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Title:	Reporting and Analysis Plan for BRF116613: A Phase II biomarker study evaluating the upfront combination of BRAF inhibitor dabrafenib with MEK inhibitor trametinib versus the combination after eight weeks of monotherapy with dabrafenib or trametinib in patients with metastatic and unresectable stage III or IV melanoma harbouring an activating BRAF mutation

Compound Number: GSK1120212 + GSK2118436

Effective Date: 06-JAN-2015

Description: The purpose of this reporting and analysis plan (RAP) is to describe the planned analyses and output to be included in the Study Report for Protocol BRAF116613. This RAP is intended to describe the biomarker, safety, efficacy analyses required for the study. This document will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

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LIST OF ABBREVIATIONS

ADaM	Analysis Data Model
AE	Adverse Event
ALT	Alanine aminotransferase (SGPT)
ANOVA	Analysis of variance
aPTT	Activated Partial thromboplastin time
AST	Aspartate aminotransferase (SGOT)
ATC	Anatomical Therapeutic Chemical
BLDPROD	Blood and Blood Supportive Care Products
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
cfDNA	Circulating free DNA
Conmed	Concomitant Medication
CPMS	Clinical Pharmacology Modelling and Simulation
CR	Complete response
CRF	Case Report Form
CSR	Clinical Study Report
CTX	Anti-Cancer Therapy
CTCAE	Common Terminology Criteria for Adverse Events
DoR	Duration of Response
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
ERK	Extracellular signal-regulated kinase
EXENDT	Exposure end date
GCT	Gamma-Glutamyl Transpeptidase
GLS	Geometric Least Squares
GSK	GlaxoSmithKline
HGB	Hemoglobin
IDSL	Integrated data standards library
INR	International normalized ratio
ITT	Intent-to-Treat
KA	Keratocanthoma
LDH	Lactate Dehydrogenase
LLN	Lower limit of Normal
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Affairs
MRI	Magnetic resonance imaging
MUGA	Multiple gated acquisition scan
NCI	National Cancer Institute
NEWCTXDT	New Anti-Cancer Start Date
NQ	Lower limit of quantification
ONCSURV	Overall Survival Analysis Dataset
ONCTTE	Oncology time to event analysis dataset

ORR	Overall response rate
PcD	Pharmacodynamic
PD	Progressive disease
p-ERK	ERK phosphorylation
PFS	Progression Free Survival
PK	Pharmacokinetic
PR	Partial response
PT	Preferred Term
PrT	Prothrombin time
QTc	Corrected QT interval on electrocardiogram
QTcB	Bazett's Corrected QT interval on electrocardiogram
QTcF	Friderica's Corrected QT interval on electrocardiogram
RADIO	Radiotherapy
RAP	Reporting and analysis plan
RECIST	Response Evaluation Criteria In Solid Tumors
RUCAM	Roussel Uclaf Causality Assessment Method
SAC	Statistical Analysis Complete
SAE	Serious adverse event(s)
SCC	Squamous cell carcinoma
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase (AST)
SGPT	Serum glutamic pyruvic transaminase (ALT)
SLD	Sum of Lesion Diameters
SOC	System Organ Class
SRT	Safety Review Team
STD	Standard Deviation
TTE	Time to Event
ULN	Upper limit of normal
WBC	White Blood Count

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1. INTRODUCTION

This reporting and analysis plan (RAP) details all planned analyses required for a Clinical Study Report of study BRF116613. This is a phase II study to evaluate the biomarkers linked to treatment response, safety, and efficacy of GSK1120212 and GSK2118436 as either a combined treatment or monotherapy.

Revision Chronology:		
2012N132406_00	2013-15-APR	Original
2012N132406_01	2013-28-OCT	Amendment No. 01

All decisions regarding primary/final analysis, as defined in this RAP document, have been made prior to Database Freeze (unblinding) of the study data.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objective

2.1.1. Primary Objective

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

2.1.2. Secondary Objectives

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

2.1.3. Exploratory Objectives

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

2.2. Study Endpoints

2.2.1. Primary Endpoint

- Percentage Change of Extracellular signal-regulated kinase (ERK) phosphorylation (p-ERK) score from baseline

2.2.2. Secondary Endpoints

- Overall response rate (ORR; defined as the percentage of patients with a confirmed or unconfirmed complete response [CR] or partial response [PR] at any time per Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1).
- Safety as measured by clinical assessments including vital signs and physical examinations, Eastern Cooperative Oncology Group (ECOG) performance status, 12-lead electrocardiograms (ECG), echocardiogram (ECHO), chemistry and haematology laboratory values, incidence of squamous cell carcinoma and keratoacanthoma (KA), and adverse events (AEs) graded according to the Common Terminology Criteria for Adverse Events (CTC-AE), version 4.0
- Plasma pharmacokinetic (PK)/ pharmacodynamic (PcD) evaluation

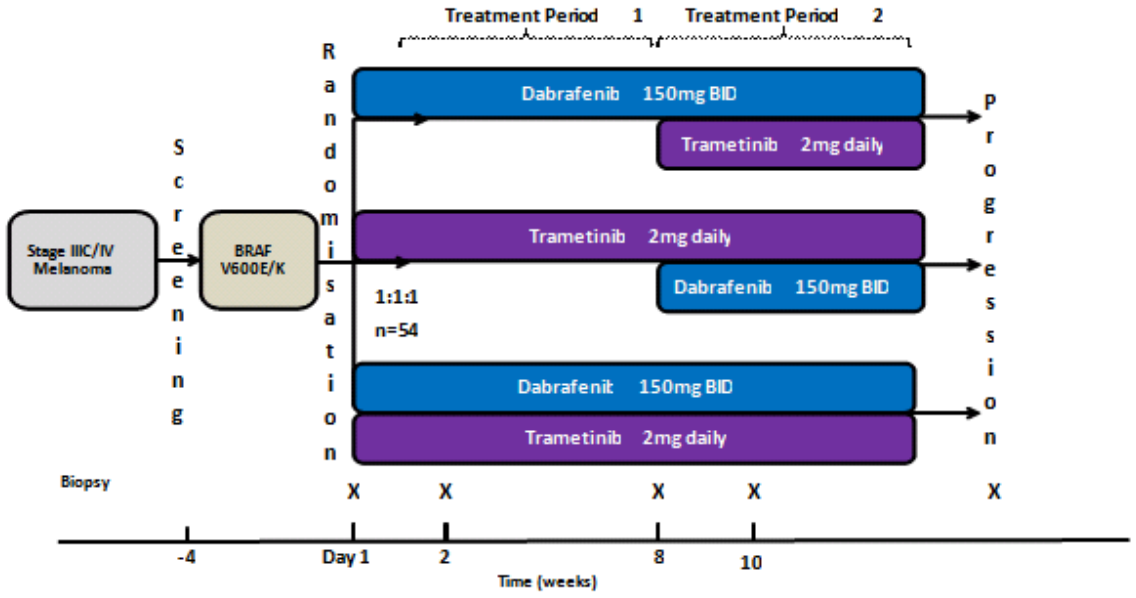
2.2.3. Exploratory Endpoints

- Inflammatory markers
- T cell function by blood immunomonitoring and lymphocyte infiltration of tumors and skin
- Progression-free survival (PFS; defined as the time from randomization until the earliest date of disease progression or death due to any cause) and Duration of response (DoR; defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause among patients who achieve an overall response).

2.3. Statistical Hypothesis

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

3. STUDY DESIGN



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

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

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

Monitoring will be performed throughout the study according to the Time and Events Table in the protocol.

Biomarker analysis will be performed on blood, tumor and skin samples according to the Time and Events Table in the protocol.

Clinical responses will be evaluated using RECIST 1.1 criteria every 8 weeks. The response evaluation may be performed earlier if clinically indicated (for example, if

patient has symptomatic deterioration suggesting rapid disease progression or to confirm clinical response at 4 weeks after achieving response).

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

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

4. PLANNED ANALYSES

4.1. Interim Analysis

No interim analyses will be performed for this study.

4.2. Final Analyses

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

5. SAMPLE SIZE CONSIDERATIONS

5.1. Sample Size Assumptions

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

5.2. Sample Size Sensitivity

The effect of changes in the assumed standard deviation on the precision (i.e., half-width of the 95% CI for percent reduction of p-ERK score from Baseline at Week 2 within a treatment group) is summarized in Table 1.

Table 1 Effects of changes in the assumption of standard deviation

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

5.3. Sample Size Re-estimation

Sample size re-estimation is not planned for this study

6. ANALYSIS POPULATIONS

The **Intent-to-Treat Population (ITT)** will consist of all randomized patients whether or not randomized treatment was administered. This population will be based on the treatment to which the patient was randomized and will be the primary population for the analysis of efficacy data. Any patient who receives a treatment randomization number will be considered to have been randomized.

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

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

7. TREATMENT COMPARISONS

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

Depending on the treatment arm, the treatment descriptor will either be listed as **GSK2118436 BID 8W then GSK1120212 QD + GSK2118436 BID** for Arm A, **GSK1120212 QD 8W then GSK1120212 QD + GSK2118436 BID for Arm B**, or **GSK1120212 QD+ GSK2118436 BID** for Arm C.

8. GENERAL CONSIDERATIONS FOR DATA ANALYSES

8.1. Reporting Conventions

Data will be listed and summarized according to GlaxoSmithKline (GSK) current reporting standards where applicable. Integrated Data Standards Library (IDSL) standards will be followed, as appropriate. Reporting and analyses will be performed

using SAS, Version 9.2 or higher. These SAS programs will be imported into HARP and the final output will be produced by running drivers in HARP. Final delivery of all statistical displays will be generated using Clinical Data Interchange Standard Consortium (CDISC) standards. Other software may be used as needed.

Deviations from the analysis in the RAP will be identified in the Clinical Study Report (CSR).

Unless otherwise stated, all listings will be sorted by centre, subject number, and visit. Unless otherwise stated, continuous variables will be summarized with the statistics mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized with frequency counts and percentages.

Unscheduled visits will be included in the listing using actual time and in calculation of maximum or minimum value over time. However, unscheduled visits will not be included in summaries by planned time.

For summary by planned time, not all plan times are needed to be included in the summary table.

8.2. Multicentre Studies

Data from all participating centres, if applicable, will be pooled prior to analysis. It is anticipated that patient accrual will be spread thinly across centres and summaries of data by centre would be unlikely to be informative and will not, therefore, be provided. However, a summary of subject recruitment by centre will be produced.

8.3. Examination of Subgroups

Exploratory subgroup analyses may be performed, if appropriate. Variables that form the basis of subgroup analyses of some biomarker, safety, and efficacy data including, but not limit to, baseline ECOG performance status, number of prior chemotherapies, age, gender, race and tobacco use.

8.4. Multiple Comparisons and Multiplicity

Adjustment for multiple comparisons is not needed for this study. As there is a single primary endpoint, percentage Change of Erk phosphorylation score from baseline, the nominal levels of significance for the primary analysis will not be affected by multiple comparisons.

9. DATA HANDLING CONVENTIONS

9.1. Premature Withdrawal and Missing Data

Patients will receive study treatment when on combination therapy until disease progression, death or unacceptable adverse event, including haematologic or other nonhaematologic toxicity, and/or meeting stopping criteria for liver chemistry. All

patients will be followed for survival until death, or withdrawal from the study, whichever comes first. A patient will be allowed to continue on monotherapy (either dabrafenib or trametinib) if only one study drug is permanently discontinued.

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

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

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

A patient will be considered to have completed the study if the patient has disease progression or dies during the study treatment. Patients who withdraw from the study will be included in analyses up to the time of withdrawal, regardless of the duration of treatment.

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

As the length of treatment for any patient will depend on the efficacy and toxicity of the treatment, the duration of follow-up will vary among patients. Consequently, there will be no imputation for missing data. Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such. Subjects with unknown or missing best response will be assumed to be non-responders and will be included in the denominator when calculating percentages.

Subjects with the designation of treatment relationship for adverse events (AEs) and serious adverse events (SAEs) missing will have the worst case assumed to impute the relationship: if the relationship to study treatment is missing, it will be assumed to be "Yes" for summary of drug-related AE or SAE.

In the event that the study is prematurely discontinued, all available data will be listed and a review will be carried out by the study team to assess which statistical analyses are still considered appropriate.

9.2. Derived and Transformed Data

The following sections provide a general description of the derived and transformed variables used to describe and analyze the data. Separate analysis dataset specifications provide full details on all data derivations and transformations including descriptions of standard integrated data standards library (IDSL) algorithms including standard Oncology algorithms. The analysis dataset specifications will clearly communicate the content and source of the datasets supporting the statistical analyses.

9.2.1. Reference dates

There are three reference dates:

- Because age is an eligibility requirement, the reference date for age is the date of screening.
- The safety reference date is the treatment start date, and will be used to calculate study day for safety measures.
- The efficacy reference date is the date of randomization and will be used to calculate study day for efficacy measures and baseline characteristics (such as time since initial diagnosis), as well as efficacy durations.

9.2.2. Study Day for Safety Measures

If the date of interest occurs on or after the safety reference date then the safety study day will be calculated as (date of interest - safety reference date) + 1. If the date of interest occurs before the safety reference date then the safety study day will be calculated as (date of interest – safety reference date). There is no safety study day 0.

9.2.3. Study Day for Efficacy

If the date of interest occurs on or after the efficacy reference date then efficacy study day will be calculated as (date of interest - efficacy reference date) + 1. If the date of interest occurs prior to the efficacy reference date then efficacy study day will be calculated as (date of interest – efficacy reference date). There is no efficacy study day 0.

9.2.4. Duration and Elapsed Time

Durations (e.g., the duration of an adverse event, duration of exposure, etc.) are calculated as the stop date minus the start date plus one.

For elapsed time (e.g., the time since initial diagnosis):

- If the reference date is on or after the event date, then the elapsed time is the reference date minus the event date + 1.
- If the reference date is before the event date then the elapsed time is the reference date minus the event date.

When reporting time to event (TTE) durations such as duration of response (DOR) in months, divide the number of days by 30.4375; to report in weeks divide the number of days by 7; to report in years divide the number of days by 365.25. These algorithms for time to event return decimal numbers, and ignore the actual numbers of days in the months or years between start date and stop date. The "year" used in these algorithms is 365.25 days long, and the "month" is one twelfth of that year.

For converting all other durations (e.g. duration of adverse events, duration of exposure, age) to weeks, months or years use the following:

- To report the duration in weeks divide the number of days by 7.
- To report the duration in months use:

  (YEAR(stopdate+1) - YEAR(startdate)) * 12 + (MONTH(stopdate+1) - month(startdate) -1) + (DAY(stopdate+1) >= DAY(startdate))

- To report the duration in years use:

  intck('year', startdate, stopdate+1) - (month(stopdate+1)<month(startdate) or (month(stopdate+1)=month(startdate) and day(stopdate+1)<day(startdate)))

The algorithms above for age and duration return whole numbers for months and years, accurately accounting for the actual numbers of days in the months or years between the start date and the stop date.

9.2.5. Imputation of Partial Dates

Imputed partial dates will not be used to derive study day, duration (e.g. duration of adverse events), or elapsed time variables. In addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset (ONCSURV).

With the exception of new anti-cancer start date (NEWCTXDT) on the Oncology time to event analysis dataset (ONCTTE) [,][and] exposure end date (EXENDT) on the Exposure analysis dataset, [and other variables and datasets] imputed dates will also not be stored on datasets.

Imputed dates will not be displayed in listings. However, where necessary, display macros may impute dates as temporary variables for the purpose of sorting data in listings only. In addition partial dates may be imputed for ‘slotting’ data to study time periods (Section 9.3) or for specific analysis purposes as outlined below.

The partial date imputation will follow Analysis Data Model (ADaM) conventions. The ADaM approach is to populate the numeric date variables with the imputed date and add a flag variable to the dataset that indicates the level of imputation. The flag variable can contain the values: blank, 'D', 'M', 'Y'.

Blank: indicates that no imputation was done
D='Day': indicates that the day portion of the date is imputed

M='Month': indicates that the month and day portions of the date are imputed
Y='Year': indicates that the entire date (year, month, and day) is imputed

Example of Date Variables: Date of new anti-cancer therapy
NEWCTXD_ - character date variable
NEWCTXDT - numeric date variable
NEWCDTFL - flag variable

Details on imputing partial dates for specific datasets are outlined below.

Adverse Events (AE):

Imputations in AE are used for slotting events to the appropriate study time periods and for sorting in data listings.

Dataset	Date	Missing Element	Rule
Adverse Events (AE)	Start Date	day, month, and year	• No Imputation for completely missing dates
		day, month	• If study treatment start date is missing (i.e. subject did not start study treatment), then set start date = January 1. • Else if study treatment start date is not missing: ○ If year of start date = year of study treatment start date then • If stop date contains a full date and stop date is earlier than study treatment start date then set start date = January 1. • Else set start date = study treatment start date. ○ Else set start date = January 1.
		day	• If study treatment start date is missing (i.e. subject did not start study treatment), then set start date = 1st of month. • Else if study treatment start date is not missing: ○ If month and year of start date = month and year of study treatment start date then • If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 1st of month. • Else set start date = study treatment start date. ○ Else set start date = 1st of month.
	End Date		• No imputation for partial end dates will be performed

Anti-Cancer Therapy (CTX) and Radiotherapy (RADIO):

Start and end dates are generally not imputed. If start or end dates need to be imputed for an analysis (e.g. to calculate duration or elapsed time as covariates for efficacy analyses), the rules for imputation will be defined within the algorithm of the derived covariate. Additionally, post treatment CTX and RADIO start dates may be imputed to determine date of new anti-cancer therapy. In this case only, NEWCTXDT (not all CTX and RADIO start dates) will be stored on appropriate efficacy datasets. Imputed partial dates will not be used to derive ATMPCTX (time since most recent prior therapy). In addition, the CTXTRTCD variable, and not any variables which use imputed partial dates, will be used to differentiate prior and follow-up CTX and RADIO.

Dataset	Date	Missing Element	Rule
Anti-Cancer Therapy (CTX) Radiotherapy (RADIO)	Start Date	day, month, and year	No Imputation for completely missing dates
		day, month	If partial date contains a year only set to January 1st.
		day	If partial date contains a month and year set to the 1st of the month.
	End Date		No imputation for partial end dates will be performed

Surgery:

SURGERY date is generally not imputed. If SURGERY date needs to be imputed for an analysis (e.g. to calculate duration, elapsed time as covariates for efficacy analyses, or if surgery is on a lesion being tracked), the rules for imputation will be defined within the algorithm of the derived covariate. Additionally, post treatment SURGERY dates maybe imputed (where applicable) to determine date of new anti-cancer therapy. In this case only, NEWCTXDT (not specific SURGERY date) will be stored on appropriate efficacy datasets. The SPCATCD variable, and not any variables which use imputed partial dates, will be used to differentiate prior, on, and follow-up SURGERY data. The derived ATTYPE and ATTYPECD variables are not needed for reporting of data because SPCATCD can be used. Therefore, imputed dates are not needed for derivation of ATTYPE and ATTYPECD.

Dataset	Missing Element	Rule
Surgery	day, month, and year	• No Imputation for completely missing dates
	day, month	• If partial date contains a year only set to January 1st.
	day	• If partial date contains a month and year set to the 1st of the month

Concomitant Medication (Conmed) and Blood and Blood Supportive Care Products:

Impute start and end dates for use in derivation of the reference variables (CONMEDS.CMSTRF/BLDPROD.BLSTRF, CONMEDS.CMENRF/BLDPROD.BLENRF), but do not permanently store the imputed start and end dates in the CONMEDS and BLDPROD AR datasets. The reference variables will be used to differentiate before, during and after for the concomitant medication start and end dates. The derived ATTYPE and ATTYPECD variables are not needed for reporting of data.

Dataset	Date	Missing Element	Rule
Concomitant Medication (Conmed) Blood and Blood Supportive Care Products (BLDPROD)	Start Date	day, month, and year	• No Imputation for completely missing dates

		day, month	• If study treatment start date is missing (i.e. subject did not start study treatment), then set start date = January 1.
			• Else if study treatment start date is not missing:
			  ○ If year of start date = year of study treatment start date then
			  ▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date = January 1.
			  ▪ Else set start date = study treatment

			start date. o Else set start date = January 1.
		day	• If study treatment start date is missing (i.e. subject did not start study treatment), then set start date = 1st of month. • Else if study treatment start date is not missing: o If month and year of start date = month and year of study treatment start date then ▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 1st of month. ▪ Else set start date = study treatment start date. o Else set start date = 1st of month.
	End Date	day, month, and year	• No Imputation for completely missing dates
		day, month	• If partial end date contains year only, set end date = earliest of December 31 or date of last contact.
		day	• If partial end date contains month and year, set end date = earliest of last day of the month or date of last contact (MSTONE.LCONTDT).

ONCTTE, RESP2, and RESP2EX1:

Start dates for follow-up CTX, RADIO (where applicable), and SURGERY (where applicable) will be temporarily imputed in order to define event and censoring rules for progression-free survival, response rate, or duration of response (i.e. start date for new anti-cancer therapy). Dates will only be imputed when a month and year are available but the day is missing. The imputed date(s) will not be stored on the CTX, RADIO, or SURGERY datasets. The following rules will be used to impute the date when partial start dates are present on CTX RADIO, and/or SURGERY:

Dataset	Date	Missing Element	Rule
Anti-Cancer Therapy (CTX) Where applicable: Radiotherapy	Start Date	day, month, and year	• No Imputation for completely missing dates

(RADIO) Surgery			
		day, month	• No imputation for missing day and month (note the eCRF should only allow for missing day)
		day	• If partial date falls in the same month as the last dose of study treatment, then assign to earlier of (date of last dose of study treatment+1, last day of month). • If partial date falls in the same month as the subject's last assessment and the subject's last assessment is PD, then assign to earlier of (date of PD+1, last day of month). • If both rules above apply, then assign to latest of the 2 dates • Otherwise, impute missing day to the first of the month.
	End Date		• No imputation for partial end dates will be performed

NEWCTXDT is derived as the earliest date of new anti-cancer therapy (e.g. chemotherapy), radiotherapy (where applicable), or cancer related surgical procedure (where applicable) and will include imputed dates. If NEWCTXDT is an imputed date, then the flag variable NEWCDTFL is assigned the value of 'D' to indicate that the day portion of the date is imputed (following ADaM convention).

As multiple dates are used to derive NEWCTXDT ensure that NEWCDTFL is only set to 'D' if the derived date is imputed. For example if the date of new radiotherapy is imputed but the date of new anti-cancer therapy is prior to date of new radiotherapy and the new anti-cancer therapy date is not a partial date then the NEWCDTFL should be set to missing as the date used for NEWCTXDT is not an imputed date.

Covariates:

If the algorithms for covariates (e.g. prognostic factors) include any partial dates, then the algorithms must specify the date imputation rules used in the derivations. The following imputation rules are the standard rules to be used when algorithms for covariates require date imputations.

Variable	Example of when to impute	Rule
Prior CTX start date Prior RADIO start date	• Impute to derive duration ○ Duration of prior [Herceptin] Therapy	• Only impute when a month and year are available but the day is missing. • Impute to first day of the month. • Do not store imputed date • Use only for relevant efficacy analyses (i.e. not to be used for general radiotherapy or anti-cancer therapy summaries)

Prior CTX end date
 	
Prior RADIO end date
	• Impute to derive elapsed time and duration
	  ○ Duration of prior [Herceptin] Therapy
	  ○ Time from Last dose of [Herceptin] to Randomization
		• Only impute when a month and year are available but the day is missing.
		• Impute to last day of the month, also must be prior to 'start'
		  ○ if 'start' is the first of the month assign to 'start', else assign to 'start'-1), where 'start' is either the date of randomization or the start of study treatment.
		• Do not store imputed date
		• Use only for relevant efficacy analyses (i.e. not to be used for general radiotherapy or anti-cancer therapy summaries)

Any DISCHA1 dates.
For example:
 	
• DIAGDT
• LSTRECDT
• LPROGDT
	• Impute to derive elapsed time
	  ○ Time from initial diagnosis to randomization for use as a covariate
	  ○ Time from progression on last therapy until randomization for use as a covariate
		• If both month and day are missing, impute to January 1st
		• else if day is missing, impute to first day of the month.
		• Do not store imputed date
		• Use only for relevant efficacy analyses (i.e. not to be used for general disease characteristic summaries)

9.2.6. Imputation of Missing Exposure End Dates

In general, completely missing dates are not imputed. However, subjects in oncology trials may still be on study treatment when analyses are performed and so may have missing exposure end dates in their last dosing record. Missing exposure end dates for subjects who are still on study treatment at the time of an analysis will be imputed. For subjects with missing exposure end dates at the time of data cutoff, the exposure end date will be imputed to the earliest of: the date of the data cutoff, the date of withdrawal from the study, or the death date. The imputed exposure end date will be used to calculate cumulative dose and exposure duration. The imputed exposure end date will be stored in the EXPOSURE analysis dataset (EXENDT) and an exposure end date imputation flag variable will be derived indicating which exposure end date records are imputed. Imputed exposure end dates will also be stored on the MSTONE analysis dataset (MSTENDT).

For subjects who have missing end dates in their last exposure record because they are still on study treatment, the on-therapy indicator variables ATTYPE and ATTYPECD are assigned to on-therapy for all records where the 'dataset'.'date' is after or on the study treatment start date.

9.2.7. Baseline Definition

Baseline will be defined as the most recent non-missing value prior to the first dose of study treatment. For laboratory data, baseline will be defined as the most recent non-missing value from a central laboratory prior to the first dose of study treatment.

The following table indicates the baseline day to be used in any change from baseline listings / summaries / graphical presentations or as a covariate in a statistical analysis:

Parameter	Baseline Days Collected		Baseline To Be Used in Analysis / Summaries
	Screening[1]	Day 1	
Safety :			
ECOG	X		Screening
Brain Magnetic Resonance Imaging (MRI) /Computed Tomography (CT)	X (5 weeks)		Screening
Lesion Assessment	X (5 weeks)		Screening
Vital Signs	X		Screening[2]
Physical examination	X		Screening[2]
Ophthalmic examination	X		Screening[2]
ECG	X (5 weeks)		Screening
ECHO	X (5 weeks)		Screening
Chemistry and Haematology[3]	X		
PD :			
Tumor		X	Day 1
Skin		X	Day 1
Blood sample for biomarker		X	Day 1
Blood sample for circulating free DNA (cfDNA)		X	Day 1
Clinical Activity:			
Disease Assessment	X		Screening

1. ≤ 28 days before 1st dose except where noted
2. Use the mean of replicate assessments at any given time point as the value for that time point in all summaries, figures and statistical analyses.
3. Screening labs performed within 2 weeks prior to randomization do not need to be repeated

9.2.8. Change from baseline

Change from baseline will be presented for safety data as described in Section 12.

Change from baseline is calculated as:

- For records occurring after baseline: (visit value) – baseline value.

Percent change from baseline is calculated as:

- For records occurring after baseline: ((change from baseline) / baseline value) * 100

If either the baseline or visit value is missing, the change from baseline and/or percent change from baseline is set to missing as well.

9.2.9. Multiple Assessments

All data will be reported according to the nominal visit date for which it was reported (that is, no visit windows will be applied during dataset creation). Unscheduled data is included only in summary sections and in shift summaries of laboratory (e.g., vital signs/ECG) data labelled worst- case. For summaries that collapse data across multiple planned time intervals, select the worst-case data at each collapsed interval.

If multiple assessments on different days are reported for the same scheduled assessment, then the latest assessment for that scheduled assessment will be analyzed.

If multiple assessments are reported on the same date for the same scheduled planned time, then the worst-case result will be analyzed, with the exception of laboratory data reported from both central and local laboratories. If laboratory data is reported from both central and local laboratories with the same date, then the central laboratory data will be analyzed to provide consistency with measurements from other subjects. For example, for ECG data where 3 assessments are collected for each scheduled planned time, the first 3 measures will be used to compute the mean values for ECG intervals at each scheduled planned time.

Data from all assessments (scheduled and unscheduled), including multiple assessments, will be included in listings.

9.2.10. Actual Treatment

The subjects' actual treatment will be derived from exposure data and stored in variables ATRTCD and ATRTGRP. If a subject's actual treatment is the same as the assigned treatment, then actual treatment is the assigned treatment. If a subject receives a study treatment that is different from the assigned treatment for the entire time of treatment, then actual treatment is the different treatment (the treatment actually received).

9.3. Study Time Periods

Data from all assessments (scheduled and unscheduled), including multiple assessments, will be included in listings. Summaries by planned time will include data from scheduled assessments 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, when summarized, will be included only in calculation of the maximum or minimum value over time such as worst case post-baseline.

9.3.1. Time in relation to treatment

Adverse events, serious adverse events, death, laboratory data, vitals, ECG, ECHO/Multiple gated acquisition scan (MUGA), and questionnaire data (ECOG, FACIT-F, FKSI-19, SQLQ, CTSQ, MRU, and KPS), will be assigned to the study time periods defined below. Partial dates will be imputed into full dates, if applicable, for slotting data to the appropriate categories below (see Section 9.2.5). Flag variables (ATTYPECD/ATTYPE) indicating the study time periods will be added to these datasets.

Pre-therapy is defined as the time prior to the subject's first dose of study treatment.

On-therapy is defined as the time from first dose of study treatment to the last dose date of study treatment.

Post-therapy is defined as any time beyond the on-therapy period.

9.3.2. Study time periods for concomitant medications

Concomitant Medication and Blood and Blood Supportive Care Product start and end dates will be assigned to study time periods in relation to first dose of study treatment as defined below. The start date references time flag variables (CMSTRF, BLSTRF) and end date reference time flag variables (CMENRF and BLENRF) will be added to the CONMEDS and BLDPROD datasets, respectively.

- **Start relative to treatment (CMSTRF and BLSTRF, respectively):** Assign to 'BEFORE" if start date is prior to study treatment start date or if subject has not taken any study treatment or (start date is missing and end date is before study treatment start date). Else assign to 'DURING' if the start date falls into the on-therapy period as defined above or if subject is ongoing (not all study treatment discontinuation records completed) or start date is missing. Else assign to 'AFTER' if start date is after the on-therapy period (defined above).
- End relative to treatment (CMENRF and BLENRF, respectively): Assign to 'BEFORE" if end date is prior to study treatment start date or if subject has not taken any study treatment. Else assign to 'DURING' if start date falls into the on-therapy period as defined above or if subject is ongoing (not all study treatment discontinuation records completed) or (end date is missing and –STRF not 'AFTER'). Else assign to 'AFTER' if start date is after the on-therapy period (defined above) or (end date is missing and –STRF='AFTER').

Only on-therapy blood and blood supportive care products that start after the start of study treatment are included in the Blood Products and Blood Supportive Care Product summaries. Therefore, for summary tables, include BLDPROD records where BLSTRF in ('DURING') and BLENRF in ('DURING','AFTER'). All data will be reported in listings.

CONMEDS.CMSTRF and CONMEDS.CMENRF are used to select data to include in the Concomitant Medication summaries as follows:

- Summary of Concomitant Medications: This summary will contain medications including those with start date prior to study treatment start date and continue (missing end date or end date after study treatment start date) on therapy. Note that any medications with start date and end date prior to study treatment start date will be excluded. In addition, any medication that was started during post-therapy (see above for definition of post-therapy) will be excluded. Include CONMED records where CMSTRF in ('BEFORE','DURING') and CMENRF in ('DURING','AFTER').
- Summary of Concomitant Medications with On-Therapy Onset: This summary will contain medications with start date after study treatment start date. In addition, any

medication that was started during post-therapy (see above for definition of post-therapy) will be excluded. Include CONMED records where CMSTRF in ('DURING') and CMENRF in ('DURING','AFTER').

9.4. Values of Potential Clinical Importance

9.4.1. Laboratory Parameters

Reference ranges for all laboratory parameters collected throughout the study are provided by the laboratory. A laboratory value that is outside the reference range is considered either high abnormal (value above the upper limit of the reference range) or low abnormal (value below the lower limit of the reference range). Note: a high abnormal or low abnormal laboratory value is not necessarily of clinical concern. The laboratory reference ranges will be provided on the listings of laboratory data. Clinical laboratory test results outside of the reference range will be flagged in the listings.

To identify laboratory values of potential clinical importance, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v4.0) will be used to assign grades to the relevant laboratory parameters. NCI-CTCAE v4.0 can be found at http://ctep.cancer.gov/reporting/ctc.html.

For laboratory data which are not listed in the NCI CTCAE v4.0, a summary of values outside the normal range will be provided.

Vital signs in the following ranges will be flagged as being of clinical concern in the corresponding listings:

9.4.2. ECG Parameters:

The following criteria will be used to flag electrocardiogram (ECG) values that are values of potential clinical importance:

To identify corrected QT interval on electrocardiogram (QTc) (Bazett's [QTcB] or Fridericia's [QTcF]) values of potential clinical importance, NCI-CTCAE v4.0 will be used to assign grades (see adverse event 'Electrocardiogram QT corrected interval prolonged'). Note that there is a slight inconsistency between CTCAE v4 and ICH E14 (Absolute QTc interval prolongation). It was decided to align with CTCAE for the oncology standard categories.

ECG Parameter	Potential Clinical Importance (PCI) Range	Unit
Absolute QTcF [QTcB] interval	>=450 to <481 (Grade 1) >=481 to <501 (Grade 2) >=501 (Grade 3)	Msec
Increase from baseline QTcF [QTcB]	Increase of >=31 to <=60 Increase of >60	Msec

The following criteria will be used to flag other ECG values that are values of potential clinical importance:

ECG Parameter	Potential Clinical Importance (PCI) Range	Unit
PR interval	<110 (L) and >220 (H)	Msec
QRS interval	<75 (L) and >110 (H)	Msec

9.4.3. Vital signs

The following criteria will be used to flag vital sign values that are values of potential clinical importance:

To identify heart rate values of potential clinical importance, NCI-CTCAE v4.0 will be used to assign categories that align with the grades for 'Sinus bradycardia', 'Sinus tachycardia', 'Supraventricular tachycardia', and 'Ventricular tachycardia'.

Vital Sign Parameter	Potential Clinical Importance (PCI) Range	Unit
Decrease from baseline Heart Rate	Decrease to <60	bpm
Increase from baseline Heart Rate	Increase to >100	bpm

To identify blood pressure values of potential clinical importance, NCI-CTCAE v4.0 will be used to assign categories that align with the grades for 'Hypertension'.

Vital Sign Parameter	Potential Clinical Importance (PCI) Range	Unit
Increase from baseline Systolic Blood Pressure	>=120 to <140 (Grade 1) >=140 to <160 (Grade 2) >=160 (Grade 3)	mmHg
Increase from baseline Diastolic Blood Pressure	>=80 to <90 (Grade 1) >=90 to <100 (Grade 2) >=100 (Grade 3)	mmHg

To identify temperature values of potential clinical importance, NCI-CTCAE v4.0 will be used to assign categories that align with the grades for 'Hypothermia' and 'Fever'.

Vital Sign Parameter	Potential Clinical Importance (PCI) Range	Unit
Increase from baseline temperature	Increase to >= 38	Degrees C
Decrease from baseline Diastolic Blood Pressure	Decrease to <= 35	Degrees C

9.4.4. Left Ventricular Ejection Fraction

The following criteria will be used to flag left ventricular ejection fraction (LVEF) values that are values of potential clinical importance:

To identify LVEF values of potential clinical importance, NCI-CTCAE v4.0 will be used to assign categories that align with the grades for 'Ejection fraction decreased'.

LVEF Parameter	Potential Clinical Importance (PCI) Range	Unit

Absolute change from baseline LVEF	• No change or any increase
	• Any decrease
	  ○ >0-<10 decrease
	  ○ 10-19 decrease
	  ○ >=20 decrease
	  ○ >=10 decrease and >= LLN
	  ○ >=10 decrease and below LLN
	  ○ >=20 decrease and >= LLN
	  ○ >=20 decrease and below LLN
		%

Relative change from baseline LVEF	• >=20 decrease and >= LLN • >=20 decrease and below LLN	%

10. STUDY POPULATION

Unless otherwise stated, all tables and listings in this section will be based on the ITT population, and all summaries and data listings will use treatment labels as specified in Section 7.

The lists of displays for Study Population, including population to use for each display, are shown in Section 18.1 of the RAP.

10.1. Disposition of Subjects

A summary of the number of subjects in each of the analysis populations described in Section 6 will be provided. In addition, the number of subjects enrolled by centre will be summarized by treatment group using the ITT population. A listing of subjects excluded from analysis populations will also be provided.

A summary of subject status and reason for study withdrawal will be provided. This display will show the number and percentage of subjects who withdrew from the study, including primary and secondary reasons for study withdrawal. Reasons for study withdrawal will be presented in the order they are displayed in the electronic case report form (eCRF).

A summary of study treatment status will be provided. This display will show the number and percentage of subjects who discontinued study treatment (or have treatment ongoing or completed the study) and a summary of the primary and secondary reasons for discontinuation of study treatment. Reasons for study treatment discontinuation will be presented in the order they are displayed in the eCRF. A listing of study treatment discontinuation will be generated. The listing will include last dose date, and reasons for study treatment discontinuation as well as study period of discontinuation.

10.2. Protocol Deviations

All protocol deviations will be summarized and listed and will include inclusion/exclusion deviations as well as other deviations. A separate summary and listing of inclusion/exclusion deviations will also be provided.

10.3. Demographic and Baseline Characteristics

The demographic characteristics (e.g. age, race, ethnicity, sex, height, and body weight) will be summarized and listed. Age, height and weight will be summarized using the mean, standard deviation, minimum, median, and maximum. In addition, age will also be categorized and summarized by 18-64, 65-74, and > 74. A separate age group breakdown table with age ranges of 18-64, 65-84, and > 84 will be created for use in any European submissions. The count and percentage will be computed for sex and ethnicity.

Race and racial combinations will be summarized and listed.

Disease history and characteristics (time since initial diagnosis in weeks, stage at initial diagnosis, date of initial diagnosis) at initial diagnosis and screening (BRAF mutation determination, and Baseline determination of target and non-target lesions), will be listed. Separate summaries of disease characteristics at initial diagnosis and screening will be provided. Medical conditions present at screening will be listed and will be summarized for both cancer-related and non-cancer related medical conditions.

A summary of disease burden at baseline will be produced. Information on metastatic disease at screening will be summarized and listed.

Substance use, including and not-limited to smoking history, alcohol use, and caffeine use, will be summarized and listed.

Prior anti-cancer therapy including chemotherapy, hormonal therapy, immunotherapy, biologic therapy, and small molecule targeted therapy will be coded using GSK Drug coding dictionary, and the following summary tables will be provided:

- Summary of prior anti-cancer therapy, in which the number and percentage of subjects who received anti-cancer therapy prior to the study will be displayed for each type of anti-cancer therapy. The types of anti-cancer therapy will be sorted in descending order from highest total incidence to the lowest total incidence.
- Summary of dictionary coded prior anti-cancer therapy, in which the number and percentage of subjects with each dictionary coded anti-cancer therapy will be displayed.
- Summary of number of prior anti-cancer therapy regimens.
- Summary of best response to most recent prior anti-cancer therapy for metastatic disease.

The relationship between Anatomical Therapeutic Chemical (ATC) level 1, ingredient, and verbatim text for anti-cancer therapy will be provided.

Prior anti-cancer radiotherapy will be listed.

Prior surgical procedures will be listed and summarized. Separate summaries will be provided for cancer related and non-cancer related surgical procedures.

10.4. Treatment Compliance

A listing of planned and actual treatments will be produced.

A listing of drug accountability data (dispensed and returned) will be produced.

For dabrafenib and trametinib, the number of capsules dispensed and returned at each visit interval according to the eCRF will be listed. An assessment of percentage compliance during each visit interval will be calculated and listed. For each subject, an assessment of overall percentage compliance will be calculated looking at the entire interval of dosing (i.e. number of days between start of investigational product and stop of investigational product). The formula to calculate compliance is as follows:

$$\frac{Total\ \#\ of\ capsules\ dispensed - Total\ \#\ of\ capsules\ returned}{\#\ of\ days\ in\ visit\ interval * \#\ capsules\ prescribed\ per\ day} x\ 100$$

Where
$\#\ of\ dates\ in\ visit\ interval = Date\ returned - Date\ dispensed + 1$
$\#\ of\ dates\ in\ visit\ interval = Date\ returned - Date\ dispensed + 1$ in the visit interval.

Compliance will be considered unknown if it cannot be calculated because of missing data. The calculated percentage compliances will be summarized for the subjects in the ITT population. Percentage overall compliance will be summarized using the mean, standard deviation, minimum, median, and maximum. In additional, percentage overall compliance will be categorized and summarized by < 80%, 80%-105%, and >105%.

A listing of overall compliance will be produced.

In addition, summaries of study treatment exposure and dose modifications (e.g. number of dose reductions, number of dose interruptions) will further characterize compliance. These analyses are described in the Extent of Exposure section (Section 12.1).

10.5. Concomitant Medications

Concomitant medications will be coded using GSK Drug coding dictionary, summarized, and listed. The summary of concomitant medications will show the number and percentage of subjects taking concomitant medications by Ingredient. Multi-ingredient products will be summarized by their separate ingredients rather than as a combination of ingredients. Anatomical Therapeutic Chemical (ATC) classification Level 1 (Body System) information will be included on the listing but not in the summary.

In the summary of concomitant medications, each subject is counted once within each unique ingredient. For example, if a subject takes Amoxicillin on two separate occasions, the subject is counted only once under the ingredient "Amoxicillin".

In the summary of concomitant medications, the ingredients will be summarized by the base only, using CMBASECD and CMBASE. [OR In the summary of concomitant medications, the ingredients will be summarized by the combination of base and salts, using CMCOMPCD and CMCOMP.]

Blood products or blood supportive care products with onset date within the on-therapy window will be included in the summary tables. The frequency and percentage of subjects using blood products and blood supportive care products after the start of study medication will be provided. Supporting listings will also be provided.

Follow-up anti-cancer therapy will be listed.

11. PHOSPHORYLATION OF ERK ENDPOINT ANALYSIS

The primary objective of this trial is to evaluate the percentage reduction of p-ERK score from baseline and characterize safety and efficacy of different treatment sequence with the p-ERK score changes. The primary end point will be analyzed with a descriptive intent only. Hence no hypothesis testing will be performed. The Biomarker Population will be used for the reporting and the analysis of the primary endpoint, and all members of the biomarker population will have a positive BRAF V600E/K mutation.

We also will conduct an exploratory sensitivity analysis among all subjects with BRAF V600E mutation based on central lab testing for primary P-ERK Biomarker Analyses listed in Section 11.2.1. A summary will be created that lists the samples obtained for Immuohistochemistry Analysis. The lists of displays for P-ERK, including population to use for each display, are shown in Section 18.1.5 of the RAP.

11.1. Interim Analysis

No formal interim analysis will be conducted in this study.

11.2. Investigator Assessment of H-Score

The primary endpoint analysis will be the evaluation of the percentage change of the mean Phosphorylated Extracellular Signal-regulated Kinase (p-ERK) H-Score from baseline. At the beginning of IP treatment, the p-ERK H-Score will be determined for all participants in the biomarker population.

Change in biomarker status is most prominent within two weeks of start of treatment. Patients from arm A and arm B will be given combination therapy starting from week 9 after completion of 8 weeks of monotherapy. Therefore, changes in biomarker between screening and week 2 as well as between week 8 and week 10 will be summarized and listed. All visits for biomarker samples have a window of ± 7 days.

More specifically, the procedure for calculating the p-ERK score is shown below:

- Intra-tumoral expression levels of ERK, a tumor tissue biomarker, will be measured using immunohistochemistry methods that incorporated both intensity and distribution of staining. A value designated the H-Score will be derived by summing the percentages of cells staining at each intensity multiplied by the weighted intensity of staining (0, 1+, 2+, 3+: 3+ indicates the strongest staining, 2+ indicates medium staining, 1+ indicates weak staining, and 0 indicates no staining). H-Scores range from a minimum score of 0 to a maximum score of 300; the maximum score indicates the strongest expression. We will also collect a summary staining score for the tumor tissue which has potential values of 0 (no staining), 1+ (weak staining), 2+ (medium staining), and 3+ (strong staining).

$$\begin{aligned} H-Score = {} & (3 * \%\ Cells\ with\ strongest\ staining) \\ & + (2 * \%\ Cells\ with\ medium\ staining) \\ & + (1 * \%\ Cells\ with\ weak\ staining) \\ & + (0 * \%\ Cells\ with\ no\ staining) \end{aligned}$$

All p-ERK H-Score data will be recorded on the eCRF, including data on % positivity for all participants in the biomarker population, which is calculated using the equation below:

$$\begin{aligned} \%\ Positivity = {} & \%\ of\ cells\ with\ weak\ staining \\ & + \%\ of\ cells\ with\ medium\ staining \\ & + \%\ of\ cells\ with\ strong\ staining \end{aligned}$$

Summary statistics, graphics, and statistical modeling will be conducted on the biomarker population for each arm of the study.

11.2.1. Primary p-ERK Biomarker Analyses:

Analyses from this section will utilize p-ERK H-scores from pre-dose, 2-week, 8-week, and 10-week biopsies. Summary statistics (mean, standard deviation, median, minimum, and maximum) will be reported at each time point and for change (actual and percent

changes) from baseline to two weeks in Arm C and for change from 8-week and 10-week in Arms A and B for p-ERK using H-score values.

Depending upon data availability, log_2-transformed values of p-ERK H-Score results will be analyzed by analysis of variance (ANOVA) for each cohort. In some cases, it is possible for p-ERK H-Scores to have a value of zero, and if these zero H-Scores are present in the data, we will add an offset of one to all values before conducting any log_2-transformations. This analysis will consider time and treatment as the fixed effect, and subject as a random effect. The H-Score calculation at either screening (analysis for combo arm) or week 8 (analysis from monotherapy arms) is the test comparison and the H-Score calculation at either week 2 (analysis for combo arm) or week 10 (analysis from monotherapy arms) is the reference calculation. The analysis will be performed using the mixed linear models procedure within the SAS/STAT module of the SAS system. Point and (1-2α*) interval estimates of the difference in least-square (LS) means of the test less the reference treatment will be derived using SAS code such as that described below:

```
proc mixed;
class trt time subject;
model HScore = time trt;
random subject;
lsmeans trt;
estimate 'B vs. A' trt -1 1 / cl alpha=0.05
run;
```

(In this code, trt, HScore, and time refer to treatment given, H-Score Value, and the time of H-Score analysis, respectively).

For each primary endpoint, results from these analyses will be exponentiated to obtain point and 90% confidence interval estimates of the appropriate test to reference ratios of geometric least-squares (GLS) means.

Assumptions underlying these analyses will be assessed. If the assumptions are seriously violated, then nonparametric methods will be considered.

The mean and median Intra-tumoral expression levels of ERK over time will be plotted, with treatment highlighted using appropriate graphical techniques (e.g. trellis, plotting symbol, and colour).

For further exploratory purposes and if data warrant, multivariate proportional Cox models examining the relationships between PFS and DoR and decreases in H-Score from none or mono therapy to combo therapy may be examined with age, sex, ECOG status, initial drug exposure (combo therapy vs. monotherapy), and BRAF mutation type (V600E vs. V600K) as potential covariates using backward selection. If multivariate proportional Cox models are developed, a listing containing the values for each variable as part of the Cox model will be created.

11.2.2. Exploratory Predictive p-ERK Analyses

The objective of the statistical analysis outlined in this section is to characterize potential of p-ERK to be a predictive biomarker assessed from tumor tissue and biological response as measured by changes in tumor volume.

11.2.2.1. Change from baseline

Depending upon data availability, exploratory analyses may be performed to examine potential relationships between decrease from baseline H-score from tumor biopsies, and tumor response.

Tumor response will be quantified using change from baseline of tumor measurements (% change sum of lesion diameters [SLD]). Percent change from baseline for sum of lesion diameters is set to missing if any target lesions at baseline are missing or not measured at post baseline observation. Correlation between decrease in H-score and %SLD will be evaluated using Spearman's correlation coefficient. A scatter plot will be created for each treatment arm.

Summaries of the relationship between change in H-score and CR/PR/ Stable Disease (SD)/ Progressive Disease (PD) (without confirmation) will be assessed if data permit (i.e. if there are enough subjects with CR, PR etc.).

11.2.2.2. Baseline

Depending upon data availability, exploratory analyses may be performed to examine potential relationships between baseline of H-score from tumor biopsies, and tumor response.

Tumor response will be quantified using change from baseline of tumor measurements (%SLD). Correlation matrices of baseline p-ERK H-Score and %SLD will be reported (Spearman's R, N, and p-value). A scatter plot will be created for each treatment arm.

Summaries of the relationship between baseline H-score and CR/PR/SD/PD (without confirmation) will be assessed if data permit (i.e. if there are enough subjects with CR, PR etc.).

12. SAFETY ANALYSES

Safety data will be summarized and listed by, or under the direct auspices of, the Discovery Biometrics Programmer and reviewed by the Discovery Biometrics Statistician, GlaxoSmithKline. Select safety data will be presented graphically.

Unless otherwise specified, all the safety analyses will be based on the Safety population as defined in Section 6 and summaries will include all events or assessments collected during the study. All the analyses will be performed by treatment arm.

The lists of displays for safety analyses, including population to use for each display, are shown in Section 18.1.3 of the RAP.

12.1. Extent of Exposure

Extent of exposure to dabrafenib and trametinib will be summarized separately.

The duration of exposure to study treatment in weeks (from first day to last day of treatment) will be summarised. Descriptive statistics including mean, median, standard deviation, minimum, and maximum will be calculated for time on study treatment. Moreover, time on study treatment will be categorized in different time period: < 2 months, 2 months to 4 months, >4 months to 8 months and >8 months.

The subject daily dose, defined as the cumulative dose divided by the duration of exposure for each subject, will be summarized. In addition, summary of the population level daily dose will also be provided. In this analysis, a dose on each day for each subject will be treated as an observation and the summary will be based on the dose on each individual day for all subjects.

Example of population level daily dose:

- Take 2 Subjects
  - Subject 1 dose dates:
    - 150 mg BID 01JAN2014-10JAN2014
    - 150 mg BID 13JAN2014-22JAN2014
  - Subject 2 dose dates:
    - 150 mg BID 01JAN2014-10JAN2014
    - 100 mg BID 11JAN2014-20JAN2014
  - Population level daily dose (See equation below):

$$Population\ Level\ Daily\ Dose = \frac{[(10 * 300) + (10 * 300) + (10 * 300) + (10 * 200)]}{(10 + 2 + 10 + 10 + 10)}$$

$$= 262¶$$

Dose reductions will be summarised by number of reductions and reasons for reductions. Dose escalations will be summarised by number of escalations and reasons for escalation. Dose interruptions will be summarised by number of interruptions, reasons for the interruptions, and interruption duration (days). The mean, standard deviation, median, minimum value, and maximum value will be computed for the duration of interruptions as well as the number and percentage of the interruptions ≤ 7, 8 -14, 15 - 21 and >21 days. The summaries of dose modifications will be provided only if the data warrant.

All the dose reductions, dose escalations and dose interruptions will be listed separately.

The cumulative exposure plot will be provided showing the proportion of subjects on treatment over time.

12.2. Adverse Events

An overview summary of AEs, including counts and percentages of subjects with any AE, AEs related to study treatment, AEs leading to permanent discontinuation of study treatment, AE leading to dose reductions, AEs leading to dose interruptions, SAEs, SAEs related to study treatment, fatal SAEs, and fatal SAEs related to study treatment will be produced.

A summary of non-serious AEs that occurred in strictly 5% of the subjects or above will be provided (no rounding for the percentage will be used in terms of 5% threshold, e.g. event with 4.9% incidence rate should not be included in this table). The summary will be displayed by System Organ Class (SOC) and Preferred Term (PT). Another summary will be created that highlights the number of subjects with Non-Serious AE, total number of exposed subjects, and number of non-serious AEs for any European submissions.

The relationship between Medical Dictionary for Regulatory Affairs (MedDRA) SOC, PT, and Verbatim Text will be displayed.

Adverse events (AEs) will be graded according to the CTCAE, Version 4.0. Adverse events will be coded to the preferred term (PT) level using the MedDRA dictionary.

A summary of number and percentage of subjects with any adverse events by maximum grade will be produced. AEs will be sorted by Preferred term (PT) in descending order of total incidence first and then by each treatment arm. The summary will use the following algorithms for counting the subject:

- **Preferred term row**: Subjects experiencing the same AE preferred term several times with different grades will only be counted once with the maximum grade.

- **Any event row**: Each subject with at least one adverse event will be counted only once at the maximum grade no matter how many events they have.

In addition, the frequency and percentage of AEs (all grades) will be summarized and displayed in two ways: 1) in descending order of total incidence first and then by each treatment arm by PT only and 2) in descending order of total incidence first and then by each treatment arm by System Organ Classes (SOC) and PT. In the SOC row, the number of subjects with multiple events under the same system organ class will be counted once.

A separate summary will be provided for study treatment-related AEs. A study treatment-related AE is defined as an AE for which the investigator classifies the relationship to study treatment as “Yes”. A worst case scenario approach will be taken to handle missing relatedness data, i.e. the summary table will include events with the relationship to study treatment as ‘Yes’ or missing. The summary table will be displayed in descending order of total incidence first and then by each treatment arm by PT only.

12.3. Adverse Events of Special Interest

A comprehensive list of MedDRA terms based on clinical review will be used to identify each adverse event of special interest. Change to the MedDRA dictionary may occur between the start of the study and the time of reporting and/or emerging data from on-going studies may highlight additional adverse events of special interest, therefore the list of MedDRA terms to be used for each event of interest and the specific adverse events of interest will be based on the safety review team agreement at the time of reporting. The list of MedDRA terms for each adverse event of special interest will be provided.

For subjects receiving dabrafenib monotherapy, the adverse events of special interest include but not be limited to the following:

- Cutaneous squamous cell carcinoma (cuSCC) including keratoacanthoma (KA),
- Pyrexia events
- Treatment-emergent malignancies (excluding cuSCC/KA, and cancer under study)
- Renal failure/acute renal failure events
- Uveitis
- Hypersensitivity events
- Pancreatitis events
- Hyperglycemia events

For subjects receiving trametinib monotherapy, the adverse events of special interest include but not be limited to the following:

- Skin-related toxicities (including rash)
- Diarrhoea
- Left Ventricular dysfunction (including ejection fraction decreasing)
- Ocular Events
- Pneumonitis
- Hepatic disorders
- Hypertension
- Oedema
- Hypersensitivity
- Bleeding events

For subjects receiving dabrafenib and trametinib in either the combination arm of after 8 weeks of monotheraoy, the adverse events of special interest include but not be limited to the following:

- Cutaneous squamous cell carcinoma (cuSCC) including keratoacanthoma (KA),
- Pyrexia events
- Treatment-emergent malignancies (excluding cuSCC/KA, and cancer under study)
- Renal failure/acute renal failure events
- Uveitis
- Hypersensitivity events
- Pancreatitis events
- Hyperglycaemia events
- Skin-related events (exclude SCC, KA)
- Diarrhoea
- Cardiac-related events
- Ocular events
- Pneumonitis events
- Hepatic events
- Oedema events
- Hemorrhages events
- Hypertension
- Neutropenia events
- Pulmonary embolism events

All AEs of special interest will be summarized by categories of AE of special interest, preferred term and maximum toxicity grade in one table per treatment regimen (dabrafenib monotherapy, trametinib monotherapy, and dabrafenib plus trametinib combotherapy). AEs of special interest will be sorted by categories and then by preferred term in descending order based on incidence.

The following displays will be provided for selected AEs of special interest occur in > 5 subjects per treatment regimen:

- Summary of characteristics of AE of special interest, which will summarize event characteristics (serious, study treatment-related, fatal), number of occurrences, number of subjects, maximum toxicity, outcome, and action taken. The worst case approach will be applied at subject level for the event outcome and maximum grade, i.e. a subject will only be counted once as the worst case from all the events experienced by the subject. For action taken to a event, subject will be counted once under each action, e.g. if a subject has a event leading to both study treatment discontinuation and dose reduction, the

subject will be counted once for study treatment discontinuation and dose reduction, respectively.

- Summary of onset and duration. Time to onset (days) and duration of first occurrence (days) will be summarized. In addition to descriptive statistics (mean, median, min, max), time to onset will be summarized in categories of 0-2 weeks, >2-4 weeks, >4-8 weeks, >8-12 weeks, >12-18weeks, >18-24 weeks, and >24 weeks, and duration of first occurrence will be summarized in categories of 1-5 days, 6-10days, >10 days.
- Cumulative incidence plot.

Listing will be provided which profiles all categories of AEs of special interest per treatment regimens. Other AEs of special interest may be added later. Depending on the number of events, summary and/or listing may be provided appropriately.

12.4. Deaths and Serious Adverse Events

In the event that a subject has withdrawn consent, no data after the withdrawal of consent date from this subject including death is supposed to appear in the database, which should be part of the data cleaning process. All deaths occurring any time from the time of informed consent to the clinical cut-off date will be summarised based on the number and percentage of subjects. This summary will classify subjects by time of death relative to the last dose of medication (> 30 days or ≤ 30 days) and primary cause of death (disease under study, SAE related to study treatment, or other). A supportive listing will be generated to provide subject-specific details on subjects who died.

All SAEs will be tabulated based on the number and percentage of subjects who experienced the event. Separate summaries will also be provided for study treatment-related SAEs and fatal SAEs. The summary tables will be displayed in descending order of total incidence first and then by each treatment arm for each PT term.

A study treatment-related SAE is defined as an SAE for which the investigator classifies the relationship to study treatment as "Yes". A worst case scenario approach will be taken to handle missing data, i.e. the summary table will include events with the relationship to study treatment as 'Yes' or missing.

SAEs are included in the listing of all adverse events. Separate supportive listings with subject-level details will be generated for:

- Fatal SAEs
- Non-Fatal SAEs.
- Another summary will be included which summarizes the number of subjects with serious AE, total number of exposed subjects, number of serious AEs, number of drug-related serious AEs, number of fatal serious AEs, and number of drug-related fatal serious AEs, for any European submissions.

12.5. Adverse Events Leading to Discontinuation of Study Treatment and/or Withdrawal from the Study and Other Significant Adverse Events

The following categories of AEs will be summarized separately in descending order of total incidence first and then by each treatment arm for each PT term, and separate supportive listings will be generated with subject level details for those subjects:

- AEs Leading to Discontinuation of Study Treatment
- AEs leading to Withdrawal from the Study
- AEs Leading to Dose Interruptions
- AEs Leading to Dose Reductions

12.6. Pregnancies

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 as described in the protocol. If subjects and subjects' spouse become pregnant while on the study, the information will be included in the SAE narratives and no separate table or listing will be produced.

12.7. Clinical Laboratory Evaluations

The assessment of laboratory toxicities will examine the following laboratory tests:

Hematology: Hemoglobin (HGB), White Blood Cell (WBC) count, and Platelet count. Automated WBC differential (expressed as absolute count) for basophils, eosinophilis, lymphocytes, monocytes, and total neutrophilis.

Clinical Chemistry: Sodium, Potassium, Calcium, Albumin, Total Protein, Blood Urea Nitrogen (BUN), Creatinine, Estimated Creatinine Clearance, Lactate Dehydrogenase (LDH), Gamma-Glutamyl Transpeptidase (GCT), phosphate, and C-Reactive Protein (CRP). BUN, LDH, CRP, Total Protein, and Estimated Creatinine Clearance are not gradable by CTCAE v4.0. For Sodium, Potassium, and Calcium, two bi-directional parameters (hyper and hypo), the tests will be graded by CTCAE v4.0 in both directions.

Liver Function Tests: Aspartateaminotransferase (AST) or Serum Glutamic Oxaloacetic Transaminase (SGOT), Alanine aminotransferase (ALT) or Serum Glutamic Pyruvic Transaminase (SGPT), Alkaline phosphatase, Total bilirubin (total) and Direct bilirubin (only recorded when Total bilirubin $\geq$ 2*ULN). All these tests are gradable by CTCAE v4.0.

Coagulation Tests: Prothrombin time (PrT), International Normalized Ratio (INR), and Activated Partial thromboplastin time (aPTT). All tests at screening only.

Laboratory grades will be reported using the Common Terminology Criteria for Adverse Events (CTCAE v4.0).

Summary of lab values and change from baseline by scheduled visits using mean, median, standard deviation, minimum and maximum will be provided.

Summaries of lab data by maximum toxicity grade will be provided.

Coagulation tests are only collected at baseline. Therefore this/these test(s) will not appear in any summaries of changes from baseline.

Summaries of worst case grade increase from baseline grade will be provided for all the lab tests that are gradable by CTCAE v4.0. These summaries will display the number and percentage of subjects with a maximum post baseline grade increasing from their baseline grade. Any increase in grade from baseline will be summarized along with any increase to a maximum grade of 3 and any increase to a maximum grade of 4. Missing baseline grade will be assumed as grade 0. In addition, the summary will include grade increase from baseline by scheduled visits. For laboratory tests that are graded for both low and high values, summaries will be done separately and labeled by direction, e.g. sodium will be summarized as hyponatremia and hypernatremia.

For lab tests that are not gradable by CTCAE v4.0, summaries of worst case changes from baseline with respect to normal range will be generated. Decreases to low, changes to normal or no changes from baseline, and increases to high will be summarized at each scheduled visit as well as for the worst case post baseline. If a subject has a decrease to low and an increase to high during the same time interval, then the subject is counted in both the "Decrease to Low" categories and the "Increase to High" categories. In addition, the summary will include worst case changes from baseline with respect to normal range by scheduled visits.

Separate summary tables for hematology, chemistry, liver function, and coagulation, laboratory tests will be produced.

Detailed derivation of baseline assessment is specified in Section 9.2.

Unless otherwise specified, the denominator in percentage calculation at each scheduled visit will be based on the number of subjects with non-missing value at each particular visit.

12.7.1. Analyses of Liver Function Tests

Summaries of hepatobiliary laboratory events including possible Hy's law cases will be provided in addition to what has been described above.

Possible Hy's law cases are defined as any elevated ALT>3 × Upper Limit Normal (ULN), total bilirubin≥2×ULN and ALP<3×ULN/missing. Total bilirubin≥2×ULN can be within 28 days following the ALT elevation and if direct bilirubin is available on the same day, it must be ≥ 35% of total bilirubin. ALP<3xULN/missing means the criteria is satisfied unless the ALP is >=3xULN at any time of bilirubin elevation within the 28 days window.

If data warrant, a summary of liver re-challenges, adaptations and recovery will be provided.

12.8. Other Safety Measures

Vital Signs

Values of vital signs as well as the change from baseline will be summarized by scheduled visit using mean, median, standard deviation, minimum and maximum.

In addition vital signs or blood pressure values will be categorized as follows:

- Systolic Blood Pressure (BP) (mmHg): Grade 0 (<120), Grade 1 (≥120-<140), Grade 2 (≥140-<160) and Grade 3 (≥160)
- Diastolic BP (mmHg): Grade 0 (<80), Grade 1 (≥80-<90), Grade 2 (≥90-<100), and Grade 3 (≥100)
- Heart rate: <60, 60-100, and >100
- Temperature: <35, 35-38, ≥38

Summaries of increase in vital signs or blood pressure from the baseline with respect to the categories defined above will be performed. These summaries will display the number and percentage of subjects with any grade increase, increase to grade 2 and increase to grade 3 in the worst case post baseline only.

Performance Status

ECOG performance status will be summarized at baseline and each post baseline scheduled visit. Summaries will use frequency and percentage of subjects at each planned assessment time. A summary of change from baseline by scheduled visits will be performed, as well as the worst case post-baseline and the best case post-baseline changes during the study (improved, no change, deteriorated).

A supporting listing will also be provided.

ECG

A summary of the number and percentage of subjects who had normal and abnormal (clinically significant and not clinically significant) ECG findings will be displayed by scheduled visits as well as for the worst case post baseline.

The QTc values based on Bazett formula will be rounded to the integer and the values will be categorized into the following ranges: Grade 0 (<450), Grade 1 (450-480), Grade 2 (481-500), and Grade 3 (≥501). Summaries of grade increase will be provided. These summaries will display the number and percentage of subjects with any grade increase, increase to grade 2 and increase to grade 3 in the worst case post baseline only.

The changes in QTc values will be categorized into the clinical concern ranges which are specific to changes in QTc: 31-60 and > 60 msec. A summary of change in QTc value will display the number and percentage of subjects with a change within each range in the worst case post baseline only. Subjects with missing baseline values will be excluded from this summary.

The summaries for the QTc will use the calculated value based on Bazett formula.

Listings of abnormal ECG findings and a listing of ECG values will be provided.

LVEF

Absolute change from baseline in LVEF will be summarized in the worst case post baseline only. Only the post baseline assessments that used the same method (ECHO or MUGA) as the baseline assessments will be used to derive the change from baseline. The change from baseline will be categorized as follows:

- Any increase
- No change
- Any decrease
    - 0 - < 10% Decrease
    - 10 - <20% Decrease
    - ≥20% Decrease
- ≥10% decrease and ≥ Lower limit of normal (LLN)
- ≥10% decrease and <LLN
- ≥20% decrease and ≥LLN
- ≥20% decrease and <LLN

LVEF results will also be listed with subject level details including absolute change from baseline.

Liver Events

For any liver events that occur during the study, the liver event information for Roussel Uclaf Causality Assessment Method (RUCAM) score will be summarized, including whether the subject was age 55 or over, whether the subject became pregnant, liver imaging normal or not, a biopsy was taken or not, whether there was fasting or significant dietary change, whether the subject took any unconventional medications, timing when the event occurs (while on treatment or after stopping treatment) and summary statistics for time from first dose to start of liver event and time from last dose to start of liver event. If the number of events does not support a summary, then only listings will be produced.

For subjects with multiple events, the first event will be used for the summary tables. All events with subject level details will be displayed in a supporting listing.

Ocular Exams

Baseline data will be summarized based on the number and percentage of subjects who receive an ocular exam. As post baseline exams are only performed as clinically indicated data beyond baseline will only be listed.

13. EFFICACY

All efficacy analyses will be based on the ITT population as defined in Section 6 unless otherwise specified. All analyses will be presented by treatment arm.

Efficacy assessments are based on RECIST 1.1, criteria to assess clinical activity and disease status. Primary assessments will be based on imaging data and clinical assessments. Investigator assessments will be considered as primary assessments.

Confirmation of response (i.e., CR and PR) is not necessary per RECIST, version 1.1, as the primary endpoint of the study is not overall best response. The lists of displays for efficacy, including population to use for each display, are shown in Section 18.1.2 of the RAP.

13.1. Primary Efficacy Analyses

No primary efficacy analyses will be conducted in this study.

13.2. Secondary Efficacy Analyses

The primary efficacy endpoint, tumor response including ORR will be reported separately for each treatment arm. In addition a pooled ORR across all treatment arms will also be reported.

Anti-tumor activity will be evaluated based on RECIST 1.1 criteria for solid tumors [Eisenhauer,2009]. Since the primary endpoint of the study is not overall best response, we will generate displays for response irrespective of confirmation status.

The overall response rate (ORR) is defined as the percentage of subjects with a confirmed or unconfirmed complete or partial response by investigator assessment at any time as per RECIST 1.1 criteria. Subjects with unknown or missing response will be treated as non-responders, i.e. they will be included in the denominator when calculating the percentage. An exact 95% confidence interval (Clopper-Pearson) will be computed for this estimate. All data relating to response from the Investigator will be listed including lesion measurements, response assessments and best response.

Waterfall plots of Investigator Assessed Percent Change from Baseline in Tumor Measurement at Time of Best Response will be provided with indications of subject

number below the plot. Waterfall plots will be created for each treatment arm in the study.

13.3. Exploratory Efficacy Analyses

Provided that there are sufficient numbers of events at time of final analysis, we will examine Progression-free survival and duration of response as secondary efficacy endpoints.

13.3.1. Progression-Free Survival

Progression-Free survival (PFS) is defined as the interval of time (in months) between the date of randomization and the earlier of the date of disease progression and the date of death due to any cause. Disease progression will be based on the assessments by the Investigator.

The date of documented disease progression will be defined as the date of disease progression based on either radiographic or clinical data. The date of death should be taken from the Record of Death page. Death on study due to any cause will be included.

If there is no adequate baseline assessment, the subject will be censored at their date of randomization. Subjects without any adequate post baseline tumor assessments will be censored at the date of randomization.

Subjects who progressed or died after an extended period without adequate assessment will be censored at their date of last adequate assessment prior to progression or death even if subsequent information is available regarding progression or death. An adequate assessment is defined as an assessment where the Investigator determined response is CR, PR, or SD. The date of response at that assessment will be used for censoring.

For subjects who receive subsequent anti-cancer therapy the following rules will apply:

- If anti-cancer therapy is started **without documented disease progression or is started prior to documented disease progression**, then PFS will be censored at the date of the last adequate assessment that is no later than the date of initiation of anti-cancer therapy (i.e. if an assessment occurs on the same day as the start of new anti-cancer therapy the assessment will be used - as it will be assumed the assessment occurred prior to the administration of new anti-cancer therapy). The date of response at the last adequate assessment will be used as the censoring value.
- If a subject has only a baseline visit or does not have an adequate assessment that is no later than the date of initiation of anti-cancer therapy, PFS will be censored at the date of randomization.

If a subject has neither progressed nor died nor started new anti-cancer therapy, then PFS will be censored at the date of the last adequate assessment defined as an assessment where the Investigator determined response is CR, PR, SD. The date of response will be used as the censoring date.

A summary of the assignments for progression and censoring dates for PFS are specified in Table 2.

Table 2 Assignments for Progression and Censoring Dates for PFS Analysis

Situation	Date of Progression or Censoring	Outcome
No *(or inadequate)* baseline tumor assessments *(or patients with no post-baseline assessments)*	Randomization	Censored
Progression documented between scheduled visits	Date of assessment of progression[1]	Progressed
No progression *(or death)*	Date of last 'adequate' assessment of response[2]	Censored
New anticancer treatment started *(prior to documented disease progression).*[3]	Date of last 'adequate' assessment of response[2] *(on or prior to starting anti-cancer therapy)*	Censored
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
Death or progression after more than one missed visit	Date of last 'adequate' assessment of response[2] *(prior to missed assessments)*	Censored

[1] The earliest of (i) Date of radiological assessment showing new lesion (if progression is based on new lesion); or (ii) Date of radiological assessment showing unequivocal progression in non target lesions, or (iii) Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions)

[2] An adequate assessment is defined as an assessment where the Investigator determined response is CR, PR, or SD.

[3] If PD and New anti-cancer therapy occur on the same day assume the progression was documented first e.g. outcome is progression and the date is the date of the assessment of progression). If anti-cancer therapy is started prior to any adequate assessments, censoring date should be the date of randomization.

PFS will be summarized by cohort using Kaplan-Meier curves. Median times to PFS, 1st and 3rd quartiles along with 95% CI, if there are a sufficient number of progressions or deaths, will be estimated using the Brookmeyer-Crowley method [Brookmeyer,1982]. A figure and listing of progression-free survival time will also be provided for each expansion cohort.

A supplementary table showing the details of the number at risk, number of events, and number censored with the event time will also be displayed for each expansion cohort.

13.3.2. Duration of Response

Duration of response, defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause among patients who achieve an overall response (i.e., unconfirmed or confirmed CR or PR) will be summarized. Censoring rules will follow those of the PFS analysis defined in Section 13.3.1.

If sample size permits, the median duration of response will be calculated from the Kaplan-Meier estimates. First and third quartiles will also be calculated along with associated 95% confidence intervals if there are a sufficient number of responders who subsequently progress or die due to any cause. A figure and listing of duration of response will be provided.

14. PHARMACOKINETIC ANALYSES

The reconciliation of the PK Case Report Form (CRF) and SMS2000 data will be performed by, or under the direct auspices of, Data Sciences - Oncology, GlaxoSmithKline.

The merge of PK concentration data, randomisation, and CRF data to generate a dataset with actual blood sampling times, actual time relative to dosing, and PK concentrations will be performed after DBF by, or under the direct auspices of, Oncology Quantitative Sciences (Programmer), GlaxoSmithKline.

Unless otherwise stated, all tables, figures and listings in this section will be based on the Biomarker population as defined in Section 6, and all summaries, figures and data listings will use treatment labels as specified in Section 7.

The lists of displays for PK, including population to use for each display, are shown in Section 18.1.4 of the RAP.

14.1. Drug Concentration Measures

Concentrations of GSK1120212 and GSK2118436 and its metabolites (GSK2284503, GSK2298683, and GSK2167542) will be listed and summarised by treatment group and nominal time. Standard summary statistics will be calculated (i.e. mean, standard deviation, median, minimum and maximum). Refer to the PK Guidance document GUI_51487 , "Non-Compartmental Analysis of Pharmacokinetic Data", for more information regarding the handling of concentrations below the assay's lower limit of quantification (NQ).

Individual concentration-time profiles and median/mean profiles by treatment group will be plotted using actual elapsed time for individual plots and nominal time for median/mean profiles. Each of the figures will contain one plot on the untransformed scale (i.e. a linear plot) and one plot on the log transformed scale (i.e. log-linear plot). See Pharmacokinetic Source Figures and Tables for details.

Any concentration data excluded from the derivation of PK parameters by Clinical Pharmacology Modelling and Simulation (CPMS) should be omitted from any figures and summaries, and flagged with an asterisk in the relevant data listings, with a footnote to indicate that these values have been omitted from subsequent analyses.

14.2. Population Pharmacokinetic Analyses

If data warrant, pharmacokinetic data will be analyzed using a population approach. A nonlinear mixed effects model will be used to determine population pharmacokinetic

parameters such as CL/F (apparent clearance following oral dosing) and other parameters as data permit and identify relevant covariates (e.g., age, weight, or disease related covariates) that explain variability. Concentration data will be pooled with data from other studies. Details on the population analysis will be the focus of a separate analysis plan and will be the responsibility of CPMS.

15. PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES

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

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

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

16. BIOMARKER ANALYSES

The results of translational research investigations not related to the H-Score of p-ERK will be reported separately from the main clinical study report. All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data. Further details on the translational research analyses will described under a separate RAP.

17. REFERENCES

GlaxoSmithKline Document Number 2012N132406_01. Phase II biomarker study evaluating the upfront combination of BRAF inhibitor dabrafenib with MEK inhibitor trametinib versus the combination after eight weeks of monotherapy with dabrafenib or trametinib in patients with metastatic and unresectable stage III or IV melanoma harbouring an activating BRAF mutation. Effective Date: 28-OCT-2013

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics, 1982; 38:29-41.

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours. Revised RECIST guidelines (version 1.1). *Eur J Cancer.* 2009; 45:228-247

GUI_51487 (4.0). Non-Compartmental Analysis of Pharmacokinetic Data, CPMS Global. Effective Date: October, 28, 2014

18. ATTACHMENTS

18.1. Table of Contents for Data Display Specifications

The following flexible system will be used to number the listings, tables and figures:

- Study Population:
  - tables, 1.xxxx
  - ICH-listings, 21.xxxx
  - Other-listings, 30.xxxx (30.0010 – 30.0110)
- Efficacy:
  - tables, 2.xxxx;
  - figures, 12.xxxx;
  - ICH-listings, 22.xxxx
- Safety:
  - tables, 3.xxxx;
  - figures, 13.xxxx;
  - ICH-listings, 23.xxxx
  - Other-listings, 30.xxxx (30.0240 – 30.0330)
- Pharmacokinetic:
  - tables, 4.xxxx;
  - figures, 14.xxxx;
  - ICH-listings, 24.xxxx
- Biomarker:
  - tables, 5.xxxx;
  - figures, 15.xxxx
  - Listings, 25.xxxx

Note: please specify which value will be used as baseline in the listing for lab, ECG, and vital sign.

Listed below are the planned figures, tables and listings to be produced for inclusion in clinical study report

18.1.1. Study Population (Section 1)

18.1.1.1. Tables

Table No.	*Title*	*Population*	*Component / Therapeutic Area (hyperlinked to IDSL LN DB)*	*IDSL No. or Example Shell No.*	*Study-Specific Display Notes*	*Deliverable Priority*
1.0010	Summary of Study Populations	ITT	Subject Accountability/Oncology	**POP1**	Percentages for each cell are based on 'N' at the top of each column.	SAC
1.1010	Summary of Number of Subjects by Centre	ITT	Enrollment/Core	**NS1**		SAC
1.1110	Summary of Subject Disposition	ITT	Disposition/Core	**ES8**		SAC
1.1220	Summary of Study Treatment Status	ITT	Investigational Product Discontinuation/Core	**SD4**	Reasons for discontinuation will be presented in the order they are displayed on the eCRF. Only include 'Missing' rows where applicable.	SAC
1.1310	Summary of Inclusion/Exclusion Criteria Deviations	ITT	Inclusion & Exclusion Criteria/Core	**IE1**		SAC
1.1410	Summary of Protocol Deviations	ITT	Protocol Deviations/Core	**DV1A**		SAC
1.2010	Summary of Demographic Characteristics	ITT	Demography/Core	**DM1**		SAC
1.2011	Age Group Breakdown for the Trial	ITT			See Mock-Up. Based on new EMA requirements. Use combined data from all three arms.	SAC
1.2020	Summary of Race and Racial Combinations	ITT	Demography/Core	**DM5**		SAC
1.2110	Summary of Disease Burden at Baseline	ITT	Lesion Assessments/ Oncology	**LA1**		SAC
1.2120	Summary of Substance Use	ITT	Substance Use/Core	**SU1**		SAC
1.3110	Summary of Cancer Related Medical Conditions at Screening	ITT	Medical Conditions/Core	**MH1**		SAC
1.3112	Summary of Non-Cancer-Related Medical Conditions at Screening	ITT	Medical Conditions/Core	**MH1**		SAC

Table No.	*Title*	*Population*	*Component / Therapeutic Area (hyperlinked to IDSL LN DB)*	*IDSL No. or Example Shell No.*	*Study-Specific Display Notes*	*Deliverable Priority*
1.3210	Summary of Disease Characteristics at Initial Diagnosis	ITT	Disease Characteristics/Oncology	**DC1**	Sections include: Time since initial diagnosis (weeks), and Primary Tumour Type	SAC
1.3220	Summary of Disease Characteristics at Screening	ITT	Disease Characteristics/Oncology	**DC2**	Sections include: Measurable disease at baseline, Presence of non-target lesions at baseline, and Stage	SAC
1.3230	Summary of Metastatic Disease at Screening	ITT	Metastatic Disease/Oncology	**MD1**		SAC
1.4010	Summary of Prior Anti-Cancer Therapy	ITT	Anti-Cancer Therapy/Oncology	**AC2**		SAC
1.4020	Summary of Prior Dictionary Coded Anti-Cancer Therapy	ITT	Concomitant Medication/Core	**CM1**		SAC
1.4030	Summary of Number of Prior Anti-Cancer Therapy Regimens	ITT	Anti-Cancer Therapy/ Oncology	**AC3**	Therapies should be sorted in highest to lowest incidence. Total column is required.	SAC
1.4040	Summary of Best Response to Most Recent Prior Anti-Cancer Therapy	ITT	Anti-Cancer Therapy/ Oncology	**AC4**		SAC
1.4110	Summary of Prior Cancer-Related Surgical Procedures	ITT	Surgical-Medical Procedures/Oncology	**OSP1**		SAC
1.4110	Summary of Prior Non-Cancer Related Surgical Procedures	ITT	Surgical-Medical Procedures/Oncology	**OSP1**		SAC
1.5010	Summary of Concomitant Medications by Ingredient	ITT	Concomitant Medications/Core	**CM8**	Medications will be sorted in descending order of total incidence across treatment groups for the ATC level 1 (CM1 only) and in descending order of total incidence of ingredient within ATC level (CM1) or overall (CM8). In case of a tie, sort tied ingredients alphabetically.	SAC
1.5011	Summary of Blood or Blood Supportive Care Products while On-Therapy	ITT	Concomitant Medications/Core	**CM8**	Medications will be sorted in descending order of total incidence across treatment groups for the ATC level 1 (CM1 only) and in descending order of total incidence of ingredient within ATC level (CM1) or overall (CM8). In case of a tie, sort tied ingredients alphabetically.	SAC

Table No.	*Title*	*Population*	*Component / Therapeutic Area (hyperlinked to IDSL LN DB)*	*IDSL No. or Example Shell No.*	*Study-Specific Display Notes*	*Deliverable Priority*
1.6010	Summary of Overall Compliance Based on Exposure	ITT	Compliance	**COMP1**		SAC

18.1.1.2. ICH Listings

Listing No.	Title	Population	Component / Therapeutic Area (hyperlinked to IDSL LN DB)	IDSL No. or Example Shell No.	Study-Specific Display Notes	Deliverable Priority
21.0010	Listing of Randomized [Planned] and Actual Treatments	ITT	Randomization Number/Core	**TA1**		SAC
21.0020	Listing of Subjects Excluded from Analysis Populations	ITT	Subject Accountability/Oncology	**POP2**		SAC
21.0030	Listing of Study Treatment Discontinuation Record	ITT	Investigational Product Discontinuation/Core	**SD2**		SAC
21.0040	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	ITT	Inclusion & Exclusion Criteria/Core	**IE3**		SAC
21.0050	Listing of Protocol Deviations	ITT	Protocol Deviations/Core	**DV2**		SAC
21.0060	Listing of Demographic Characteristics	ITT	Demography/Core	**DM2**		SAC
21.0070	Listing of Race	ITT	Demography/Core	**DM9**		SAC
21.0800	Listing of Overall Compliance	ITT	Compliance	**COMP2**		SAC
21.0090	Listing of Drug Accountability	ITT	Compliance	**COMP3C**		SAC
21.0091	Listing of Randomized and Actual Treatments	ITT	Compliance	**COMP2**		SAC

18.1.1.3. Other Study Population Listings

Listing No.	Title	Population	Component / Therapeutic Area (hyperlinked to IDSL LN DB)	IDSL No. or Example Shell No.	Study-Specific Display Notes	Deliverable Priority
30.0010	Listing of Substance Use	ITT	Substance Use/Core	**SU2**		SAC
30.0020	Listing of Current Cancer Related Medical Conditions	ITT	Medical Conditions/Core	**MH2**	If conditions not coded, classification column will not be included on the listing.	SAC
30.0021	Listing of Past Cancer Related Medical Conditions	ITT	Medical Conditions/Core	**MH2**	If conditions not coded, classification column will not be included on the listing.	SAC
30.0022	Listing of Current Non-Cancer Related Medical Conditions	ITT	Medical Conditions/Core	**MH2**	If conditions not coded, classification column will not be included on the listing.	SAC
30.0023	Listing of Past Non-Cancer Related Medical Conditions	ITT	Medical Conditions/Core	**MH2**	If conditions not coded, classification column will not be included on the listing.	SAC
30.0030	Listing of Disease Characteristics at Initial Diagnosis	ITT	Disease Characteristics/Oncology	**DC3**	Should include time since initial diagnosis in weeks, stage at initial diagnosis, and date of initial diagnosis	SAC
30.0040	Listing of Disease Characteristics at Screening	ITT	Disease Characteristics/Oncology	**DC4**	Sections include: Measurable disease at baseline, Presence of non-target lesions at baseline, and Stage	SAC
30.0050	Listing of Metastatic Disease at Screening	ITT	Metastatic Disease/ Oncology	**MD2**		SAC
30.0060	Listing of Prior Anti-Cancer Therapy	ITT	Anti-Cancer Therapy/Oncology	**AC6**		SAC
30.0070	Listing of Prior Anti-Cancer Radiotherapy	ITT	Anti-Cancer Therapy/ Oncology	**AC7**		SAC
30.0080	Listing of Prior Cancer Related Surgical Procedures	ITT	Surgical-Medical Procedures/Oncology	**OSP3**		SAC
30.0081	Listing of Prior Non-Cancer Related Surgical Procedures	ITT	Surgical-Medical Procedures/Oncology	**OSP3**		SAC
30.0090	Listing of Post Treatment Anti-Cancer Therapy	ITT	Follow-up/Oncology	**FAC3**		SAC

Listing No.	Title	Population	Component / Therapeutic Area (hyperlinked to IDSL LN DB)	IDSL No. or Example Shell No.	Study-Specific Display Notes	Deliverable Priority
30.0100	Listing of Concomitant Medications	ITT	Concomitant Medications/Core	**CM2**		SAC
30.0101	Listing of Blood or Blood Supportive Care Products while On-Therapy	ITT	Concomitant Medications/Core	**CM2**		SAC
30.0110	Relationship between ATC Level 1, Ingredient, and Verbatim Text for Anti-Cancer Therapy	ITT		**See Mock-Up**	Have Treatment information above columns. Column order is ATC Level 1, Ingredient, and Verbatim Text	SAC

18.1.2. Efficacy (Section 2)

18.1.2.1. Tables

Table No.	Title	Population	Component / Therapeutic Area (hyperlinked to IDSL LN DB)	IDSL No. or Example Shell No.	Study-Specific Display Notes	Deliverable Priority
2.0010	Summary of Investigator Assessed Progression-Free Survival	ITT	Time to Event/ Core Standards/	**TTE1**	Input dataset: ONCSURV (overall survival) or ONCTTE (PFS, Time to Response, etc.). If data warrant.	SAC
2.0011	Summary of Investigator Assessed Duration of Response	ITT	Time to Event/ Core Standards/	**TTE1**	Input dataset: ONCSURV (overall survival) or ONCTTE (PFS, Time to Response, etc.). If data warrant	SAC
2.1010	Summary of Investigator Assessed Best Response with confirmation for Subjects with Measurable Disease at Baseline (RECIST 1.1 Criteria)	ITT	Response Displays/ Oncology Core/	**RE1a**	Input dataset: RESP2 (investigator) or RESP2EX1 (independent reviewer)	SAC
2.1011	Summary of Investigator Assessed Best Response without confirmation for Subjects with Measurable Disease at Baseline (RECIST 1.1 Criteria)	ITT	Response Displays/ Oncology Core/	**RE1a**	Input dataset: RESP2 (investigator) or RESP2EX1 (independent reviewer)	SAC

18.1.2.2. Figures

Figure No.	*Title*	*Population*	*Component / Therapeutic Area (hyperlinked to IDSL LN DB)*	*IDSL No. or Example Shell No.*	**Study-Specific Display Notes**	*Deliverable Priority*
12.0010	Graph of Kaplan Meier Investigator Progression-Free Survival Curves with 95% Confidence Band	ITT	Time to Event/ Core Standards/	**TTE10**	Input dataset: ONCSURV (overall survival) or ONCTTE (PFS, Time to Response, etc.). If data warrant	SAC
12.0011	Graph of Kaplan Meier Investigator Duration of Response Curves with 95% Confidence Band	ITT	Time to Event/ Core Standards/	**TTE10**	Input dataset: ONCSURV (overall survival) or ONCTTE (PFS, Time to Response, etc.). If data warrant	SAC
12.0020	Investigator Assessed Percent Change at Maximum Reduction from Baseline in Tumour Measurement for those with Dabrafenib monotherapy before combotherapy	ITT	Response Displays/ Oncology Core/	**RE8a**	Input dataset: RESP2 (investigator) and RESP2EX1 (independent reviewer)	SAC
12.0021	Investigator Assessed Percent Change at Maximum Reduction from Baseline in Tumour Measurement for those with Trametinib monotherapy before combotherapy	ITT	Response Displays/ Oncology Core/	**RE8a**	Input dataset: RESP2 (investigator) and RESP2EX1 (independent reviewer)	SAC
12.0022	Investigator Assessed Percent Change at Maximum Reduction from Baseline in Tumour Measurement for those assigned to combotherapy arm	ITT	Response Displays/ Oncology Core/	**RE8a**	Input dataset: RESP2 (investigator) and RESP2EX1 (independent reviewer)	SAC

18.1.2.3. ICH Listings

Listing No.	*Title*	*Population*	*Component / Therapeutic Area (hyperlinked to IDSL LN DB)*	*IDSL No. or Example Shell No.*	**Study-Specific Display Notes**	*Deliverable Priority*
22.0010	Listing of Progression-Free Survival	ITT	Time to Event/ Core Standards/	**TTE9**	Input dataset: ONCSURV (overall survival) or ONCTTE (PFS, Time to Response, etc.)	SAC
22.0011	Listing of Duration of Response	ITT	Time to Event/ Core Standards/	**TTE9**	Input dataset: ONCSURV (overall survival) or ONCTTE (PFS, Time to Response, etc.)	SAC
22.0020	Listing of Investigator Assessed Target Lesion Assessments (RECIST 1.1 Criteria)	ITT	Lesion Displays/ Oncology Core/	**LA2**	Input dataset: LESION (investigator) or LESIONEX1 (independent reviewer)	SAC
22.0030	Listing of Investigator Assessed Non Target Lesion Assessments (RECIST 1.1 Criteria)	ITT	Lesion Displays/ Oncology Core/	**LA3**	Input dataset: LESION (investigator) or LESIONEX1 (independent reviewer)	SAC
22.0040	Listing of Investigator Assessed New Lesions (RECIST 1.1 Criteria)	ITT	Lesion Displays/ Oncology Core/	**LA4**	Input dataset: LESION (investigator) or LESIONEX1 (independent reviewer)	SAC
22.0050	Listing of Investigator Assessed Tumour Responses with confirmation (RECIST1.1 Criteria)	ITT	Response Displays/ Oncology Core/	**RE5**	Input dataset: RESP1 (investigator) or RESP1EX1 (independent reviewer)	SAC
22.0051	Listing of Investigator Assessed Tumour Responses without confirmation (RECIST1.1 Criteria)	ITT	Response Displays/ Oncology Core/	**RE5**	Input dataset: RESP1 (investigator) or RESP1EX1 (independent reviewer)	SAC

18.1.3. Safety (Section 3)

18.1.3.1. Tables

Table No.	*Title*	*Population*	*Component / Therapeutic Area (hyperlinked to IDSL LN DB)*	*IDSL No. or Example Shell No.*	*Study-Specific Display Notes*	*Deliverable Priority*
3.0010	Summary of Exposure to Dabrafenib	Safety	Exposure Displays/ Oncology Core/	**OEX1**		SAC
3.0011	Summary of Exposure to Trametinib	Safety	Exposure Displays/ Oncology Core/	**OEX1**		SAC
3.0040	Summary of Dose Reductions	Safety	Dose Modifications Displays/ Oncology Core/	**ODMOD1**		SAC
3.0041	Summary of Dose Interruptions	Safety	Dose Modifications Displays/ Oncology Core/	**ODMOD2**		SAC
3.0044	Summary of Dose Escalations	Safety	Dose Modifications Displays/ Oncology Core/	**ODMOD8**		SAC
3.1010	Adverse Event Overview	Safety	Adverse Events Displays/ Core/	**AE13**		SAC
3.1020	Summary of All Adverse Events	Safety	Adverse Events Displays/ Core/	**AE1**	Displayed by SOC and PT, and sorted in descending order (for all patients). Have 4 columns (1 for each treatment arm + total).	SAC
3.1030	Summary of Frequent Adverse Events	Safety	Adverse Events Displays/ Core/	**AE3**		SAC
3.1040	Summary of Common Non-Serious Adverse Events	Safety	Adverse Events Displays/ Core/	**AE1**		SAC

Table No.	*Title*	*Population*	*Component / Therapeutic Area (hyperlinked to IDSL LN DB)*	*IDSL No. or Example Shell No.*	*Study-Specific Display Notes*	*Deliverable Priority*
3.1041	Summary of Non-Serious Adverse Events by Preferred Term with Occurrences ≥ 5%	Safety	t_ae_non_ser.rtf		See Mock-Up~~/~~	SAC
3.1070	Summary of Adverse Events By Maximum Grade by Preferred Term	Safety	Adverse Events Displays/ Oncology Core/	**OAE7**		SAC
3.1071	Summary of Adverse Events By Maximum Grade by System Organ Class and Preferred Term	Safety	Adverse Events Displays/ Oncology Core/	**OAE1**		SAC
3.1110	Summary of Adverse Events Related to Study Treatment	Safety	Adverse Events Displays/ Core/	**AE1**		SAC
3.1120	Summary of Adverse Events Related to Study Treatment by Maximum Grade	Safety	Adverse Events Displays/ Oncology Core/	**OAE7**		SAC
3.1210	Summary of Serious Adverse Events by Preferred Term	Safety	Adverse Events Displays/ Core/	**AE3**		SAC
3.1211	Summary of Serious Adverse Events by Preferred Term by System Organ Class and Preferred Term	Safety	Adverse Events Displays/ Core/	**AE1**		SAC
3.1310	Summary of Serious Adverse Events Related to Study Treatment by Preferred Term	Safety	Adverse Events Displays/ Core/	**AE3**		SAC
3.1311	Summary of Serious Adverse Events Related to Study Treatment by System Organ Class and Preferred Term	Safety	Adverse Events Displays/ Core/	**AE1**		SAC
3.1600	Summary of All Adverse Events of Special Interest by Maximum Toxicity Grade and Preferred Term for Dabrafenib Monotherapy	Safety	BRF113928 Comboin reporting effort, Table 3.1711		AESIs will be sorted by categories and then by preferred term in descending order	SAC
3.1601	Summary of Characteristics for Selected Adverse Events of Special Interest for Dabrafenib Monotherapy	Safety	Adverse Events of Special Interest Displays/ Core/	**ESI1**		SAC

Table No.	*Title*	*Population*	*Component / Therapeutic Area (hyperlinked to IDSL LN DB)*	*IDSL No. or Example Shell No.*	*Study-Specific Display Notes*	*Deliverable Priority*
3.1611	Summary of Onset and Duration for Selected Adverse Events of Special Interest for Dabrafenib Monotherapy	Safety	Adverse Events of Special Interest Displays/ Core/	**ESI2A**		SAC
3.1700	Summary of All Adverse Events of Special Interest by Maximum Toxicity Grade and Preferred Term for Trametinib Monotherapy	Safety	BRF113928 Comboin reporting effort, Table 3.1711		AESIs will be sorted by categories and then by preferred term in descending order	SAC
3.1701	Summary of Characteristics for Selected Adverse Events of Special Interest for Trametinib Monotherapy	Safety	Adverse Events of Special Interest Displays/ Core/	**ESI1**		SAC
3.1711	Summary of Onset and Duration for Selected Adverse Events of Special Interest for Trametinib Monotherapy	Safety	Adverse Events of Special Interest Displays/ Core/	**ESI2A**		SAC
3.1800	Summary of All Adverse Events of Special Interest by Maximum Toxicity Grade and Preferred Term for Combination Treatment	Safety	BRF113928 Comboin reporting effort, Table 3.1711		AESIs will be sorted by categories and then by preferred term in descending order	SAC
3.1801	Summary of Characteristics for Selected Adverse Events of Special Interest for Combination Treatment	Safety	Adverse Events of Special Interest Displays/ Core/	**ESI1**		SAC
3.1811	Summary of Onset and Duration Characteristics for Selected Adverse Events of Special Interest for Combination Treatment	Safety	Adverse Events of Special Interest Displays/ Core/	**ESI2A**		SAC
3.2010	Summary of Deaths	Safety	Death Displays/ Oncology Core/	**DTH1A**		SAC
3.3010	Summary of Laboratory Values for Hematology Tests	Safety	Lab Displays/ Core/	**LB1**		SAC
3.3011	Summary of Laboratory Values for Clinical Chemistry Tests	Safety	Lab Displays/ Core/	**LB1**		SAC
3.3012	Summary of Laboratory Values for Liver Function Tests	Safety	Lab Displays/ Core/	**LB1**		SAC
3.3013	Summary of Laboratory Values for Coagulation Tests	Safety	Lab Displays/ Core/	**LB1**		SAC
3.3020	Summary of Laboratory Grade Changes from Baseline Grade for Hematology Tests	Safety	Lab Displays/ Oncology Core/	**OLB9C**		SAC

Table No.	*Title*	*Population*	*Component / Therapeutic Area (hyperlinked to IDSL LN DB)*	*IDSL No. or Example Shell No.*	*Study-Specific Display Notes*	*Deliverable Priority*
3.3021	Summary of Laboratory Grade Changes from Baseline Grade for Clinical Chemistry Tests	Safety	Lab Displays/ Oncology Core/	**OLB9C**		SAC
3.3022	Summary of Laboratory Grade Changes from Baseline Grade for Liver Function Tests	Safety	Lab Displays/ Oncology Core/	**OLB9C**		SAC
3.3030	Summary of Laboratory Changes from Baseline With Respect to the Normal Range for Hematology Tests	Safety	Lab Displays/ Oncology Core/	**OLB11C**		SAC
3.3031	Summary of Laboratory Changes from Baseline With Respect to the Normal Range for Clinical Chemistry Tests	Safety	Lab Displays/ Oncology Core/	**OLB11C**		SAC
3.3060	Summary of Laboratory Results by Maximum Grade for Hematology Tests	Safety	Lab Displays/ Oncology Core/	**OLB1**		SAC
3.3061	Summary of Laboratory Results by Maximum Grade for Hematology Tests for Clinical Chemistry Tests	Safety	Lab Displays/ Oncology Core/	**OLB1**		SAC
3.3062	Summary of Laboratory Results by Maximum Grade for Hematology Tests for Liver Function Tests	Safety	Lab Displays/ Oncology Core/	**OLB1**		SAC
3.3063	Summary of Laboratory Results by Maximum Grade for Coagulation Tests	Safety	Lab Displays/ Oncology Core/	**OLB1**		SAC
3.4010	Summary of Vital Signs	Safety	Vital Sign Displays/ Core/	**VS1**		SAC
3.4020	Summary of Vital Sign Changes from Baseline	Safety	Vital Sign Displays/ Core/	**VS1**		SAC
3.4030	Summary of Changes in Heart Rate from Baseline	Safety	Vital Sign Displays/ Oncology Core/	**OVT1C**		SAC
3.4040	Summary of Increases in Blood Pressure from Baseline	Safety	Vital Sign Displays/ Oncology Core/	**OVT2C**		SAC
3.4050	Summary of Changes in Temperature from Baseline	Safety	Vital Sign Displays/ Oncology Core/	**OVT1C**		SAC
3.4060	Summary of Decreases in Systolic Blood Pressure from Baseline	Safety	Vital Sign Displays/ Oncology Core/	**OVT2C**		SAC

Table No.	*Title*	*Population*	*Component / Therapeutic Area (hyperlinked to IDSL LN DB)*	*IDSL No. or Example Shell No.*	*Study-Specific Display Notes*	*Deliverable Priority*
3.4090	Summary of Left Ventricular Ejection Fraction Change from Baseline	Safety	LVEF (ECHO/MUGA) Displays/ Oncology Core/	**OLVEF1B**		SAC
3.4110	Summary of ECOG	Safety	Performance Status Displays/ Oncology Core/	**PS1A**		SAC
3.4120	Summary of Change in ECOG from Baseline	Safety	Performance Status Displays/ Oncology Core/	**PS4A**		SAC
3.6010	Summary of ECG findings	Safety	ECG Displays/ Core/	**EG1**		SAC
3.6030	Summary of Increases in QTc	Safety	QTc Displays/ Oncology Core/	**OECG1C**		SAC
3.6040	Summary of Amount of Increase from Baseline Value in QTc	Safety	QTc Displays/ Oncology Core/	**OECG2C**		SAC
3.8020	Summary of Hepatobiliary Laboratory Abnormalities	Safety	Liver Signal/Event Displays/ Oncology Core/	**OLIVER1**		SAC
3.8030	Summary of Liver Event Information for RUCAM Score	Safety	Liver Signal/Event Displays/ Oncology Core/	**LIVER1**		SAC
3.8040	Summary of Liver Re-Challenges, Adaptations, and Recovery	Safety	Liver Signal/Event Displays/ Oncology Core/	**OLIVER4**	If data warrant. Added mock-up to Section 18.2.2.	SAC
3.8100	Summary of Baseline Ocular Exam	Safety		**See Mockup**	Have our three treatment arms as columns to the right of the ocular test result column	SAC
3.9900	Summary of Serious Adverse Events by Preferred Term Including Drug-Related Status and Fatal Status	Safety	t_ae_ser.ema.rtf	**See Mockup**		SAC

18.1.3.2. Figures

Figure No.	*Title*	*Population*	*Component / Therapeutic Area (hyperlinked to IDSL LN DB)*	*IDSL No. or Example Shell No.*	*Study-Specific Display Notes*	*Deliverable Priority*
13.0020	Plot of Cumulative Exposure to Dabrafenib	Safety	Exposure Displays/ Oncology Core/	**OEX13B**		SAC
13.0021	Plot of Cumulative Exposure to Trametinib	Safety	Exposure Displays/ Oncology Core/	**OEX13B**		SAC
13.0100	Cumulative Incidence for Selected Adverse Event of Special interest for Dabrafenib Monotherapy	Safety	Safety Events of Special Interest Statistical Display Standards	**ESI9**		SAC
13.0200	Cumulative Incidence for Selected Adverse Event of Special interest for Trametinib Monotherapy	Safety	Safety Events of Special Interest Statistical Display Standards	**ESI9**		SAC
13.0300	Cumulative Incidence for Selected Adverse Event of Special interest for Combination Treatment	Safety	Safety Events of Special Interest Statistical Display Standards	**ESI9**		SAC

18.1.3.3. ICH Listings

Listing No.	*Title*	*Population*	*Component / Therapeutic Area (hyperlinked to IDSL LN DB)*	*IDSL No. or Example Shell No.*	*Study-Specific Display Notes*	*Deliverable Priority*
23.0020	Listing of Dose Reductions	Safety	Dose Modifications Displays/ Oncology Core	**ODMOD10a**		SAC
23.0030	Listing of Dose Interruptions	Safety	Dose Modifications Displays/ Oncology Core/	**ODMOD11a**		SAC
23.0080	Listing of Dose Escalations	Safety	Dose Modifications Displays/ Oncology Core/	**ODMOD15a**		SAC
23.0090	Listing of Relationship Between System Organ Class and Verbatim Text	Safety	Adverse Events Displays/ Core/	**AE2**		SAC
23.0110	Listing of All Adverse Events	Safety	Adverse Events Displays/ Oncology Core/	**OAE4**		SAC
23.0111	Listing of Adverse Event Profiles for Dabrafenib Monotherapy	Safety	Adverse Events of Special Interest Displays/ Core/	**ESI8**		SAC
23.0112	Listing of Adverse Event Profiles for Trametinib Monotherapy	Safety	Adverse Events of Special Interest Displays/ Core/	**ESI8**		SAC
23.0113	Listing of Adverse Event Profiles for Combination Treatment	Safety	Adverse Events of Special Interest Displays/ Core/	**ESI8**		SAC
23.0120	Listing of Fatal Serious Adverse Events	Safety	Adverse Events Displays/ Oncology Core/	**OAE4**		SAC
23.0130	Listing of Non-Fatal Serious Adverse Events	Safety	Adverse Events Displays/ Oncology Core/	**OAE4**		SAC
23.0140	Listing of Adverse Events Leading to Permanent Discontinuation of Study Treatment	Safety	Adverse Events Displays/ Oncology Core/	**OAE4**		SAC

Listing No.	*Title*	*Population*	*Component / Therapeutic Area (hyperlinked to IDSL LN DB)*	*IDSL No. or Example Shell No.*	*Study-Specific Display Notes*	*Deliverable Priority*
23.0150	Listing of Adverse Events Leading to Withdrawal from Study	Safety	Adverse Events Displays/ Oncology Core/	**OAE4**		SAC
23.0160	Listing of Adverse Events that Lead to Dose Interruptions	Safety	Adverse Events Displays/ Oncology Core/	**OAE4**		SAC
23.0211	Listing of Adverse Events that Lead to Dose Reductions	Safety	Adverse Events Displays/ Oncology Core/	**OAE4**		SAC
23.0250	Listing of Deaths	Safety	Death Displays/ Oncology Core/	**DTH3**		SAC
23.0290	Listing of ECOG	Safety	Performance Status Displays/ Oncology Core/	**PS5A**		SAC

18.1.3.4. Other Study Population Listings

Listing No.	*Title*	*Population*	*Component / Therapeutic Area (hyperlinked to IDSL LN DB)*	*IDSL No. or Example Shell No.*	*Study-Specific Display Notes*	*Deliverable Priority*
30.0240	Listing of Abnormal ECG Findings	Safety	ECG Displays/ Core/	**EG5**		SAC
30.0241	Listing of ECG Findings	Safety	ECG Displays/ Core/	**EG5**		SAC
30.0280	Listing of Left Ventricular Ejection Fraction Results	Safety	LVEF (ECHO/MUGA) Displays/ Oncology Core/	**OLVEF2A**		SAC
30.0291	Listing of Liver Stopping Event Information for RUCAM Scores	Safety	Liver Signal/Event Displays/ Oncology Core/	**LIVER6**		SAC
30.0330	Listing of Ophthalmic Exam Results	Safety		**See Mockup**	Replace Cohort with Treatment	SAC

18.1.4. Pharmacokinetics (Section 4)

18.1.4.1. Tables

Table No.	*Title*	*Population*	*Component / Therapeutic Area (hyperlinked to IDSL LN DB)*	*IDSL No. or Example Shell No.*	*Study-Specific Display Notes*	*Deliverable Priority*
4.0010	Summary of GSK1120212 Pharmacokinetic Concentration-Time Data	Biomarker	PK	**PK01**	Macro name: pkct1. PK will be measured at 2 weeks, 8 weeks, and 10 weeks into treatment	SAC
4.0011	Summary of GSK2118436 Pharmacokinetic Concentration-Time Data	Biomarker	PK	**PK01**	Macro name: pkct1. PK will be measured at 2 weeks, 8 weeks, and 10 weeks into treatment	SAC
4.0012	Summary of GSK2284503 Pharmacokinetic Concentration-Time Data	Biomarker	PK	**PK01**	Macro name: pkct1. PK will be measured at 2 weeks, 8 weeks, and 10 weeks into treatment	SAC
4.0013	Summary of GSK2298683 Pharmacokinetic Concentration-Time Data	Biomarker	PK	**PK01**	Macro name: pkct1. PK will be measured at 2 weeks, 8 weeks, and 10 weeks into treatment	SAC
4.0014	Summary of GSK2167542 Pharmacokinetic Concentration-Time Data	Biomarker	PK	**PK01**	Macro name: pkct1. PK will be measured at 2 weeks, 8 weeks, and 10 weeks into treatment	SAC

18.1.4.2. Figures

Figure No.	*Title*	*Population*	*Component / Therapeutic Area (hyperlinked to IDSL LN DB)*	*IDSL No. or Example Shell No.*	*Study-Specific Display Notes*	*Deliverable Priority*
14.0010	Mean GSK1120212 Concentration-Time Plots (Linear and Semi-log)	Biomarker	PK	**PK17**	Macro name: pkcf2. Have each relevant combination of treatment time (weeks 2, 8, and 10) and treatment on graph.	SAC
14.0011	Mean GSK2118436 Concentration-Time Plots (Linear and Semi-log)	Biomarker	PK	**PK17**	Macro name: pkcf2. Have each relevant combination of treatment time (weeks 2, 8, and 10) and treatment on graph.	SAC
14.0012	Mean GSK2284503 Concentration-Time Plots (Linear and Semi-log)	Biomarker	PK	**PK17**	Macro name: pkcf2. Have each relevant combination of treatment time (weeks 2, 8, and 10) and treatment on graph.	SAC
14.0013	Mean GSK2298683 Concentration-Time Plots (Linear and Semi-log)	Biomarker	PK	**PK17**	Macro name: pkcf2. Have each relevant combination of treatment time (weeks 2, 8, and 10) and treatment on graph.	SAC
14.0014	Mean GSK2167542 Concentration-Time Plots (Linear and Semi-log)	Biomarker	PK	**PK17**	Macro name: pkcf2. Have each relevant combination of treatment time (weeks 2, 8, and 10) and treatment on graph.	SAC
14.0020	Median GSK1120212 Concentration-Time Plots (Linear and Semi-log)	Biomarker	PK	**PK18**	Macro name: pkcf3. Have each relevant combination of treatment time (weeks 2, 8, and 10) and treatment on graph.	SAC
14.0021	Median GSK2118436 Concentration-Time Plots (Linear and Semi-log)	Biomarker	PK	**PK18**	Macro name: pkcf3. Have each relevant combination of treatment time (weeks 2, 8, and 10) and treatment on graph.	SAC
14.0022	Median GSK2284503 Concentration-Time Plots (Linear and Semi-log)	Biomarker	PK	**PK18**	Macro name: pkcf3. Have each relevant combination of treatment time (weeks 2, 8, and 10) and treatment on graph.	SAC
14.0023	Median GSK2298683 Concentration-Time Plots (Linear and Semi-log)	Biomarker	PK	**PK18**	Macro name: pkcf3. Have each relevant combination of treatment time (weeks 2, 8, and 10) and treatment on graph.	SAC
14.0024	Median GSK2167542 Concentration-Time Plots (Linear and Semi-log)	Biomarker	PK	**PK18**	Macro name: pkcf3. Have each relevant combination of treatment time (weeks 2, 8, and 10) and treatment on graph.	SAC

Figure No.	*Title*	*Population*	*Component / Therapeutic Area (hyperlinked to IDSL LN DB)*	*IDSL No. or Example Shell No.*	*Study-Specific Display Notes*	*Deliverable Priority*
14.2010	Individual GSK1120212 Concentration-Time Plots (Linear and Semi-log)	Biomarker	PK	**PK16a**	Macro name: pkcf1. Will plot for visit time at 2 weeks, 8 weeks, and 10 weeks	SAC
14.2011	Individual GSK2118436 Concentration-Time Plots (Linear and Semi-log)	Biomarker	PK	**PK16a**	Macro name: pkcf1. Will plot for visit time at 2 weeks, 8 weeks, and 10 weeks	SAC
14.2012	Individual GSK2284503 Concentration-Time Plots (Linear and Semi-log)	Biomarker	PK	**PK16a**	Macro name: pkcf1. Will plot for visit time at 2 weeks, 8 weeks, and 10 weeks	SAC
14.2013	Individual GSK2298683 Concentration-Time Plots (Linear and Semi-log)	Biomarker	PK	**PK16a**	Macro name: pkcf1. Will plot for visit time at 2 weeks, 8 weeks, and 10 weeks	SAC
14.2014	Individual GSK2167542 Concentration-Time Plots (Linear and Semi-log)	Biomarker	PK	**PK16a**	Macro name: pkcf1. Will plot for visit time at 2 weeks, 8 weeks, and 10 weeks	SAC

18.1.4.3. ICH Listings

Listing No.	*Title*	*Population*	*Component / Therapeutic Area (hyperlinked to IDSL LN DB)*	*IDSL No. or Example Shell No.*	*Study-Specific Display Notes*	*Deliverable Priority*
24.1010	Listing of GSK1120212 Pharmacokinetic Concentration-Time Data	Biomarker	PK	**PK07**	Macro name: pkcl1p or pkcl1x. For visit, use week 2, week 8, and week 10 if data warrant.	SAC
24.1011	Listing of GSK2118436 Pharmacokinetic Concentration-Time Data	Biomarker	PK	**PK07**	Macro name: pkcl1p or pkcl1x. For visit, use week 2, week 8, and week 10 if data warrant.	SAC
24.1012	Listing of GSK2284503 Pharmacokinetic Concentration-Time Data	Biomarker	PK	**PK07**	Macro name: pkcl1p or pkcl1x. For visit, use week 2, week 8, and week 10 if data warrant.	SAC
24.1013	Listing of GSK2298683 Pharmacokinetic Concentration-Time Data	Biomarker	PK	**PK07**	Macro name: pkcl1p or pkcl1x. For visit, use week 2, week 8, and week 10 if data warrant.	SAC
24.1014	Listing of GSK2167542 Pharmacokinetic Concentration-Time Data	Biomarker	PK	**PK07**	Macro name: pkcl1p or pkcl1x. For visit, use week 2, week 8, and week 10 if data warrant.	SAC

18.1.5. Biomarker (Section 5)

18.1.5.1. Tables

Table No.	*Title*	*Population*	*Component / Therapeutic Area (hyperlinked to IDSL LN DB)*	*IDSL No. or Example Shell No.*	*Study-Specific Display Notes*	*Deliverable Priority*
5.0010	Summary of Samples Obtained for P-ERK IHC Analysis	Biomarker		**See HScore1 Mock-Up**	Display is Built off of the Immunogenicity Display IMM1. For each visit, we are looking for the number and percentage of people with p-ERK IHC Analysis	SAC
5.0020	Summary of p-ERK IHC Scores at Screening	Biomarker		**See HScore2 Mock-Up**	Display is built off of the LA1 display. Change the elements in Table to reflect p-ERK analysis	SAC
5.0021	Summary of p-ERK IHC Scores at Week 2	Biomarker		**See HScore2 Mock-Up**	Display is built off of the LA1 display. Change the elements in Table to reflect p-ERK analysis	SAC
5.0022	Summary of-ERK IHC Scores at Week 8	Biomarker		**See HScore2 Mock-Up**	Display is built off of the LA1 display. Change the elements in Table to reflect p-ERK analysis	SAC
5.0023	Summary of-ERK IHC Scores at Week 10	Biomarker		**See HScore2 Mock-Up**	Display is built off of the LA1 display. Change the elements in Table to reflect p-ERK analysis	SAC
5.0030	Descriptive Summary of Changes in H-Score from Weeks 8 to 10 among those with Monotherapy at Start of Study	Biomarker		**See HScore3 Mock-Up**	Display is built off of the descriptive summary table from BRF113928.	SAC
5.0031	Descriptive Summary of Changes in H-Score from Weeks 0 to 2 among those with Combotherapy at Start of Study	Biomarker		**See HScore3 Mock-Up**	Display is built off of the descriptive summary table from BRF113928.	SAC

Table No.	*Title*	*Population*	*Component / Therapeutic Area (hyperlinked to IDSL LN DB)*	*IDSL No. or Example Shell No.*	*Study-Specific Display Notes*	*Deliverable Priority*
5.0040	Mixed Model Analysis of H-Score Differences among the Different Treatment Arms Comparing or No Therapy to Combination Therapy	Biomarker		**See HScore4 Mock-Up**	Based off of the Tykerb Mixed Model Analyses for Study EGF112930.	SAC
5.0050	Multivariate Proportional Cox Model Examining the relationship between H-Score and Progression Free Survival	Biomarker		**See HScore5 Mock-Up**	Display is built off of the immunogenicity display IMM2	SAC
5.0051	Multivariate Proportional Cox Model Examining the relationship between H-Score and Duration of Response	Biomarker		**See HScore5 Mock-Up**	Display is built off of the immunogenicity display IMM2	SAC
5.0060	Summary of p-ERK IHC Scores at Screening for patients with BRAF V600E mutation	Biomarker		**See HScore2 Mock-Up**	Display is built off of the LA1 display. Change the elements in Table to reflect p-ERK analysis. Only include patients with BRAF V600E mutation.	SAC
5.0061	Summary of p-ERK IHC Scores at Week 2 for patients with BRAF V600E mutation	Biomarker		**See HScore2 Mock-Up**	Display is built off of the LA1 display. Change the elements in Table to reflect p-ERK analysis. Only include patients with BRAF V600E mutation.	SAC
5.0062	Summary of p-ERK IHC Scores at Week 8 for patients with BRAF V600E mutation	Biomarker		**See HScore2 Mock-Up**	Display is built off of the LA1 display. Change the elements in Table to reflect p-ERK analysis. Only include patients with BRAF V600E mutation.	SAC
5.0063	Summary of p-ERK IHC Scores at Week 10 for patients with BRAF V600E mutation	Biomarker		**See HScore2 Mock-Up**	Display is built off of the LA1 display. Change the elements in Table to reflect p-ERK analysis. Only include patients with BRAF V600E mutation.	SAC
5.0070	Descriptive Summary of Changes in H-Score from Weeks 8 to 10 among those with Monotherapy at Start of Study for patients with BRAF V600E mutation	Biomarker		**See HScore3 Mock-Up**	Display is built off of the descriptive summary table from BRF113928. Only include patients with BRAF V600E mutation.	SAC

Table No.	*Title*	*Population*	*Component / Therapeutic Area (hyperlinked to IDSL LN DB)*	*IDSL No. or Example Shell No.*	*Study-Specific Display Notes*	*Deliverable Priority*
5.0071	Descriptive Summary of Changes in H-Score from Weeks 0 to 2 among those with Combotherapy at Start of Study for patients with BRAF V600E mutation	Biomarker		**See HScore3 Mock-Up**	Display is built off of the descriptive summary table from BRF113928. Only include patients with BRAF V600E mutation.	SAC
5.0080	Mixed Model Analysis of H-Score Differences among the Different Treatment Arms Comparing or No Therapy to Combination Therapy for patients with BRAF V600E mutation	Biomarker		**See HScore4 Mock-Up**	Based off of the Tykerb Mixed Model Analyses for Study EGF112930 (Table 11.4). Only include patients with BRAF V600E mutation.	SAC
5.0090	Multivariate Proportional Cox Model Examining the relationship between H-Score and Progression Free Survival for patients with BRAF V600E mutation	Biomarker		**See HScore5 Mock-Up**	Display is built off of the immunogenicity display IMM2	SAC
5.0091	Multivariate Proportional Cox Model Examining the relationship between H-Score and Duration of Response for patients with BRAF V600E mutation	Biomarker		**See HScore5 Mock-Up**	Display is built off of the immunogenicity display IMM2	SAC
5.0100	Correlation of Changes in H-Score after Two Weeks of Combo Therapy and Changes in Tumor Burden	Biomarker		**See HScore6 Mock-Up**	Will contain the clinical marker of interest, Treatment Arm, Spearman's Coefficient, and Sample Size (N)	SAC
5.0110	Correlation of H-Score and Changes in Tumor Burden	Biomarker		**See HScore6 Mock-Up**	Will contain the clinical marker of interest, Treatment Arm, Spearman's Coefficient, and Sample Size (N)	SAC
5.0120	Summary of Investigator-Assessed Best Response without confirmation per percentage change category in H-Score (Using RECIST 1.1. criteria)	Biomarker		**See HScore7 Mock-Up**	Display is built off of the oncology response display RE1a	SAC

Table No.	*Title*	*Population*	*Component / Therapeutic Area (hyperlinked to IDSL LN DB)*	*IDSL No. or Example Shell No.*	*Study-Specific Display Notes*	*Deliverable Priority*
5.0130	Summary of Investigator-Assessed Best Response without confirmation per baseline H-Score category (Using RECIST 1.1. criteria)	Biomarker		**See HScore8 Mock-Up**	Display is built off of the oncology response display RE1a	SAC

18.1.5.2. Figures

Figure No.	*Title*	*Population*	*Component / Therapeutic Area (hyperlinked to IDSL LN DB)*	*IDSL No. or Example Shell No.*	**Study-Specific Display Notes**	*Deliverable Priority*
15.0010	Mean p-ERK Scores – Time Plot (Linear and Semi Log)	Biomarker		**PK17**	Replace Concentration (ng/mL) with H-Score on the y-axis, and have maximum value as 300. Replace Planned Relative Time (Hours) with Planned Screening Time (Weeks) for the x-axis and have values (0, 2, 8, and 10)	SAC
15.0011	Mean p-ERK Scores – Time Plot (Linear and Semi Log) for patients with BRAF V600E mutation	Biomarker		**PK17**	Replace Concentration (ng/mL) with H-Score on the y-axis, and have maximum value as 300. Replace Planned Relative Time (Hours) with Planned Screening Time (Weeks) for the x-axis and have values (0, 2, 8, and 10)	SAC
15.0020	Median p-ERK Scores – Time Plot (Linear and Semi Log)	Biomarker		**PK17**	Replace Concentration (ng/mL) with H-Score on the y-axis, and have maximum value as 300. Replace Planned Relative Time (Hours) with Planned Screening Time (Weeks) for the x-axis and have values (0, 2, 8, and 10)	SAC
15.0021	Median p-ERK Scores – Time Plot (Linear and Semi Log) for patients with BRAF V600E mutation	Biomarker		**PK17**	Replace Concentration (ng/mL) with H-Score on the y-axis, and have maximum value as 300. Replace Planned Relative Time (Hours) with Planned Screening Time (Weeks) for the x-axis and have values (0, 2, 8, and 10)	SAC
15.0030	Scatter plot for Correlation between Changes in H-Score after Two Weeks of Combo Therapy and Changes in Tumor Burden	Biomarker		**See HScore9 Mock-Up**	Have a different color and symbol for each drug cohort. Y-axis contains %SLD information and x-axis contains change in H-Score information. Example is for Illustrative purposes only and does not represent real data.	SAC
15.0040	Scatter plot for Correlation between Baseline Changes in Tumor Burden	Biomarker		**See HScore9 Mock-Up**	Have a different color and symbol for each drug cohort. Y-axis contains %SLD information and x-axis contains baseline H-Score information. Example is for Illustrative purposes only and does not represent real data.	SAC

18.1.5.3. Listings

Listing No.	Title	Population	Component / Therapeutic Area (hyperlinked to IDSL LN DB)	IDSL No. or Example Shell No.	Study-Specific Display Notes	Deliverable Priority
25.0010	Listing of p-ERK Results	Biomarker		**See H-Score10 Mock-Up**		SAC
25.0020	Listing of Variables Associated with Multivariate Cox Modeling Analysis	Biomarker		**See H-Score11 Mock-Up**	Only develop if multivariate Cox Model analyses will be conducted	SAC

18.2. Mock-Ups for Select Displays

18.2.1. Study Population Mock-Ups

Protocol: A18116378 Page 1 of 2
Population: All Treated Data as of 12JUN2013

Table 1.2011
Age Group Breakdown for the Trial

Treatment: Pooled Data

Age Range	Planned Number of Subjects	Actual Number of Subjects Enrolled
Adult(18-64 years)	Approximately 54 subjects aged ≥ 18	40
From 65-84 years	Approximately 54 subjects aged ≥ 18	14
85 years or older	Approximately 54 subjects aged ≥ 18	0

PPD

Protocol: BRF113928
Population: All Treated Data as of 12JUN2013

Listing 1.22
Relationship between ATC Level 1, Ingredient, and Verbatim Text for Anti-Cancer Therapy

Treatment: GSK2118436 150mg BID

ATC Level 1	Ingredient	Verbatim Text
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	BEVACIZUMAB	AVASTIN
		Avastin
		BEVACIZUMAB
		Bevacizumab (Avastin)
		Bevacizuman
		Bevicizumab
		bevacizumab
	CARBOPLATIN	CARBOPLATINE
		Carboplatin
		Carboplatine
		Carplan
		carboplatin
		carboplatine
	CISPLATIN	CisPlatin
		Cisplan
		Cisplatin
		Cisplatine
		cisplatin
		cisplatine

PPD

18.2.2. Safety Mock-Ups

Protocol: A18113678 Page 1 of 2
Population: Safety Data as of 12JUN2013

Table 3.1041
Summary of Non-Serious Adverse Events by Preferred Term with Occurrences ≥ 5%

System Organ Class Preferred Term	Treatment	Number of Subjects with Non-serious AE	Total number of exposed subjects	Number of Non-serious AE
Total number of subjects having any non-serious AE at or above >=5%	Placebo	10	12	39
	GSK 0.25 mg/kg	12	13	35
	GSK 5 mg/kg	11	12	51
Infections and infestations				
Nasopharyngitis	Placebo	4	12	5
	GSK 0.25 mg/kg	3	13	4
	GSK 5 mg/kg	4	12	8

PPD

Protocol: TAC113886
Population: All Treated Subjects

Table 10.75
Summary of Baseline Ocular Exam

Ocular Test Type	Right or Left side	Ocular Test Result	0.5mg MEK/25mg AKT (N=9)	0.5mg MEK/50mg AKT (N=7)	0.5mg MEK/75mg AKT (N=4)
Direct fundoscopic exam	Left	Abnormal, affecting vision	1 (11%)	0	0
		Abnormal, but not affecting vision and not requiring treatment	2 (22%)	0	0
		Abnormal, not affecting vision, requiring treatment	0	1 (14%)	0
		Within normal limits	6 (67%)	6 (86%)	4 (100%)
	Right	Abnormal, affecting vision	1 (11%)	0	0
		Abnormal, but not affecting vision and not requiring treatment	1 (11%)	0	0
		Abnormal, not affecting vision, requiring treatment	0	1 (14%)	0
		Within normal limits	7 (78%)	6 (86%)	4 (100%)

Protocol: TAC113886
Population: All Treated Subjects

Listing 33
Listing of Ophthalmic Exam Results

Centre ID/ Subj.	Cohort	Visit	Exam Date	Study Day	Eye	Result
PPD - This section has been excluded to protect patient privacy.						

Example OLIVER4
Protocol: XYZ100001
Population: Safety/Other study specific

Table 8.xx
Summary of Liver Re-Challenges, Adaptations and Recovery

	All Subjects (N=57)
Re-Challenge [1]	
n	3
Without Dose Reduction	0
With Reduced Dose	3 (100%)
Peak ALT before Re-Challenge [1]	
n	3
ALT ≥3xULN and ALT <5xULN	1 (33%)
ALT ≥5xULN and ALT <8xULN	1 (33%)
ALT ≥8xULN	1 (33%)
Post Re-Challenge [1]	
n	3
Recurrent Elevation of ALT	1 (33%)
No Recurrent Elevation of ALT	2 (67%)
No Follow-up	0
More Severe Elevation Following Re-Challenge[1]	
n	3
Yes	0
No	1 (33%)
No Follow-up	0

Note: This summary does not depict a true count of all re-challenges, but rather those events that meet the strict definition.
[1] Re-Challenge is defined for a subject with an ALT elevation, whose study treatment is interrupted/delayed and subsequently has an ALT value of <3xULN on or prior to re-starting study treatment.
[2] Adaptation is defined as ALT >3xULN followed by an ALT assessment returning to baseline grade or below without any dose interruption/delay between the ALT elevation and normalization.

[3] Recovery is defined as ALT <3xULN for 2 consecutive visits or <3xULN for one visit if subject discontinued and no data available. Post therapy records are included to evaluate recovery.
USER ID:directory/program.sas 01JAN2002 12:01

Example OLIVER4
Protocol: XYZ100001
Population: Safety/Other study specific

Table 8.xx
Summary of Liver Re-Challenges, Adaptations and Recovery

	All Subjects (N=100)
Time to Dose Interruption/delay (days)	
n	3
Mean	33.7
SD	21.13
Median	31.0
Min.	14
Max.	56
Duration of Interruption/delay (days)	
n	3
Mean	24.7
SD	14.98
Median	29.0
Min.	8
Max.	37
Duration of Re-Treatment (days)	
n	3
Mean	33.7
SD	21.13
Median	31.0
Min.	14
Max.	56

Note: This summary does not depict a true count of all re-challenges, but rather those events that meet the strict definition.
[1] Re-Challenge is defined for a subject with an ALT elevation, whose study treatment is interrupted/delayed and subsequently has an ALT value of <3xULN on or prior to re-starting study treatment.
[2] Adaptation is defined as ALT >3xULN followed by an ALT assessment returning to baseline grade or below without any dose interruption/delay between the ALT elevation and normalization.

[3] Recovery is defined as ALT <3xULN for 2 consecutive visits or <3xULN for one visit if subject discontinued and no data available. Post therapy records are included to evaluate recovery.
USER ID:directory/program.sas 01JAN2002 12:01

Table 8.xx
Summary of Liver Re-Challenges, Adaptations and Recovery

	All Subjects (N=100)
Time to Recurrent ALT Elevation Post Re-Challenge (days)[1]	
n	3
Mean	239.0
SD	154.50
Median	194.0
Min.	112
Max.	411
Adaptation [2]	
n	3
Without Dose Reduction	2 (67%)
With Dose Reduction	1 (33%)
Time to Adaptation (days) [2]	
n	3
Mean	33.7
SD	21.13
Median	31.0
Min.	14
Max.	56

Note: This summary does not depict a true count of all re-challenges, but rather those events that meet the strict definition.
[1] Re-Challenge is defined for a subject with an ALT elevation, whose study treatment is interrupted/delayed and subsequently has an ALT value of <3xULN on or prior to re-starting study treatment.

[2] Adaptation is defined as ALT >3xULN followed by an ALT assessment returning to baseline grade or below without any dose interruption/delay between the ALT elevation and normalization.
[3] Recovery is defined as ALT <3xULN for 2 consecutive visits or <3xULN for one visit if subject discontinued and no data available. Post therapy records are included to evaluate recovery.
USER ID:directory/program.sas 01JAN2002 12:01

Example OLIVER4
Protocol: XYZ100001
Population: Safety/Other study specific

Table 8.xx
Summary of Liver Re-Challenges, Adaptations and Recovery

	All Subjects (N=100)
Peak ALT before Adaptation [2]	
n	3
ALT ≥3xULN and ALT <5xULN	2 (67%)
ALT ≥5xULN and ALT <8xULN	1 (33%)
ALT ≥8xULN	0
Outcome of ALT Elevations	
n	8
Recovered [3]	8 (100%)
Not Recovered	0
No Follow-up	0
Outcome following ALT Elevations within 7 Days On or Prior to Study Treatment Discontinuation	
n	3
Recovered [3]	2 (67%)
Not Recovered	1 (33%)
No Follow-up	0

Note: This summary does not depict a true count of all re-challenges, but rather those events that meet the strict definition.

[1] Re-Challenge is defined for a subject with an ALT elevation, whose study treatment is interrupted/delayed and subsequently has an ALT value of <3xULN on or prior to re-starting study treatment.
[2] Adaptation is defined as ALT >3xULN followed by an ALT assessment returning to baseline grade or below without any dose interruption/delay between the ALT elevation and normalization.
[3] Recovery is defined as ALT <3xULN for 2 consecutive visits or <3xULN for one visit if subject discontinued and no data available. Post therapy records are included to evaluate recovery.

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Example OLIVER4
Protocol: XYZ100001
Population: Safety/Other study specific

Table 8.xx
Summary of Liver Re-Challenges, Adaptations and Recovery

	All Subjects (N=100)
Peak ALT for Subjects with ALT Elevations within 7 Days on or Prior to Study Treatment Discontinuation	
n	3
ALT ≥3xULN and ALT <5xULN	2 (67%)
ALT ≥5xULN and ALT <8xULN	1 (33%)
ALT ≥8xULN	0
Time to First ALT Elevation(days)	
n	3
Mean	33.7
SD	21.13
median	31.0
Min.	14
Max.	56
Time to Recovery [3](days)	
n	3
Mean	33.7
SD	21.13

median	31.0
Min.	14
Max.	56

Note: This summary does not depict a true count of all re-challenges, but rather those events that meet the strict definition.
[1] Re-Challenge is defined for a subject with an ALT elevation, whose study treatment is interrupted/delayed and subsequently has an ALT value of <3xULN on or prior to re-starting study treatment.
[2] Adaptation is defined as ALT >3xULN followed by an ALT assessment returning to baseline grade or below without any dose interruption/delay between the ALT elevation and normalization.
[3] Recovery is defined as ALT <3xULN for 2 consecutive visits or <3xULN for one visit if subject discontinued and no data available. Post therapy records are included to evaluate recovery.
USER ID:directory/program.sas 01JAN2002 12:01
Example EMASER
Protocol: A18116378
Population: Safety

Table 3.9900
Summary of Serious Adverse Events by Preferred Term Including Drug-Related Status and Fatal Status

System Organ Class Preferred Term	Treatment	Number of Subjects with Serious AE	Total number of exposed subjects	Number of Serious AEs	Number of Drug-related Serious AEs	Number of Fatal Serious AEs	Number of Drug-related Fatal Serious AEs
Total number of subjects having any serious AE	Placebo	1	12	1	0	0	0
	GSK 0.25 mg/kg	0	13	0	0	0	0
	GSK 5 mg/kg	1	12	1	0	0	0
Infections and infestations							

System Organ Class Preferred Term	Treatment	Number of Subjects with Serious AE	Total number of exposed subjects	Number of Serious AEs	Number of Drug-related Serious AEs	Number of Fatal Serious AEs	Number of Drug-related Fatal Serious AEs
Diverticulitis	Placebo	1	12	1	0	0	0
	GSK 0.25 mg/kg	0	13	0	0	0	0
	GSK 5 mg/kg	0	12	0	0	0	0

PPD

18.2.3. Immunohistochemistry Mock-Ups

Example: HScore1
Protocol: BRF116613 Page 1 of x
Population: Biomarker

Table X
Summary of Samples Obtained for p-ERK Immunohistochemistry Analysis

Visit	Planned Time	Trt A (N=100)	Trt B (N=100)	Trt C (N=100)
Visit 1	Screening	x/n (%)	x/n (%)	x/n (%)
Visit 2	Week 2	x/n (%)	x/n (%)	x/n (%)
Visit 3	Week 8	x/n (%)	x/n (%)	x/n (%)
Visit 4	Week 10	x/n (%)	x/n (%)	x/n (%)

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Example HScore2
Protocol: BRF116613 Page 1 of 1
Population: Biomarker

Table X
Summary of p-ERK Immunohistochemistry Scores at Screening

	Treatment A (N=100)	Treatment B (N=100)	Treatment C (N = 100)	Total (N=200)
p-ERK IHC H-Score	100	98		198
200-300	30 (30%)	22 (22%)		52 (26%)
100-199	55 (55%)	67 (68%)		122 (62%)

1-99	15 (15%)	9 (9%)	24 (12%)
0 or Unknown	0 (0%)	0 (0%)	0 (0%)
p-ERK Score Summary Statistics			
Mean	158		
SD	49		
Median	137		
Minimum	0		
Maximum	297		
Screening Intensity	100	98	198
3+	0 (0%)	0 (0%)	0 (0%)
2+	55 (55%)	69 (70%)	124 (63%)
1+	35 (35%)	35 (36%)	70 (35%)
0	15 (15%)	9 (9%)	24 (12%)
Unknown	2 (2%)	0	2 (1%)
% Positivity	100	98	198
100	0 (0%)	0 (0%)	0 (0%)
67-99	30 (30%)	22 (22%)	52 (26%)
34-66	55 (55%)	67 (68%)	122 (62%)
1-33	15 (15%)	9 (9%)	24 (12%)
0	2 (2%)	0	2 (1%)

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Example: HScore3
Protocol: BRF116613
Population: Biomarker

Table X
Descriptive Summary of Changes in H-Score from Weeks 8 to 10 among Those with Monotherapy at Start of Study

Total H-Score Changes	Trt A (N=18)	Trt B (N=18)	Total (N=36)
Any Increase or No Changes	x/n (%)	x/n (%)	x/n (%)
Total Decrease in Score of 1-100	x/n (%)	x/n (%)	x/n (%)
Total Decrease in Score of 101-200	x/n (%)	x/n (%)	x/n (%)
Total Decrease in Score of 201-300	x/n (%)	x/n (%)	x/n (%)
Unknown	x/n (%)	x/n (%)	x/n (%)
Summary Statistics for Total H-Score Changes			
Mean			
Standard Deviation			
Median			
Minimum			
Maximum			
Percentage Change in H-Score			
Any Increase or No Changes			
Any Decrease up to 80 percent			
Any Decrease > 80 percent			
Summary Statistics for Percentage H-Score Changes			
Mean			
Standard Deviation			
Median			
Minimum			
Maximum			

Example HScore4
Protocol: BRF116613
Population: Biomarker

Table X
Mixed Model Analysis of H-Score Differences among the Different Treatment Arms
Comparing Monotherapy or No Therapy to Combination Therapy

Treatment Arm	Comparison	N	LS Mean Num.	LS Mean Demon.	Ratio Estimate	Lower 90% Confidence Limit	Upper 90% Confidence Limit
GSK2118436 BID 8W then GSK1120212 QD + GSK2118436 BID	B vs A						
GSK1120212 QD 8W then GSK1120212 QD + GSK2118436 BID	B vs A						
GSK1120212 QD + GSK2118436 BID	B vs A						

Comparison for H-Score Times: B = Combo Therapy and A = Monotherapy or No Therapy (for Cohort that has Combination Therapy at start of study)

Example HScore5
Protocol: IMM123456
Population: Safety

Table X
Multivariate Proportional Cox Model Examining the relationship between H-Score and Progression Free Survival/Duration of Response

Parameter	Parameter Estimate	P-Value	HR	Low 95% CI	High 95% CI
Decrease in H-Score (Log 2 Scale)					
Age					
Sex					
ECOG Status					
Initial Combo therapy					
V600E Status					

Example HScore6
Protocol: BRF116613 Page 1 of 1
Population: Biomarker

Table X

Correlation of Changes in H-Score after Two Weeks of Combo Therapy and Changes in Tumor Burden

Clinical Marker of Interest	Treatment Arm	Spearman's Coefficient	N
% Change in Sum of Lesion Diameters	GSK2118436 BID 8W then GSK1120212 QD + GSK2118436 BID		
% Change in Sum of Lesion Diameters	GSK1120212 QD 8W then GSK1120212 QD + GSK2118436 BID		
% Change in Sum of Lesion Diameters	GSK1120212 QD + GSK2118436 BID		

Example HScore7
Protocol: XYZ100001 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific (Data as of: 30MAY2003)

Table X

Summary of Investigator/Independent Reviewer/etc.-Assessed Best Response (without or with confirmation) per baseline H-Score Category(RECIST 1.1 Criteria)

	Treatment A (N=300)	Treatment B (N=200)	Treatment C (N=200)	Total (N = 54)
p-ERK IHC H-Score btw. 200-300				
Complete Response	22 (7%)	10 (5%)	10 (5%)	
Partial Response	30 (10%)	40 (20%)	50 (25%)	
Stable Disease	153 (50%)	110 (55%)	100 (50%)	
Non-CR/Non-PD	3 (1%)	0	0	
Progressive Disease	70 (23%)	33 (17%)	33 (17%)	
Not Evaluable	25 (9%)	7 (3%)	7 (3%)	
Response Rate				

CR+PR	52 (17.3%)	50 (25.0%)	60 (30.0%)
95% Confidence Interval	(13.2%, 22.1%)	(19.2%, 31.6%)	(23.7%, 36.9%)
p-ERK IHC H-Score btw. 100-200			
Complete Response	22 (7%)	10 (5%)	10 (5%)
Partial Response	30 (10%)	40 (20%)	50 (25%)
Stable Disease	153 (50%)	110 (55%)	100 (50%)
Non-CR/Non-PD	3 (1%)	0	0
Progressive Disease	70 (23%)	33 (17%)	33 (17%)
Not Evaluable	25 (9%)	7 (3%)	7 (3%)
Response Rate			
CR+PR	52 (17.3%)	50 (25.0%)	60 (30.0%)
95% Confidence Interval	(13.2%, 22.1%)	(19.2%, 31.6%)	(23.7%, 36.9%)
p-ERK IHC H-Score btw. 1-99			
Complete Response	22 (7%)	10 (5%)	10 (5%)
Partial Response	30 (10%)	40 (20%)	50 (25%)
Stable Disease	153 (50%)	110 (55%)	100 (50%)
Non-CR/Non-PD	3 (1%)	0	0
Progressive Disease	70 (23%)	33 (17%)	33 (17%)
Not Evaluable	25 (9%)	7 (3%)	7 (3%)
Response Rate			
CR+PR	52 (17.3%)	50 (25.0%)	60 (30.0%)
95% Confidence Interval	(13.2%, 22.1%)	(19.2%, 31.6%)	(23.7%, 36.9%)
p-ERK IHC H-Score either 0 or Unknown			
Complete Response	22 (7%)	10 (5%)	10 (5%)
Partial Response	30 (10%)	40 (20%)	50 (25%)
Stable Disease	153 (50%)	110 (55%)	100 (50%)
Non-CR/Non-PD	3 (1%)	0	0
Progressive Disease	70 (23%)	33 (17%)	33 (17%)
Not Evaluable	25 (9%)	7 (3%)	7 (3%)
Response Rate			
CR+PR	52 (17.3%)	50 (25.0%)	60 (30.0%)
95% Confidence Interval	(13.2%, 22.1%)	(19.2%, 31.6%)	(23.7%, 36.9%)

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Example HScore8
Protocol: XYZ100001
Population: Intent-to-Treat/Safety/Other study specific (Data as of: 30MAY2003)

Table X

Summary of Investigator/Independent Reviewer/etc.-Assessed Best Response (without or with confirmation) per percentage change category in H-Score (RECIST 1.1 Criteria)

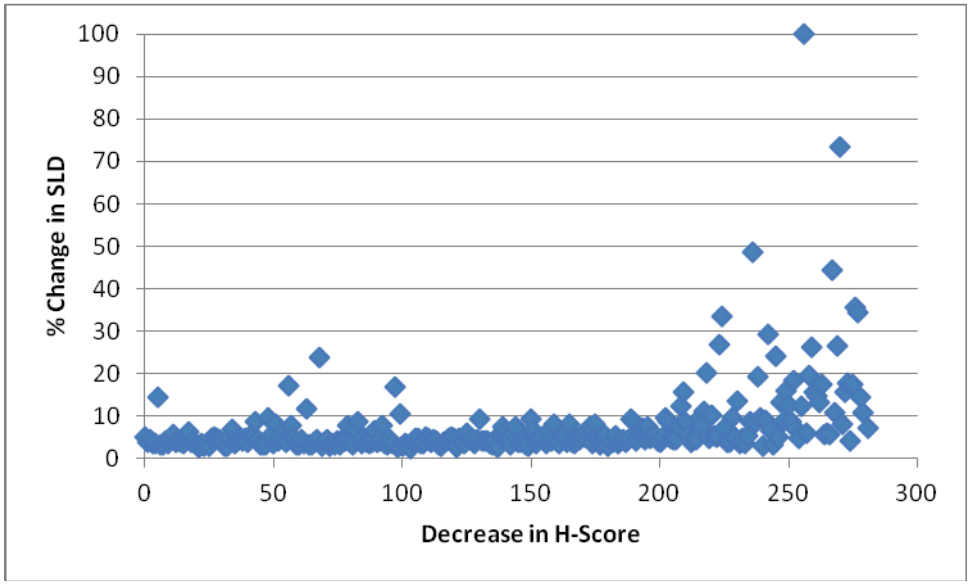
	Treatment A (N=300)	Treatment B (N=200)	Treatment C (N=200)	Total (N = 54)
Any Increase or No Changes				
Complete Response	22 (7%)	10 (5%)	10 (5%)	
Partial Response	30 (10%)	40 (20%)	50 (25%)	
Stable Disease	153 (50%)	110 (55%)	100 (50%)	
Non-CR/Non-PD	3 (1%)	0	0	
Progressive Disease	70 (23%)	33 (17%)	33 (17%)	
Not Evaluable	25 (9%)	7 (3%)	7 (3%)	
Response Rate				
CR+PR	52 (17.3%)	50 (25.0%)	60 (30.0%)	
95% Confidence Interval	(13.2%, 22.1%)	(19.2%, 31.6%)	(23.7%, 36.9%)	
Any Decrease up to 80 percent				
Complete Response	22 (7%)	10 (5%)	10 (5%)	
Partial Response	30 (10%)	40 (20%)	50 (25%)	
Stable Disease	153 (50%)	110 (55%)	100 (50%)	
Non-CR/Non-PD	3 (1%)	0	0	
Progressive Disease	70 (23%)	33 (17%)	33 (17%)	
Not Evaluable	25 (9%)	7 (3%)	7 (3%)	
Response Rate				
CR+PR	52 (17.3%)	50 (25.0%)	60 (30.0%)	
95% Confidence Interval	(13.2%, 22.1%)	(19.2%, 31.6%)	(23.7%, 36.9%)	
Any Decrease > 80 percent				
Complete Response	22 (7%)	10 (5%)	10 (5%)	
Partial Response	30 (10%)	40 (20%)	50 (25%)	
Stable Disease	153 (50%)	110 (55%)	100 (50%)	
Non-CR/Non-PD	3 (1%)	0	0	
Progressive Disease	70 (23%)	33 (17%)	33 (17%)	
Not Evaluable	25 (9%)	7 (3%)	7 (3%)	
Response Rate				

CR+PR	52 (17.3%)	50 (25.0%)	60 (30.0%)
95% Confidence Interval	(13.2%, 22.1%)	(19.2%, 31.6%)	(23.7%, 36.9%)

Example HScore9
Protocol: BRF116613
Population: Biomarker

Figure X
Scatter plot for Correlation between Decreases in H-Score after Two Weeks of Combo Therapy and Changes in Tumor Burden

Treatment Arm: GSK2118436 QD 8W then GSK1120212 + GSK2118436 QD



Example HScore10
Protocol: IMM123456
Population: Safety

Listing X
Listing of p-ERK results

Treatment	Inv./ Subj.	BRAF Mutation Type	Planned Time	Study Day	Staining Intensity	H-Score	Change from Baseline (%)	Change from Week 8 (%)	Positivity (%)
PPD - This section has been excluded to protect patient privacy.									

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Example HScore11
Protocol: IMM123456
Population: Safety

Listing X
Listing of Key Variables Associated with Multivariate Cox Modelling Analysis

Treatment	Inv./Subj.	Age	Sex	Race	ECOG Status	BRAF mutation type
PPD - This section has been excluded to protect patient privacy.						

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