Revised text, inclusion criterion 3:

3. Histologically- or cytologically-confirmed diagnosis of advanced or metastatic BRAF V600E~~or V600K~~ mutation positive colorectal cancer (CRC), as determined by relevant genetic testing and documented in source. For subjects enrolled based on local mutation testing, confirmation of mutation will occur following registration in Part 1 and Part 2.

Rationale: The majority of mutations observed in BRAF-mutation-positive colorectal patients are BRAF V600E; this revision is to more accurately reflect the study population.

Section 4.2.1.1 Part 1 and Part 2 Inclusion Criteria, Addition to Table 18 Definitions for Adequate Baseline Organ Function

Previous table:

System	Laboratory Values
Hematologic	
Absolute neutrophil count	$\geq 1.2 \times 10^9$/L
Hemoglobin	≥9 g/dL or 5.6 mmol/L
Platelets	$\geq 75 \times 10^9$/L
Prothrombin Time / International Normalized Ratio (PT/INR) and Partial Thromboplastin Time (PTT)	≤1.5 x ULN
Chemistry	
Mg++	≥ LLN
Hepatic	

System	Laboratory Values
Albumin	≥2.5 g/dL or 25 g/L
Total bilirubin	≤1.5 x ULN
AST and ALT	≤ 2.5× ULN
Renal	
Creatinine **or**	≤ 1.5 ULN
Calculated creatinine clearance[a] **or**	≥ 50 mL/min
Cardiac	
Left Ventricular Ejection fraction (LVEF)	≥ LLN by ECHO or multigated acquisition scan (MUGA)[b]

b. Calculated by the Cockcroft-Gault formula.
c. Same method as used at baseline must be use throughout the study, ECHO is the preferred method

Revised table:

System	Laboratory Values
Hematologic	
Absolute neutrophil count	≥1.2 × 10^9/L
Hemoglobin	≥9 g/dL or 5.6 mmol/L
Platelets	≥75 × 10^9/L
Prothrombin Time / International Normalized Ratio (PT/INR) and Partial Thromboplastin Time (PTT)	≤1.5 x ULN
Chemistry	
Mg++	≥ LLN
Hepatic	
Albumin	≥2.5 g/dL or 25 g/L
Total bilirubin	≤1.5 x ULN
AST and ALT	≤ 2.5× ULN
Renal	
Creatinine **or**	≤ 1.5 ULN
Calculated creatinine clearance[a] **or** 24-hour urine creatinine clearance	≥ 50 mL/min
Cardiac	
Left Ventricular Ejection fraction (LVEF)	≥ LLN by ECHO or multigated acquisition scan (MUGA)[b]

d. Calculated by the Cockcroft-Gault formula.
e. Same method as used at baseline must be use throughout the study, ECHO is the preferred method

Rationale: Correction; previous version inadvertently omitted "24-hour urine creatinine clearance"

Section 4.2.1.1 Part 1 and Part 2 Inclusion Criteria, Addition of inclusion criterion 11:

11. Subjects enrolled in France: In France, a subject will be eligible for inclusion in this study only if either affiliated to, or a beneficiary of, a social security category.

Rationale: The inclusion criterion was added to clarify enrollment at French sites.

Section 4.2.1.2 Part 1 and Part 2 Exclusion Criteria, exclusion criterion 7:

Previous text:

7. Prior exposure to EGFR inhibitors, including anti-EGFR antibodies or EGFR (Part 2 ONLY)

Revised text:

7. Prior exposure to EGFR inhibitors, including anti-EGFR antibodies ~~or EGFR~~ (Part 2 ONLY)

Rationale: To clarify excluded prior therapies.

Section 4.2.1.2 Part 1 and Part 2 Exclusion Criteria, exclusion criterion 11:

Previous text:

11. Known Human Immunodeficiency Virus (HIV), Hepatitis B, or Hepatitis C infection. Subjects who have evidence of clearance of Hepatitis B or Hepatitis C infection can be enrolled with approval of the GSK Medical Monitor.

Revised text:

11. Known Human Immunodeficiency Virus (HIV), Hepatitis B, or Hepatitis C infection. ~~Subjects who have evidence of clearance of Hepatitis B or Hepatitis C infection can be enrolled with approval of the GSK Medical Monitor.~~

Rationale: There are potential safety issues with enrollment of patients with Hepatitis B or C infection; revised for safety reasons.

Section 4.2.1.2 Part 1 and Part 2 Exclusion Criteria, deletion of exclusion criterion 12:

Deleted exclusion criterion 12:

Current use of therapeutic warfarin. Therapeutic dosing of warfarin is defined as resulting in an INR >1.3. Low molecular weight heparin (LMWH) is permitted provided that the subject's PT and PTT meet entry criteria. Subjects requiring therapeutic levels of LMWH must receive approval from GSK Medical Monitor and must be monitored appropriately as clinically indicated.

Rationale: Emerging data from ongoing clinical studies shows that therapeutic warfarin may be used with approval of GSK Medical Monitor and with close monitoring of PT/INR.

Section 4.2.2.1 Part 3 Inclusion Criteria, inclusion criterion 3:

Previous text:

3. Histologically- or cytologically-confirmed diagnosis of BRAFV600E or V600K mutation positive advanced or metastatic colorectal cancer (CRC who are eligible to receive fluoropyrimidine-containing chemotherapy regimen that have experienced documented radiographic progression on one prior line of fluoropyrimidine-containing chemotherapy (previous anti-EGFR therapy is excluded),

Revised text:

3. Histologically- or cytologically-confirmed diagnosis of BRAFV600E ~~or V600K~~ mutation positive advanced or metastatic colorectal cancer (CRC who are eligible to receive fluoropyrimidine-containing chemotherapy regimen that have experienced documented radiographic progression on one prior line of fluoropyrimidine-containing chemotherapy (previous anti-EGFR therapy is excluded),

Rationale: The majority of mutations observed in BRAF-mutation-positive colorectal patients are BRAF V600E; this revision is to more accurately reflect the study population.

Section 4.2.2.1 Part 3 Inclusion Criteria, inclusion criterion 5:

Previous text:

5. Tumor type criteria:

- BRAF mutation-positive colorectal cancer (i.e., BRAFV600E or V600K), as determined by relevant genetic testing and documented in source. Enrollment in Part 3 will only occur following centralized determination of BRAFV600E or V600K mutation.

5. Tumor type criteria:

- BRAF V600E mutation-positive colorectal cancer ~~(i.e., BRAFV600E or V600K),~~ as determined by relevant genetic testing and documented in source. Enrollment in Part 3 will ~~only occur following centralized determination of BRAFV600E or V600K~~ require prospective testing for BRAF mutation~~.~~ V600E using a CLIA certified BRAF mutation assay that will be performed in a central laboratory.

Rationale: The majority of mutations observed in BRAF-mutation-positive colorectal patients are BRAF V600E; this revision is to more accurately reflect the study population.

Section 4.2.2.1 Part 3 Inclusion Criteria, Addition of inclusion criterion 14:

14. Subjects enrolled in France: In France, a subject will be eligible for inclusion in this study only if either affiliated to, or a beneficiary of, a social security category.

Rationale: The inclusion criterion was added to clarify enrollment at French sites.

Section 4.2.2.2 Part 3 Exclusion Criteria, exclusion criterion 10:

Previous text:

10. Known Human Immunodeficiency Virus (HIV), Hepatitis B, or Hepatitis C infection. Subjects who have evidence of clearance of Hepatitis B or Hepatitis C infection can be enrolled with approval of the GSK Medical Monitor.

Revised text:

10. Known Human Immunodeficiency Virus (HIV), Hepatitis B, or Hepatitis C infection. ~~Subjects who have evidence of clearance of Hepatitis B or Hepatitis C infection can be enrolled with approval of the GSK Medical Monitor.~~

Rationale: There are potential safety issues with enrollment of patients with Hepatitis B or C infection; revised for safety reasons.

Section 4.2.2.2 Part 3 Exclusion Criteria, deletion of exclusion criterion 11:

Deleted exclusion criterion 11:

11. Current use of therapeutic warfarin. Therapeutic dosing of warfarin is defined as resulting in an INR >1.3. Low molecular weight heparin (LMWH) is permitted provided that the subject's PT and PTT meet entry criteria. Subjects requiring therapeutic levels of LMWH must receive approval from GSK Medical Monitor and must be monitored appropriately as clinically indicated.

Rationale: Emerging data from ongoing clinical studies shows that therapeutic warfarin may be used with approval of GSK Medical Monitor and with close monitoring of PT/INR.

Section 5.1.2 Part 2

Previous text:

For Part 2, efficacy will be evaluated to decide whether to proceed with further development based on the clinical activity seen in Part 1 and Part 2. Futility analysis criteria will be based on 2-stage Green-Dahlberg design's [Green, 1992] interim analysis criteria. The criteria will be based on a historically unimportant response rate of 15% versus a response rate of interest of 30%.

When at least 4 responders out of 20 subjects are observed in a treatment arm, after each subject has been followed at least 12 weeks, further development of the corresponding treatment in Part 3 will follow. If less than 4 responders are observed, the accrued efficacy data will be evaluated for possibility of further development to Part 3.
The final decision with respect to continuation of the trial to Part 3 will be made by the Sponsor based on safety considerations as well as available efficacy data with input from participating investigators.

Revised text:

For Part 2, efficacy will be evaluated to decide whether to proceed with further development based on the clinical activity seen in Part 1 and Part 2. Futility analysis criteria at the end of Part 2 will be based on 2-stage Green-Dahlberg design's [Green, 1992] interim analysis criteria. The criteria will be based on a historically unimportant response rate of 15% versus a response rate of interest of 30%. The Part 2 portion of the study will employ a Bayesian design that allows the trial to be monitored more frequently at multiple stages. Bayesian statistics will be employed to calculate the predictive probability that the response rate ≥30% and ≥15% at interim assuming a Beta prior for the Binomial distributed data. Predictive probability calculates the probability that the response rate ≥30% or ≥15% at the end of Part 2 (after 20 subjects) given the responses have already been observed. It predicts what is likely to happen at the end of Part 2 so is more meaningful and straightforward than posterior probability. A weak prior Beta (0.003, 0.007) is used, which is equivalent to the information present in 0.01 subject.

An initial total of 10 subjects will be recruited at a dose level based on the recommended dose for each treatment (including the subjects treated in Part 1 at the same dose). The number of subjects will be increased up to a total of 20 depending on the results observed. The tables below show the decision rules for the 10^{th} to 19^{th} evaluable subjects, specifying the number of subjects with a confirmed response needed for continuing enrolment or stopping for futility. The methodology is based on the predictive probability of success if enrolment continues to 20 subjects [Lee, 2008]. These rules are intended as a guideline. Actual decisions will depend on the totality of the data.

Table 20 Decision Making Criteria at Interim Analysis for Futility and Efficacy

Number of Evaluable Patients	≤ This Number of Confirmed Responses to Stop Early for Futility	≥ This Number of Confirmed Responses to Declare ORR≥0.3
10	0	5
11	0	5
12	0	6
13	0	6
14	0	6
15	0	7
16	1	7
17	1	7
18	1	8
19	1	8

For the interim looks in each cohort separately, if the predictive probability that the confirmed response rate ≥15% (historical control) is small (i.e., less than 10% chance), or equivalent to observe no confirmed response in the first enrolled 10-15 evaluable subjects in that cohort (e.g., after they have either progressed, or withdrew from the study, or lost to follow-up, or ongoing but have completed at least one post treatment disease assessment) and observe less than 1 confirmed response in the first 16-19 evaluable subjects, the enrollment for that cohort may be stopped due to futility. Otherwise, the

enrolment of the respective cohort will continue to the target sample size of 20. If the predictive probability that the response rate of ≥30% is large (i.e., greater than 80% chance), strong statistical evidence has been provided in favor of further development of the treatment for the target population.

When at least 4 responders out of 20 subjects are observed in a treatment arm, after each subject has been followed at least 12 weeks, further development of the corresponding treatment in Part 3 will follow. If less than 4 responders are observed, the accrued efficacy data will be evaluated for possibility of further development to Part 3.

The final decision with respect to continuation of the trial to Part 3 will be made by the Sponsor based on safety considerations as well as available efficacy data with input from participating investigators.

Rationale: Text was revised to incorporate a Bayesian design in Part 2.

Section 5.1.3 Part 3, first paragraph

Previous text:

The primary objective of Part 3 is to compare progression free survival (PFS) and of the combinations of trametinib plus dabrafenib plus panitumumab and/or dabrafenib plus panitumumab versus standard of care in subjects with BRAF-V600E or V600K mutation positive CRC. There will be two primary comparisons of interest in this study based on comparing each of the panitumumab combination arms with chemotherapy comparator

Revised text:

The primary objective of Part 3 is to compare progression free survival (PFS) and of the combinations of trametinib plus dabrafenib plus panitumumab and/or dabrafenib plus panitumumab versus standard of care in subjects with BRAF-V600E ~~or V600K~~ mutation positive CRC. There will be two primary comparisons of interest in this study based on comparing each of the panitumumab combination arms with chemotherapy comparator.

Rationale: The majority of mutations observed in BRAF-mutation-positive colorectal patients are BRAF V600E; this revision is to more accurately reflect the study population.

Section 5.2.1.2 Part 2

Previous text:

Part 2 will enroll approximately 30 subjects in total. Approximately 40 subjects will be evaluated at the end of Part 2, including those enrolled in Part 1 at the same dose levels.

To determine the sample size for each cohort, a traditional, 2-stage Green-Dahlberg design [Green, 1992] was evaluated and the sample size for the first stage will be used for the futility analysis. To test the hypotheses (RR=30% vs RR=15%), using a Green-Dahlberg design, 20 subjects per arm would be needed for Stage 1 (assuming a type 1 error of 5% and power of 95%). The chance to effectively terminate the trial after 20 subjects due to futility (true RR=15%) is 65%; the risk to incorrectly stop the trial after 20 subjects if the treatment is effective (true RR =40%) is less than 2% (Table 20).

Table 20 Futility Analysis Design Performance

True RR	Probability of Early Termination, after 20 pts
15%	0.648
20%	0.411
30%	0.107
40%	0.016

A Bayesian posterior probability will also be calculated to further inform decision making. Since neither BRAF in combination with panitumumab nor MEK in combination with BRAF and panitumumab has been tested previously in the clinic in CRC subjects, a Beta (0.005, 0.005) prior is assumed. The posterior probabilities of RR exceeding 20%, 30% and 40% based on 20 subjects are shown in Table 21.

Table 21 Bayesian Posterior Probabilities of Response Rate for Given Number of Observed Responses

# of Responses Observed out of 20 Subjects	Posterior Probability RR ≥20%	Posterior Probability RR ≥30%	Posterior Probability RR ≥40%
4	0.45	0.14	0.024
5	0.69	0.29	0.075
6	0.83	0.48	0.17
7	0.93	0.66	0.31
8	0.97	0.81	0.49

Revised text:

Part 2 will enroll approximately 30 subjects in total. Approximately 40 subjects will be evaluated at the end of Part 2, including those enrolled in Part 1 at the same dose levels.

To determine the maximum sample size for each cohort, a traditional, 2-stage Green-Dahlberg design [Green, 1992] was evaluated and the sample size for the first stage will be used for the futility analysis. To test the hypotheses (RR=30% vs RR=15%), using a Green-Dahlberg design, 20 subjects per arm would be needed for Stage 1 (assuming a type 1 error of 5% and power of 95%). The chance to effectively terminate the trial after 20 subjects due to futility (true RR=15%) is 65%; the risk to incorrectly stop the trial after 20 subjects if the treatment is effective (true RR =40%) is less than 2% (Table 22).

Table 22 Futility Analysis Design Performance

True RR	Probability of Early Termination, after 20 pts
15%	0.648
20%	0.411
30%	0.107
40%	0.016

A Bayesian posterior probability will also be calculated to further inform decision making. Since neither BRAF in combination with panitumumab nor MEK in combination with BRAF and panitumumab has been tested previously in the clinic in CRC subjects, a Beta (0.003, 0.007) ~~(0.005, 0.005)~~ prior is assumed. This prior is equivalent to the prior information from 0.01 subject. The posterior probabilities of RR exceeding 20%, 30% and 40% based on 20 subjects are shown in Table 23.

Table 23 Bayesian Posterior Probabilities of Response Rate for Given Number of Observed Responses

# of Responses Observed out of 20 Subjects	Posterior Probability RR ≥20%	Posterior Probability RR ≥30%	Posterior Probability RR ≥40%
4	0.45	0.14	0.024
5	0.69	0.29	0.075
6	0.83	0.48	0.17
7	0.93	0.66	0.31
8	0.97	0.81	0.49

Using this sample size, a Bayesian design that allows the trial to be monitored more frequently at multiple stages was evaluated. A Bayesian analysis expresses uncertainty about a parameter in terms of probability. A prior is defined to characterize the level of knowledge about a parameter before the data are collected. Once the data are collected, a posterior distribution is formed using the prior and the likelihood (i.e., the data). Since none of the treatment has been tested previously in the clinic in the target population, a weak prior Beta (0.003, 0.007) is assumed. Thus, the posterior distribution for the response rate will be primarily driven by the data and can be derived as follows: Let p denote the response rate for the treatment, the number of responses in the current n patients, x, follows a binomial distribution, Binomial (n, p). Taking the Bayesian method and combining the weak prior and the likelihood of the observed data x, the posterior

distribution of the response rate follows a beta distribution, *i.e.,* p ~ Beta (0.003 + x, 0.007 + n-x) with the posterior mean (0.003 + x)/(0.01 + n).

Based on this posterior distribution of the response rate, the predictive probability that the response rate ≥15% or ≥30% after 19 subjects will be calculated for decision-making as described in the Section 5.1.2 (Hypotheses). The decision rule and a minimal required sample size of 10 patients for the first interim look is determined to generate the design that leads to a reasonable chance of early termination due to futility.

The design property, by utilizing the decision rule specified in Section 5.1.2, and sample size of 20 patients are shown (Table 24). The probability of early termination of the trial is calculated by simulations. The probability of early termination after the first 19 evaluable subjects is 33% under the null hypothesized response rate, and the risk to incorrectly stop the trial early if the drug is effective is approximately 5%. Thus, the study will employ the Bayesian design that allows the trial to be monitored more frequently at multiple stages with the constraint of satisfactory stop for futility rate.

Table 24 Bayesian Design Performance by Response Rate

If True Response Rate to The Treatment is: (%)	Prob (early stop for futility)
0.15	0.326
0.2	0.180
0.3	0.047

Rationale: Text was revised to incorporate a Bayesian design in Part 2.

Section 5.3.7.2 Part 2, paragraph 3

Previous text:

In the expansion cohorts in Part 2, if an increased incidence of DLTs (*i.e.*, ≥4 subjects of the first 10 subjects enrolled) is observed, the dosing regimen may be adjusted for all future subjects in a specific cohort or for the whole study population.

Revised text:

In the expansion cohorts in Part 2, if an increased incidence of ~~DLTs~~ (clinically significant toxicity *i.e.*, ≥4 subjects of the first 10 subjects enrolled) is observed, the dosing regimen may be adjusted for all future subjects in a specific cohort or for the whole study population.

Rationale: Correction; DLT evaluation is in Part 1/ dose escalation only.

Section 5.3.8.5 Other Safety Measures

Previous text:

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

Revised text:

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

Rationale: Revisions allow for use of MUGA at institutions that cannot perform ECHO.

Section 6.1 Demographic/ Medical History Assessments, paragraph 2

Previous text:

Medical/medication/alcohol history will be assessed as related to the eligibility criteria listed in Section 4.2. Cardiovascular medical history/risk factors will also be assessed at baseline.

Revised text:

Medical~~/medication/alcohol history will be assessed~~, surgical, and treatment history including date (month and year) of first diagnosis and histology, ~~as related to the eligibility criteria listed in Section 4.2.~~ as well as cardiovascular medical history~~/~~ and risk factors ~~will also~~, alcohol and tobacco history, plus family history will be taken as part of the medical history and disease status. Additional information may be requested to evaluate eligibility per Section 4.2 ~~assessed at baseline~~.

Rationale: Text was revised to clarify that patients' complete medical and medication history will be reviewed to determine eligibility and safety once enrolled in ongoing study.

Section 6.2 Safety, Electrocardiogram (ECG)

Previous text:

Twelve-lead ECGs will be obtained as indicated in the Time and Events table (Section 3.8) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Results of the ECG will be transmitted to a central storage facility. At each assessment, a 12-lead ECG will be performed by qualified personnel at the site after the subject has rested at least 5 minutes in a semi-recumbent or supine position. Those QTc values greater than 480msec as calculated by the machine must be confirmed manually using Fridericia's formula given below:

$$QTcF=QT\ X\ (1/RR)^{1/3}$$

Revised text:

Twelve-lead ECGs will be obtained as indicated in the Time and Events table (Section 3.8) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Results of the ECG will be transmitted to a central storage facility. At each assessment, a 12-lead ECG will be performed by qualified personnel at the site after the subject has rested at least 5 minutes in a semi-recumbent or supine position. Those QTc values greater than 480msec as calculated by the machine must be confirmed manually using ~~Fridericia's~~Bazett's formula [Bazett, 1920] given below:

~~$QTcF=QT\ X\ (1/RR)^{1/3}$~~

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

Rationale: QT correction method was revised from Fridericia's formula to Bazett's to be consistent with other ongoing clinical studies of dabrafenib and/or trametinib.

Section 6.2 Safety, Echocardiogram (ECHO)

Previous text:

Echocardiogram (ECHO)

ECHO will be performed to assess cardiac ejection fraction and cardiac valve abnormalities as indicated in the Time and Events table (Section 3.8). Results will be transmitted to a central storage facility. Echocardiography should include an evaluation for left ventricular ejection fraction (LVEF) and both right- and left-sided valvular lesions. For each subject the same procedure should be performed at screening and any following visit to allow direct comparison. Additional ECHO assessments may be performed as clinically indicated.

Revised text:

Echocardiogram (ECHO) or Multiple Gated Acquisition (MUGA):

ECHO ~~will be performed~~ is the preferred method to assess cardiac ejection fraction and cardiac valve abnormalities; MUGA is acceptable only if ECHO is not available. Assessments should be performed as indicated in the Time and Events table (Section 3.8). Results will be transmitted to a central storage facility. Echocardiography should include an evaluation for left ventricular ejection fraction (LVEF) and both right- and left-sided valvular lesions. For each subject the same procedure should be performed at screening and any following visit to allow direct comparison. Additional ECHO/ MUGA assessments may be performed as clinically indicated.

Rationale: Revisions allow for use of MUGA at institutions that cannot perform ECHO.

Section 6.2 Safety, Clinical Laboratory Assessments

Previous text:

Glucose, fasting	Total carbon dioxide (CO_2)	Alkaline phosphatase	Inorganic phosphorus

Other screening tests

FSH and estradiol (as needed in women of non-child bearing potential only)

Revised text:

Glucose fasting glucose at screening only	Total carbon dioxide (CO_2)	Alkaline phosphatase	Inorganic phosphorus

Other screening tests

FSH and estradiol (as needed in women of non-child bearing potential only)
Coagulation (at screening, repeated only if clinically indicated)

Rationale: Fasting blood glucose is required at screening only; all other blood glucose assessments may be performed without regard to fasting status. Text regarding coagulation at screening was added to ensure that the assessment was performed as indicated.

Section 6.3.1 Follow-up Assessements for Subjects Permanently Discontinued from Study Treatment

New section added:

Subjects will be followed for progression, survival and new anti-cancer therapy (including radiotherapy) every 8 weeks. If subjects are unable or unwilling to attend clinic visits during follow-up, contact to assess survival may be made via another form of communication (e.g., phone, email, etc.).

Subjects who permanently discontinue study treatment without disease progression will have radiographic disease assessments performed as indicated in the Time and Events Table (Section 3.8) until disease progression, new anti-cancer therapy start, or death is documented.

Subjects enrolled in Part 1 are to be followed until progression for collection of PFS data. Subjects enrolled in Part 2 and Part 3 are to be followed until progression for collection of PFS data and until death for collection of overall survival (OS) data.

Rationale: Collection of efficacy data.

Section 6.6.1 Fresh Pre- and Post-dose Tumor Tissues, paragraph 1

Previous text:

Tumor specimens that can be sampled easily will be requested in Part 1 and Part 2. These biopsies will be taken during the screening period, e.g., within 14 days before treatment, and within 2 to 4 hrs after dosing on Day 15 (+3 days) in those subjects who have signed the corresponding section of the informed consent. A biopsy is also requested at tumor progression. Details of the tumor biopsy collection including processing, storage and shipping procedures will be provided in the SPM.

Revised text:

Tumor specimens that are accessible and can be sampled easily will be requested in Part 1 and Part 2. These biopsies will be taken during the screening period, e.g., within 14 days before treatment, and within 2 to 4 hrs after dosing on Day 15 (+3 days) in those subjects who have signed the corresponding section of the informed consent. A biopsy is also requested at tumor progression. Details of the tumor biopsy collection including processing, storage and shipping procedures will be provided in the SPM.

Rationale: Patients with inaccessible tumor lesions may be exposed to undue risk with mandatory biopsy.

Section 8.1 Permitted Medications, paragraph 1

Previous text:

The investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical phase of the study (final study visit).

Revised text:

The investigator must be informed as soon as possible about any medication taken from the time of screening until 30 days after the ~~end~~ last dose of ~~the clinical phase of the~~ study ~~(final study visit).~~treatment.

Rationale: Patients will be followed for safety review for 30 days after the last dose of study treatment, including review of concomitant medications.

Section 8.2 Prohibited Medications, bullet 4

Previous text:

- Dabrafenib is metabolized primarily by CYP2C8 and CYP3A4. Drugs that are strong inhibitors or inducers of CYP3A or CYP2C8 are prohibited because they may alter dabrafenib concentrations. The list may be modified based on emerging data. These include but are not limited to those listed in Table 23, consider therapeutic substitutions for these medications.

Revised text:

- Dabrafenib is metabolized primarily by ~~CYP2C8~~ Cytochrome P450 (CYP) 2C8 and CYP3A4. Co-administration of dabrafenib with ketoconazole, a CYP3A4 inhibition, or with gemfibrozil, a CYP2C8 inhibitor, resulted in increases in dabrafenib AUC of 71% and 47%, respectively. Drugs that are strong inhibitors or inducers of CYP3A ~~or~~ and CYP2C8 (see list in Table 26~~are prohibited because~~) may only be used under special circumstances (e.g. as a single use for a procedure) while treatment with study drug is interrupted as they may alter dabrafenib concentrations. ~~The list may be modified based on emerging data. These include but are not limited to those listed in~~, consider therapeutic substitutions for these medications. Approval of the GSK medical monitor is required in these situations. The list may be modified based on emerging data.

Rationale: Emerging data from ongoing clinical studies shows that therapeutic warfarin may be used with approval of GSK Medical Monitor and with close monitoring of PT/INR.

Section 8.2, Table 26 Prohibited Medications

Additions:

Miscellaneous	bosentan, St John's wort

Antiretroviral	ritonavir, saquinavir, atazanavir

Rationale: Emerging data from ongoing clinical studies.

Section 8.3, Cautionary Medications

Previous text:

- Dabrafenib has been shown to induce CYP3A4 in vivo using midazolam. Dabrafenib is an in vitro inducer of CYP2B6 and and 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 subjects for loss of efficacy or consider substitutions of these medications.

Revised text:

- Dabrafenib has been shown to induce CYP3A4 and CYP2C9 in vivo using midazolam. (CYP3A4 substrate) and S-warfarin (CYP2C9 substrate). Dabrafenib is an in vitro inducer of CYP2B6 and other enzymes such as CYP2C8, ~~CYP2C9, and~~ CYP2C19, UDP-glucuronyl transferases., and transporters may also be affected. Co-administration of dabrafenib and medications which are affected by the induction of these enzymes (including warfarin) may result in loss of efficacy. If co-administration of these medications is necessary, investigators should monitor subjects for loss of efficacy or consider substitutions of these medications.
- Therapeutic level dosing of warfarin can be used with approval by the GSK Medical Monitor and close monitoring of PT/INR by the site. Exposure decreased by 37% due to enzyme induction when on treatment, thus warfarin dosing may need to be adjusted based upon PT/INR. Consequently, when discontinuing dabrafenib, warfarin exposure may be increased and thus close monitoring via PT/INR and warfarin dose adjustments must be made as clinically appropriate. Prophylactic low dose warfarin may be given to maintain central catheter patency.
- Dabrafenib solubility is pH-dependent with decreased solubility at higher pH. Drugs such as proton pump inhibitors that inhibit gastric acid secretion to elevate gastric pH may decrease the solubility of dabrafenib and reduce its bioavailability. No clinical study has been conducted to evaluate the effect of pH on dabrafenib pharmacokinetics. In an ad-hoc analysis, no differences in C_{max} and AUC were noted between subjects who reported taking pH-elevating products relative to other subjects. Due to the theoretical risk that pH-elevating agents may decrease oral bioavailability and exposure to dabrafenib, these medicinal products that increase gastric pH should be used with caution when administered with dabrafenib.

Rationale: Emerging data from ongoing clinical studies shows that therapeutic warfarin may be used with approval of GSK Medical Monitor and with close monitoring of PT/INR.

Section 8.2, Table 27 Cautionary Medications

Additions:

	USE WITH CAUTION: Moderate inhibitors of CYP3A ~~and~~ or CYP2C8 since concentrations of dabrafenib may be increased
Class/Therapeutic Area	Moderate CYP3A and CYP2C8 Inhibitors

Class/Therapeutic Area	CYP3A4, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or Transporter Substrates that May be Affected by Induction

HMG-CoA Reductase Inhibitors	Atorvastatin, lovastatin, simvastatin, rosuvastatin, pravastatin

USE WITH CAUTION: Co-administration of drugs that increase gastric pH should be used with caution when administered with dabrafenib.	
pH altering agents	dexlansoprazole. esomeprazole, famotidine, ilaprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, ranitidine

Rationale: Emerging data from ongoing clinical studies.

Section 9.2 Subject Completion Criteria, paragraphs 1 and 2

Previous text:

For Part 1 (dose-escalation phase), Part 2 (expansion cohorts) and Part 3 (randomized Phase 2), a completed subject is one who has discontinued study treatment for reasons listed in Section 3.7 and completed a post-treatment follow-up visit, or has died while receiving study treatment, or was followed to progression or death.

Revised text:

For Part 1 (dose-escalation phase~~), Part 2 (expansion cohorts) and Part 3 (randomized Phase 2)~~,) subjects who are not treated with the RP2D, a completed subject is one who has discontinued study treatment for reasons listed in Section 3.7 and was followed to progression, or to death.

For Part 1 subjects who are treated at RP2D, for Part 2 (expansion cohorts) subjects and for Part 3 (randomized Phase 2) subjects, a completed ~~a post-~~subject is one who has discontinued study treatment for reasons listed in Section 3.7 ~~follow-up visit~~, and was followed to death or has died while receiving study treatment~~, or was followed to progression or death.~~

Rationale: Clarification of which subjects will be followed for progression and overall survival after discontinuation of study treatment.

10.3.1 Preparation, bullet 2

Previous text:

- Withdraw the necessary amount of panitumumab for a dose of 6 mg/kg.

Revised text:

- Withdraw the necessary amount of panitumumab for ~~a~~ the study- prescribed dose ~~of 6 mg/kg~~.

Rationale: Clarification of preparation of panitumumab for dosing in the event a dose less than 6mg/kg is required.

Section 11.2.1 Sentinel Events

Added section:

A Sentinel Event is a GSK-defined SAE that is not necessarily drug-related but has been associated historically with adverse reactions for other drugs and is therefore worthy of heightened pharmacovigilance. The GSK Medical Monitor is accountable for reviewing all SAEs for possible Sentinel Events which is mandated at GSK. The GSK medical monitor may request additional clinical information on an urgent basis if a possible Sentinel Event is identified on SAE review. The current GSK-defined Sentinel Events are listed below:

Acquired Long QT Syndrome

- Agranulocytosis/Severe Neutropenia

Anaphylaxis & Anaphylactoid Reactions

- Hepatotoxicity
- Acute Renal Failure
- Seizure
- Stevens Johnson syndrome/Toxic epidermal necrosis

Rationale: Section was added to address specific SAEs that may require additional reporting and review by site investigator and GSK Medical Monitor.

Section 11.3 Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Added section:

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis), or other safety assessments (e.g., electrocardiogram [ECGs], radiological scans, vital signs measurements) 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

an adverse event (AE) or serious adverse event (SAE), 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, dose reduction, and/or dose interruption/delay.

Any new primary cancer must be reported as a SAE.

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

Rationale: Section was added to clarify reporting of SAEs.

Section 11.3.1 Cardiovascular Events

Added section:

Investigators will be required to fill out event specific data collection tools for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularisation

This information should be recorded in the specific cardiovascular eCRF within one week of when the AE/SAE(s) are first reported.

Rationale: Section was added to address cardiovascular SAEs that have specific eCRF pages for completion and that may require additional reporting and review by site investigator and GSK Medical Monitor.

Section 11.6 Prompt Reporting of SAEs to GSK, addition to table

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"	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	"CV events" and/or "death" data collection tool(s) if applicable	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	Updated "CV events" and/or "death" data collection tool(s) if applicable

Rationale: Text was added to address cardiovascular SAEs and requirements for reporting.

Section 13.9 Independent Data Monitoring Committee

Previous text:

An IDMC will be utilized during the conduct of this study to review all available data in Part 3. An IDMC is generally assembled when there are significant safety or efficacy issues that warrant external objective medical and/or statistical review in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. The schedule of any planned interim analysis and the analysis plan for IDMC review is described in the charter. A copy of the IDMC charter available from GSK upon request.

Revised text:

An IDMC will be utilized during the conduct of this study to review all available data in Part 3. An IDMC is generally assembled when there are significant safety or efficacy issues that warrant external objective medical and/or statistical review in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. The schedule of any planned interim analysis and the analysis plan for IDMC review is described in the charter. A copy of the IDMC charter ~~is~~will be available from GSK, prior to start of Part 3, upon request.

Rationale: Clarification to the timing of the IDMC charter.

SECTION 14 REFERENCES

Added:

Bailey S, Neuenschwander B, Laird G, Branson M. A Bayesian case study in oncology phase I combination dose-finding using logisitic regression with covariates. J Biopharm Stats. 2009; 19 (3):469-484.

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

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Lee JJ, Liu DD. A predictive probability design for Phase II cancer clinical trials. *Clin Trials*. 2008. 5(2):93-106.

Deleted:

~~Gasparini, M, Bailey, S and Neuenschwander, B. 2009. A note on modeling drug-drug interactions in oncology combination trials. Under Submission to *J. Royal Statist. Society. Series C* (Applied Statistics).~~

APPENDIX 2 BLOOD REQUIREMENTS

Previous text:

Part 1: Dose Escalation Cohorts

Test	Sample Volume	Total Volume for Screening, One 4-wk treatment period and Follow-up
Hematology/Clin Chem	5 mL	35
Coagulation	5 mL	5
PK & Metabolite Analysis	4 mL	28
PK & Metabolite Analysis	2 mL	8
[redacted]		
Serum Pregnancy Test	1 mL	1
Total		**129mL/subject**

Part 2: Expansion Cohorts

Test	Sample Volume	Total Volume for Screening, One 4-wk treatment period and Follow-up
Hematology/Clin Chem	5 mL	25
Coagulation	5 mL	5
PK & Metabolite Analysis	4 mL	16
PK & Metabolite Analysis	2 mL	8
[redacted]		
Serum Pregnancy Test	1 mL	1
Total		**107mL/subject**

Part 3: Randomized Phase II Study

Test	Sample Volume	Total Volume for Screening, One 4-wk treatment period and Follow-up
Hematology/Clin Chem	5 mL	25
Coagulation	5 mL	5
[redacted]		
Serum Pregnancy Test	1 mL	1
Total		**83mL/subject**

Revised text:

Part 1: Dose Escalation Cohorts

Test	Sample Volume	Total Volume for Screening, One 4-wk treatment period and Follow-up
Hematology/Clin Chem	5 mL	~~35~~25
Coagulation	5 mL	5
PK ~~& Metabolite~~ Analysis (panitumumab)	4 mL	~~28~~20
PK & Metabolite Analysis (dabrafenib, trametinib)	~~2~~4 mL	~~8~~48
[redacted]		
Serum Pregnancy Test	1 mL	1
Total		**~~129mL~~155mL/subject plus any wasteage associated with collection**

Part 2: Expansion Cohorts

Test	Sample Volume	Total Volume for Screening, One 4-wk treatment period and Follow-up
Hematology/Clin Chem	5 mL	~~25~~20
Coagulation	5 mL	5
PK ~~& Metabolite~~ Analysis (panitumumab)	4 mL	16
PK & Metabolite Analysis (dabrafenib, trametinib)	~~2~~4 mL	~~8~~48
[redacted]		
Serum Pregnancy Test	1 mL	1
Total		**~~107mL~~146mL/subject plus any wasteage associated with collection**

Part 3: Randomized Phase II Study

Test	Sample Volume	Total Volume for Screening, One 4-wk treatment period and Follow-up
Hematology/Clin Chem	5 mL	~~25~~20
Coagulation	5 mL	5
[redacted]		
Serum Pregnancy Test	1 mL	1
Total		**~~83mL~~82mL /subject plus any wasteage associated with collection**

Rationale: Volumes were revised based on supply of collection tubes.

APPENDIX 5: ADDITIONAL WITHHOLDING AND STOPPING CRITERIA FOR SUBJECTS ENROLLED IN FRANCE

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 [Bazett, 1920]

f. 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.

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

Guidelines for Valvular Toxicity for Subjects Enrolled in France

- Subjects who have an asymptomatic, moderate regurgitation or stenosis by ECHO (Grade 2 mitral/tricuspid/aortic valvular toxicity per CTCAE v4.0) should temporarily discontinue dabrafenib 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.

- If the valve recovers to baseline any time during the next 4 weeks, after consultation and approval of the GSK medical monitor, the subject may be restarted on dabrafenib at a reduced dose(s). For such subjects, 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.
- If repeat ECHO does not reveal valve recovery to baseline within 4 weeks, then the subject should permanently discontinue dabrafenib. The valve should continue to be monitored via ECHO every 4 weeks for 16 weeks or until resolution.

- Subjects with a Grade 3 or 4 (symptomatic, severe regurgitation/stenosis by imaging, with symptoms controlled by medical intervention) valvular toxicity must discontinue dabrafenib. 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 subject may restart dabrafenib at a reduced dose after consultation and approval of the GSK medical monitor. For such subjects, 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 subjects who experience a valvular toxicity will be required by GSK for review.

Rationale: Added section in response to review by Agence Nationale de Securite du Medicament et des Produits de Sante (ANSM), to address cardiovascular safety monitoring.

APPENDIX 6: BAZETT'S CORRECTION

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.

Rationale: Added formula for Bazett's correction.