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Title:	Reporting and Analysis Plan for BRF117277 : A Phase II, Open-Label, Multicentre Study of Dabrafenib plus Trametinib in Subjects with BRAF Mutation-Positive Melanoma that has Metastasized to the Brain (Amendment 1)

Compound Number: GSK2118436, GSK1120212 / NCT02039947

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Description: This document details the reporting and analysis plan for BRF117277, a non-randomized, multi-center Phase II study to evaluate efficacy and safety of combined therapy with dabrafenib and trametinib in patients with BRAF mutation-positive melanoma with brain metastases. Four cohorts based on type of mutation, ECOG performance score, presence of symptoms and prior local therapy of brain lesions will be treated. The primary objective is to assess the intracranial response rate in subjects with locally confirmed BRAF V600E-mutation positive melanoma that has metastasized to the brain without symptoms and have not undergone prior local therapy for brain metastases, ECOG score of 0-1 (Cohort A). Other secondary objectives include intracranial, extracranial, and overall response in all cohorts, progression-free and overall survival, duration of intracranial, extracranial, and overall response in all cohorts, and the incidence and severity of adverse events by cohort.

Subject: Oncology, Reporting and Analysis Plan, melanoma, brain metastases, BRAF inhibitor, BRAF V600E mutation, BRAF V600K mutation, BRAF V600R mutation, BRAF V600D mutation, intracranial

Author's Name, Title and Functional Area: [redacted]

Approved Via E-mail by:

Email approval on file

Revision Chronology

Date	Version
2015-FEB-10	Original
2017-FEB-23	Amendment No. 1
2018-MAR-05	Amendment No. 2

1) Minor correction to typographical errors throughout the document.
2) Title page: Updated description about study objective - to assess the intracranial response rate in subjects with locally confirmed BRAF V600E-mutation positive melanoma.
3) Section 2: Updated study objectives to be consistent with the study protocol amendment No.5 – 1. Primary endpoint amended to allow for locally confirmed BRAF V600E (followed by central confirmation as with all other cohorts) and 2. Secondary endpoint number 9: OS changed from 5 to 3 year.
4) Section 3: Updated Study design - Cohort A patient population updated to allow for locally confirmed BRAF V600E (followed by central confirmation as with all other cohorts) and definition of study closure updated from "where all subjects still in follow up have had at least 5 years follow up…" to "where all subjects still in follow up have had at least 3 years follow up…".
5) Updated Protocol reference information from "Protocol Amendment 01, dated 27 April 2014 GlaxoSimthKline Document Number (2013N168168437_01)" to "Protocol Amendment 05, dated 13 July 2016 GlaxoSimthKline Document Number (2013N168437_07)".
6) Section 4 and 4.2: reference to 5 year survival changed to 3.
7) Section 5.1: To clarify the significance level at the time of primary analysis, added "and the primary endpoint test in the primary analysis will be performed at 5% level".
8) [redacted]
9) Added section 9.2.15 to clarify how to apply analysis cut-off date.
10) Section 10.3, 10.5 and 10.6: Updated the drug dictionary reference from "GSK Drug coding dictionary" to "WHODrug coding dictionary".
11) Section 11.1: added "As a window of ± 7 days is allowed for scheduling, 7 weeks (or 49 days) will be used for analysis" to clarify the stable disease criteria.
12) As independent reviewer-assessment has been done, removed all the hypothetical wording ("If done") removed.

13) Section 11.2: Added detailed derivation rules for the date of last contact.

14) Section 11.2: Added "The duration of intracranial, extracranial, and overall response per independent reviewer-assessment will also be summarized. Figures and listings of duration of independent reviewer-assessed response will also be provided.".

15) Section 11.2: Added "Frequency of patients with PFS events will be presented and also separately by types of PFS event, i.e. progression or death.".

16) Section 11.2: Added "PFS per independent reviewer-assessment will be summarized. A figure and listing of progression-free survival time per independent reviewer will also be provided."

17) Section 12.3: "Summaries of exposure-adjusted incidence rates will be produced for each AE of special interest" deleted.

18) Section 12.3: Updated the list of adverse event of special interest following MedDRA19.1.

19) Section 12.7.1: "A trellis display of LFT shifts from baseline to maximum values will be provided." Deleted.

20) Section 12.8: Deleted analysis about neurological exam as the data is not available to produce these displays.

21) Section 14.1: Modify the Table of Contents for data displays to be consistent with the updated AESI and the required analysis per team's discussion and agreement. To be specific, The following changes have been made,

    a. Updated all AESI related displays to be consistent with the latest MedDRA 19.1.

    b. Removed "2.0061 Kaplan-Meier Estimates of Overall Survival at 3 Years by Cohort" from the list of displays for primary analysis.

    c. Added "2.0061 Kaplan-Meier Estimates of Overall Survival at 3 Years by Cohort" to the list of displays for end of study analysis.

    d. Removed all the displays for Summaries of exposure-adjusted incidence rates for each AE of special interest.

    e. Updated "1.1220 Summary of Study Treatment Status by Cohort" to "1.1220 Summary of Study Treatment Status for Trametinib by Cohort".

    f. Added "1.1221 Summary of Study Treatment Status for Dabrafenib by Cohort".

    g. Removed "3.9020 Summary of Neurological Examinations by Cohort" and "30.0340 Listing of Neurological Assessments".

    h. Removed "12.0080 Trellis Display of Patient Profiles of LFT Results by Cohort".

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Abbreviations

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
ATS	All Treated Subjects
CI	Confidence Interval
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Events
CTX	Anti-cancer Therapy Dataset
DIR	Duration of Intracranial Response
DER	Duration of Extracranial Response
DOR	Duration of Overall Response
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Easter Cooperative Oncology Group
eCRF	Electronic Case Report Form
ER	Extracranial Response
GSK	GlaxoSmithKline
IDMC	Independent Data Review Committee
IDSL	Integrated Data Standards Library
IR	Intracranial Response
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Medical Affairs
NCI	National Cancer Institutes
OR	Overall Response
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-free Survival
PR	Partial Response
PT	Preferred Term
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease
SOC	System Organ Class
SRT	Safety Review Team
ULN	Upper Limit of Normal

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1. INTRODUCTION

This reporting and analysis plan (RAP) details all planned analyses required for a Clinical Study Report of study BRF117277. This is a phase II study to evaluate the efficacy and safety of BRF117277 using a non-randomized, open-label, multiple cohort design.

For further information on the study design, see Protocol Amendment 05, dated 13 July 2017, GlaxoSimthKline Document Number (2013N168437_07).

[redacted]

The content of this RAP is based on the SOP and Information for Authors: Reporting and Analysis Plans [redacted] effective 23 March 2011.

All decisions regarding final analysis, as defined in this RAP document, have been made prior to Database Freeze of the study data. Interim analyses are detailed within Section 4.1, where applicable.

2. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To assess the intracranial response (IR) of subjects with locally confirmed BRAF V600E-mutation positive melanoma that has metastasized to the brain without symptoms and have not undergone prior local therapy for brain metastases, ECOG score of 0-1 (Cohort A).	• IR is defined as the proportion of subjects with a confirmed intracranial complete response (CR) or partial response (PR) as per investigator assessment using modified RECIST 1.1 guidelines.
Secondary	
1. To assess cohort B for IR of subjects with locally confirmed BRAF V600E cutaneous melanoma with metastases to the brain confirmed by MRI, asymptomatic with prior local therapy for brain metastases; ECOG score of 0-1. 2. To assess cohort C for IR of subjects with locally confirmed BRAF V600 D/K/R cutaneous melanoma with metastases to the brain confirmed by MRI, asymptomatic, with or without prior local therapy; ECOG score of 0-1. 3. To assess cohort D for IR of subjects with locally confirmed BRAF V600 D/E/K/R cutaneous melanoma with metastases to the brain confirmed by MRI, symptomatic; with or without prior local therapy; ECOG score of 0-2.	• IR is defined as the percentage of subjects with a confirmed intracranial complete response (CR) or partial response (PR) as per investigator assessment using modified RECIST 1.1 guidelines.

Objectives	Endpoints
4. To assess Cohorts A, B, C and D for Disease Control for intracranial, extracranial and overall response (IDC, EDC and ODC respectively)	• Intracranial Disease Control (IDC) is defined as CR+PR+SD for intracranial disease • Extracranial Disease Control (EDC) is defined as CR+PR+SD for extracranial disease • Overall Disease Control (ODC) is defined as CR+PR+SD for overall disease
5. To assess Cohorts A, B, C and D for extracranial response rate (ER)	• Extracranial response (ER), defined as the percentage of subjects with a best extracranial response of a confirmed CR or PR by investigator assessment using modified RECIST 1.1
6. To assess Cohorts A, B, C and D for overall response rate (OR)	• Overall response (OR), defined as the percentage of subjects with a best overall confirmed response of CR or PR by investigator assessment
7. To assess Cohorts A, B, C and D for duration of response for intracranial, extracranial and overall response (DIR, DER and DOR respectively)	• Duration of intracranial, extracranial and overall response (DIR, DER and DOR), defined as the time from first documented evidence of CR or PR until time of first documented intracranial, extracranial, or overall disease progression.
8. To assess Cohorts A, B, C and D for progression-free survival (PFS)	• PFS, defined as the interval between first dose and the earliest date of disease progression or death due to any cause

Objectives	Endpoints
9. To assess C Cohorts A, B, C and D for overall survival (OS) and long-term (particularly 5-year) OS	• Overall survival (OS), defined as the time from first dose until death due to any cause
10. To assess Cohorts A, B, C and D to characterize the safety of dabrafenib and trametinib combination therapy.	• Assessment of safety of dabrafenib and trametinib measured by the frequency and severity of adverse events, skin assessments, laboratory abnormalities, vital signs, and assessment data (12-lead electrocardiograms (ECG), echocardiograms, and clinical monitoring/observation including neurological examination)
[redacted]	

2.1. Statistical Hypotheses

The primary efficacy objective of this study is to assess the intracranial response (IR) rate in BRAF V600E mutation positive subjects assessed by Investigators using modified RECIST 1.1 criteria for Cohort A:

- Cohort A: 75 Subjects who are treatment-naive for brain metastases, asymptomatic and stable on corticosteroids.

The study is designed to provide evidence to support the null hypothesis, H_0: IRR $\leq$ 35% or to reject it in favor of the alternative hypothesis, H_A: IRR $\geq$ 50% for BRAF V600E mutation-positive subjects in Cohort A.

This hypothesis will be tested using a one-sided test for superiority with α=0.05. There will be no other testing; therefore, there will be no adjustment of the Type I error for multiple testing.

3. STUDY DESIGN

This study will evaluate the safety and efficacy of 4 cohorts, each receiving the same treatment. **Cohort A:** Seventy-five subjects with locally confirmed BRAF V600E cutaneous melanoma with metastases to the brain confirmed by MRI, asymptomatic, without prior local (brain) therapy and ECOG score of 0-1. **Cohort B:** Fifteen subjects with locally confirmed BRAF V600E cutaneous melanoma with metastases to the brain confirmed by MRI, asymptomatic, with prior local (brain) therapy and ECOG score of 0-1. **Cohort C:** Up to fifteen subjects with locally confirmed BRAF V600D/K/R cutaneous melanoma with metastases to the brain confirmed by MRI, asymptomatic, with or without prior local (brain) therapy and ECOG score of 0-1. **Cohort D:** Fifteen subjects with locally confirmed BRAF V600D/E/K or R cutaneous melanoma with metastases to the brain confirmed by MRI, symptomatic, with or without prior local (brain) therapy and ECOG score of 0-2.

Subjects will receive dabrafenib 150 mg twice daily and trametinib 2 mg once daily until evidence of disease progression, death, or unacceptable toxicity. Subjects will be required to meet all eligibility criteria and return to clinic on a monthly basis for clinical, skin and laboratory assessments. Intracranial and extracranial disease will be assessed at baseline, Week 4, Week 8, and every 8 weeks thereafter. After Week 40, disease assessments may be performed every 12 weeks. Response to treatment will be evaluated using modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

An Independent Data Monitoring Committee (IDMC) will be used in this study.

Protocol-specified guidelines for dose adjustments, interruptions and discontinuation due to adverse events are provided in Protocol Amendment 05, dated 13 July 2016 GlaxoSimthKline Document Number (2013N168437_07). After discontinuation of study treatment, subjects will remain in the study for follow-up assessments including monthly skin assessments up to 6 months and updates on anti-cancer treatment until death. Subjects who have not died, but are no longer being followed for disease progression or survival are considered to have withdrawn from the study. The study will be completed when either all subjects are dead or lost to follow-up, or all subjects still in follow-up

have had at least 3 years follow-up from the date of first dose of study treatment, whichever is earlier.

4. PLANNED ANALYSES

In line with ICH E9 [European Medicines Evaluation Agency (CPMP/ICH/3633/96)], membership of the analysis populations will be determined using the definitions in Section 6 of this RAP.

The primary efficacy analysis will be performed when all subjects in Cohort A have had the opportunity for ***three (3)*** post baseline disease assessments. At this time the final intracranial response analysis will be performed and an interim analysis of PFS and OS will be provided. The final analysis of PFS, OS, and safety will occur after all subjects have died or are otherwise lost to follow-up or 3 years from the first dose of study treatment, whichever is soonest.

4.1. Interim Analyses

There is a formal interim analysis for futility only with a statistical decision rule in this trial. For Cohort A, an interim analysis will take place after 22 subjects have been treated and had the opportunity for at least two disease assessments. The responses used in this interim analysis do not have to be confirmed. At least 8 of the 22 subjects must have an IR (intracranial CR or PR) for the trial to continue. If 7 or fewer subjects have an IR, this is evidence that the null hypothesis is true. If accrual is not complete at the time of the interim analysis, it will continue during this analysis.

An IDMC will review accumulating safety and efficacy data, including the results of the interim review of safety and efficacy and make recommendations to continue, modify, or terminate the study if there are concerns regarding safety. The specific responsibilities, review schedules and composition of the IDMC will be outlined in a separate document, the IDMC charter. The IDMC will review the study results at least once for efficacy and futility. Additional routine reviews of safety data will be scheduled as needed.

4.2. Final Analyses

The primary analyses will be performed after all subjects in Cohort A have had the opportunity for ***three (3)*** post-baseline disease assessments. This analysis will be performed after the database is frozen. After all subjects have died or are otherwise lost to follow-up or 3 years from the first dose of study treatment, whichever is soonest, the End of Study analysis will be performed on the total cumulated safety data and overall survival. This analysis will be performed after the End of Study database is frozen. The displays that will be included in this analysis are listed in Section 14.1.1.

5. SAMPLE SIZE CONSIDERATIONS

5.1. Sample Size Assumptions

The sample size is based on the hypothesized improvement in intracranial response over study GSK BRF113929 (BREAK-MB) in Cohort A. A 35% intracranial response (IR) is not clinically significant over existing therapies. An intracranial response (IR) of 50% is of clinical significance.

For the primary endpoint cohort (A), 75 BRAF V600E mutation positive subjects will be enrolled. At the time of the primary efficacy analysis, at least 33 subjects with an IR (44%) are required to establish that the evidence does not support the null hypothesis. The sample size is based on a one-sided superiority test of binomial proportions with an overall Type I error rate 0.05 incorporating an interim analysis with the spending function proposed by Lan,(1983) with Pocock Boundary. The null hypothesis in Cohort A will be tested assuming IR of 35% against an IR of 50% using a one-sided test for superiority with α=0.05 and power=82%. There will be no other testing; therefore, there will be no adjustment of the Type I error for multiple testing and the primary endpoint test in the primary analysis will be performed at 5% level.

5.2. Sample Size Sensitivity

Table 1 shows statistical power for the test of the null hypothesis in Cohort A under the assumed IR of 35%. It includes statistical power for scenarios where the alternative response rate is lower and higher. All statistical power calculations assume 75 BRAF V600E mutation positive subjects in the Cohort A All Treated Subjects population.

Table 1 Statistical Power Scenarios with 75 BRAF V600E Mutation Positive Subjects in Cohort A

IR	Statistical Power
40%	22.9%
45%	53.8%
50%	82.1%
55%	96.2%

5.3. Sample Size Re-estimation

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

6. ANALYSIS POPULATIONS

6.1. All Treated Populations

All subjects who receive at least one dose of study medication will comprise the All Treated subjects (ATS) population.

The V600E population will comprise all BRAF V600E mutation positive subjects in the ATS population.

The V600D/K/R population will comprise all BRAF V600D/K/R mutation positive subjects in the ATS population.

6.2. All Enrolled

The All Enrolled population comprises all subjects who were enrolled regardless of whether they had a dose of study treatment.

6.3. Safety Population

The safety population is the ATS population.

6.4. Analysis Datasets

Primary efficacy analyses will be based on investigator-assessed results in the ATS population. If independent review of efficacy is done, those analysis results will be secondary.

Safety analyses will use the ATS population.

The V600D/K/R population, defined above and identified in the study protocol as a population to be used to report on secondary efficacy endpoints by cohorts, will ***not*** be used. This change was made to accommodate the small sample size in Cohorts B-D (15 subjects per cohort). Analyses of subgroups of 15 subjects would not generally be meaningful and are not specified *a priori*.

7. TREATMENT COMPARISONS

There are no treatment comparisons. The primary objective will be supported by testing the null hypothesis in Cohort A. The four cohorts will not be compared statistically for any endpoint.

7.1. Data Display Treatment

The following treatment descriptors will be used on all applicable displays. Results will be reported by cohort.

Treatment Group		Data Display	Order of Treatment Groups
Code	Description		
A	Dabrafenib+Trametinib	Dabrafenib+Trametinib	n/a

8. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis datasets will be created according to CDISC/ADaM standards, and data will be listed and summarized according to GSK Integrated Data Standards Library (IDSL) reporting standards. Formatting for dates, times, and decimal places will follow GSK standards except where specified.

The currently supported versions of SAS, S-Plus software, and TSCG (for figures) will be used to perform all data analyses, generate tables, figures, and listings.

All data in the database will be presented in by-subject data listings.

All data up to the time of study completion or withdrawal from the study will be included in the analysis, regardless of duration of treatment.

As the duration of treatment for a given subject will depend on efficacy and tolerability, the duration of follow-up will vary between subjects. Consequently, there will be no imputation for missing data.

Use the center ID in summaries and listings, as needed. Summary tables and listings will NOT generally be separated by investigator nor will investigator be a factor in any statistical models. Unless otherwise stated, all listings will be sorted by center ID, subject number, cohort, then by visit date.

Unless otherwise stated, continuous variables will be summarized with n, mean, median, standard deviation, minimum and maximum, and categorical variables will be summarized with frequency counts and percentages.

Summaries will be produced by cohort.

All laboratory data will be presented in GSK's standard units for reporting.

"Worst-case post-baseline" values will be derived using scheduled and unscheduled visits.

Planned times relative to study drug dosing will be used in all tables and summary figures.

Generally, only pre-specified planned times will be used in the summaries, statistical analyses and calculations of any derived parameters and unscheduled readings will be listed. However, both unscheduled and scheduled readings will be included in the computation of maximum toxicity and in post-baseline shifts displays for labs and in any listing.

Assessment windows will not be defined for the purpose of classifying measurements obtained outside scheduled assessment times.

Deviations from the analyses in the RAP will be identified in the CSR.

8.1. Multicenter Studies

Data from all participating centers will be pooled prior to analysis. It is anticipated that subject accrual will be spread thinly across centers and summaries of data by center would be unlikely to be informative and will not, therefore, be provided. However, a summary of treated subjects by center will be produced.

8.2. Other Strata and Covariates

In all efficacy analyses, there is no stratification. There are no formal plans for investigating any covariates.

8.3. Examination of Subgroups

There are no formal plans for examining subgroups except reporting adverse events by sex and age groups (<65 years old and ≥ 65 years old).

8.4. Multiple Comparisons and Multiplicity

The Type I error rate will not be adjusted for multiplicity in secondary or supporting analyses.

9. DATA HANDLING CONVENTIONS

9.1. Premature Withdrawal and Missing Data

Because study treatment is dependent on the study endpoints (e.g., progression), the length of treatment for each subject will depend on the efficacy and toxicity of the treatment, so the duration of treatment will vary across subjects. Similarly the duration of follow up will also vary. All available time-to-event data will be analyzed using suitable statistical methods; subjects with shorter treatment and follow-up due to the natural history of their disease or medical necessities of the treatment of their disease will not be considered to have missing time-to-event data. For endpoints which determine the percentage of responders, subjects with unknown or missing best overall response will be assumed to be non-responders, and will be included in the denominator when calculating the percentages.

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

Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument. These data will be indicated by the use of a “blank” in subject listing displays. Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.

Subjects with the designation of treatment relationship for adverse events (AE)s and serious adverse events (SAEs) missing will have the worst case assumed to impute the relationship: if relationship to study treatment is missing it will be assumed to be “Yes”. There will be no other imputation for missing data other than what’s described in Section 9.2 for partial dates and for missing exposure end dates.

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 core standard algorithms and 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 treatment start date 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 (progression-free survival, duration of intracranial, extracranial, and overall response, overall survival) 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.

With the exception of new anti-cancer start date on the Oncology time to event analysis dataset and exposure end date on the Exposure analysis dataset, 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 specific analysis purposes as outlined below.

The partial date imputation will follow 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:

XYZD_ - character date variable

XYZDT - numeric date variable

XYZDTFL - flag variable

Details on imputing partial dates for specific datasets follow.

Adverse Events (AE):

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

Dataset	Date	Missing Element	Rule

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: o 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		• No imputation for partial end dates will be performed

Anti-Cancer Therapy and Radiotherapy:

Start and end dates are generally not imputed. [redacted]

Imputed partial dates will not be used to derive time since most recent prior therapy. In addition, the cancer therapy treatment status variable, and not any variables that use imputed partial dates, will be used to differentiate prior and follow-up anti-cancer therapy and radiotherapy.

Dataset	Date	Missing Element	Rule
Anti-Cancer Therapy Radiotherapy	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:

The date of surgery or procedure is generally not imputed. However, post treatment surgery or procedure dates maybe imputed (if necessary) to determine date of new anti-cancer therapy. In this case only, the date of new anti-cancer therapy (not specific surgery or procedure date) will be stored on appropriate efficacy datasets. The category for surgical procedure variable, and not any variables that use imputed partial dates, will be used to differentiate prior, on, and follow-up surgical procedure data. The derived time in relation to treatment variables are not needed for reporting of data because the category for surgical procedure variable can be used. Therefore, imputed dates are not needed for derivation of time in relation to treatment.

Dataset	Missing Element	Rule
Surgical Procedures	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 and Blood and Blood Supportive Care Products:

Start and end dates for use in derivation of the reference variables for concomitant medication start and end relative to treatment will be imputed. Similarly start and end dates for use in derivation of the reference variables for blood and blood supportive care start and end relative to treatment will be imputed. However these imputed start and end dates will not be stored permanently in the analysis datasets.

The reference variables will be used to differentiate before, during and after for the concomitant medication or blood or blood supportive care start and end dates. The derived time in relation to treatment variables are not needed for reporting of these data.

Dataset	Date	Missing Element	Rule
Concomitant Medication Blood and Blood Supportive Care Products	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: o 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).

Time to Event, Response, and Response for Independent Review:

Start dates for follow-up anti-cancer therapy, radiotherapy (where applicable), and surgical procedures (where applicable) will be temporarily imputed in order to define event and censoring rules for progression-free survival; intracranial, extracranial, and overall response rate; and duration of intracranial, extracranial, and overall 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 anti-cancer therapy, radiotherapy, or surgical procedure datasets. The following rules will be used to impute the date when partial start dates are present on anti-cancer therapy radiotherapy, and/or surgical procedures dataset[s]:

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

The date of new anti-cancer therapy is derived as the earliest date of new anti-cancer therapy (e.g., chemotherapy), radiotherapy (where applicable), or a cancer-related surgical procedure (where applicable) and will include imputed dates. If the date of new anti-cancer therapy is an imputed date, then the date of new anti-cancer therapy flag variable 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 the date of new anti-cancer therapy ensure that the date of new anti-cancer therapy flag 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 flag should be set to missing as the date used for the new anti-cancer therapy is not an imputed date.

9.2.6. Imputation of Missing Exposure End Dates

The rules for imputing missing exposure end dates given in this section apply to both dabrafenib and trametinib. The study treatment end date variable will hold the last date of exposure for either dabrafenib or trametinib, that is, the latest exposure end date across all study treatments.

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 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 study treatment end date variable.

For subjects who have missing end dates in their last exposure record because they are still on study treatment, the on-therapy indicator variables (time in relation to study treatment) 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 or on the first study treatment dose date. For laboratory data, baseline will be defined as the most recent, non-missing value from a central laboratory prior to or on the first study treatment dose date. If there are no central labs collected for a subject and lab test prior to or on the first dose of study treatment, the most recent, non-missing value from a local laboratory prior to or on the first dose of study treatment will be defined as the baseline value.

For subjects who did not receive study treatment during the study, baseline will be defined as the latest, non-missing collected value.

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 will only be included in the display sections that report worst- case post-baseline.

If multiple assessments on different days are reported for the same scheduled assessment, then the earliest 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.

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. 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 treatment actually received.

9.2.11. Extended Loss to Follow-up or Extended Time without an Adequate Assessment

If two or more consecutive scheduled disease assessments are missed and are then followed by an assessment of PD or death, PFS will be censored at the last adequate assessment prior to PD or death. When the scheduled disease assessment is every 8 weeks, a window of 119 days (16 weeks + 7 day window) will be used to determine whether there was an extended time without adequate assessment. That is, if the time difference between the PFS event of PD or death and the last adequate assessment is

more than 119 days, then PFS will be censored at the last adequate assessment prior to the PFS event. If the Week 4 and Week 8 disease assessments are both missed or are inadequate (that is, the first adequate disease assessment is at Week 16), and the Week 16 disease assessment shows progressive disease, then PFS will be set to Day 1.

9.2.12. Date Associated with Response

For each disease assessment after baseline, determine the dates associated with intracranial, extracranial, and overall response. For any type of complete response (CR) or partial response (PR), assign to the latest date within the disease assessments. For any type of stable disease (SD), Non-CR/Non-PD or Not Evaluable, assign to the earliest date within the disease assessments. For any type of progressive disease (PD), assign to the earliest assessment date associated with the progression.

9.2.13. Cardiac Scan Modalities (ECHO/MUGA)

The same modality (ECHO or MUGA) for determining cardiac scan data (e.g., left ventricular ejection fraction (LVEF)) should be used to follow a subject throughout the study. The absolute change from baseline values will not be calculated for any subjects where the post-baseline value was determined by a cardiac scan modality that is different than the one used to determine baseline value.

9.2.14. Derived and Transformed Variables

See Section 11 for details on analyses for intracranial, extracranial, and overall response, progression-free survival, overall survival, duration of intracranial response, duration of extracranial response, and duration of overall response.

Prognostic Factors

The prognostic variables below will be added to the following datasets to support exploratory analyses: ADSL, demography, overall response, overall response independent review (if there is independent review), and time to event datasets.

Baseline ECOG performance status: Baseline ECOG performance status can be 0, 1, or 2, depending on cohort. Assign the baseline ECOG performance status value.

Visceral Disease at baseline can be yes or no; assign as follows:

1 = Yes

0 = No

Number of extracranial disease sites at baseline (will be adjusted based on the distribution of the data if appropriate). Sum the number of unique sites of disease at screening and assign as follows:

1 = More than 3

0 = 2 or fewer

Number of intracranial target lesions at baseline (will be adjusted based on the distribution of the data if appropriate). Sum the number of intracranial target lesions at screening and assign as follows:

4 = 5

3 = 4

2 = 3

1 = 2

0 = 1

Number of intracranial non-target lesions at baseline (will be adjusted based on the distribution of the data if appropriate). Sum the number of intracranial non-target lesions at screening and assign as follows:

4 = 5 or more

3 = 4

2 = 3

1 = 2

0 = 1

Gender covariate: Assign

1 = Female

0 = Male

AGE (continuous)

Age at baseline categorized as follows:

1 = More than 65 years old

0 = No more than 65 years old

The time since initial diagnosis of intracranial disease to treatment category:

1 = At least 1 year

0 = Less than 1 year

The time since initial diagnosis of extracranial disease to treatment category:

1 = At least 1 year

0 = Less than 1 year

Race categorized as follows:

2 = Other

1 = African-American

0 = White

Censoring Date for Progression Free Survival and Duration of Intracranial, Extracranial, and Overall Response

[redacted]

Date of new anti-cancer therapy flag: If the date of new anti-cancer therapy is an imputed date, then set to 'D'. Otherwise set to missing. See Section 9.2.5 for specific rules for imputing partial dates. As multiple dates are used to derive the date of new anti-cancer therapy ensure that the flag is only populated if the derived date is imputed. For example, if the date of new radiotherapy is imputed but the date 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 flag should be set to missing as the date used for the date of new anti-cancer therapy is not an imputed date.

9.2.15. Cut-off date

The analysis cut-off date for the primary analysis of study data will be established. The primary efficacy analysis will be performed when all subjects in cohort A have had the opportunity for three (3) post baseline disease assessments. All statistical analyses will be performed using all data collected in the database up to the data cutoff date. All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations. All events with start date before or on the cut-off date and end date after the cut-off date will be reported as 'ongoing'. The same rule will be applied to events starting before or on the cut-off date and not having documented end date. This approach applies, in particular, to adverse event and concomitant medication reports.

9.3. Study Time Periods

9.3.1. Time in Relation to Treatment

Adverse events, serious adverse events, death, laboratory data, vitals, ECG, and ECHO/MUGA data 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 (time in relation to study treatment) 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 30 days after the last dose date of study treatment.

Extension is defined as the time from overall progression + 1 day to the last dose date of study treatment.

Post-therapy is defined as any time beyond the on-therapy period if study treatment stops then, or after the extension period if study treatment is continued beyond initial progression.

Some datasets include the first dose day as On-therapy and some exclude the first dose date as On-Therapy. The first dose day (Day 1) is considered pre-therapy for ECOG, ECG, vital signs, liver events, lab tests, and cardiac scan. The first dose day (Day 1) is considered to be On-therapy for adverse events and concomitant medications.

9.3.2. Study Time Periods for Concomitant Medications and Blood and Blood Supportive Care Products

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 and end date reference time flag variables will be added to the concomitant medications and blood and blood supportive products datasets, respectively.

- Start **relative to treatment:** 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.
- **End relative to** treatment: 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 or if subject is ongoing (not all study treatment discontinuation records completed) or (end date is missing and start relative to treatment not 'AFTER'). Else assign to 'AFTER' if start date is after the on-therapy period or (end date is missing and start relative to treatment='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 blood and blood supportive care product records where start relative to treatment in ('DURING') and end relative to treatment in ('DURING','AFTER'). All data will be reported in listings.

Concomitant medication start relative to treatment and end relative to treatment flags 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 as they are not concomitant. In addition, any medication that was started during post-therapy will be excluded. Include concomitant medication records where start relative to treatment in ('BEFORE','DURING') and end relative to treatment 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.

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 QTc (Bazett's) 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 QTcB interval	≥450 to <481 (Grade 1) ≥481 to <501 (Grade 2) ≥501 (Grade 3)	Msec
Increase from baseline 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

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'.

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

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
	  o >0-<10 decrease
	  o 10-19 decrease
	  o ≥20 decrease
	  o ≥10 decrease and ≥ LLN
	  o ≥10 decrease and below LLN
	  o >10 decrease and below LLN
	  o ≥20 decrease and ≥ LLN
	  o ≥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 All Treated Subjects population, and all summaries and data listings will use treatment labels as specified in Section 7.

The list of displays for Study Population, including the population to use for each display, is shown in Section 14 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 will be summarized for All Treated Subjects population. Subjects in the All Enrolled population who are not in the All Treated Subjects population will be listed.

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 reasons for study withdrawal. Reasons for study withdrawal will be presented in the order they are displayed in the eCRF.

A summary of study treatment status will be provided. This display will show the number and percentage of subjects who have completed the study, are ongoing, or have discontinued study treatment and a summary of the primary 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.

10.2. Protocol Deviations

All the protocol deviations will be summarized and list the important protocol deviations 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, baseline height, and baseline 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, 18-64, 65-74, and>74. 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 months, stage at initial diagnosis, date of initial diagnosis) at initial diagnosis and screening 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 by past and current cancer-related categories.

A summary of extracranial disease burden at baseline will be produced.

Substance use, including smoking history and alcohol use, will be summarized and listed.

Prior anti-cancer therapy will be coded using WHODrug coding dictionary, then summarized by cohort and listed. A listing of prior anti-cancer therapy will show the relationship between ATC Level 1, Ingredient, and verbatim text. A summary of the number of prior anti-cancer therapy regimens will also be produced.

Prior anti-cancer radiotherapy will be summarized and listed. Prior cancer-related surgeries will be summarized and listed.

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.

A summary of overall compliance for dabrafenib and trametinib based on the exposure data will be produced separately. 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%.

The calculation of overall compliance is based on the entire interval of dosing for dabrafenib and trametinib. The formula for daily dose medication is compliance (%) = [total cumulative actual dose / (duration of study treatment * prescribed dose)]*100 where duration of study treatment is last dose-first dose +1.

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 Section 12.1 ‘Extent of Exposure’.

10.5. Concomitant Medications

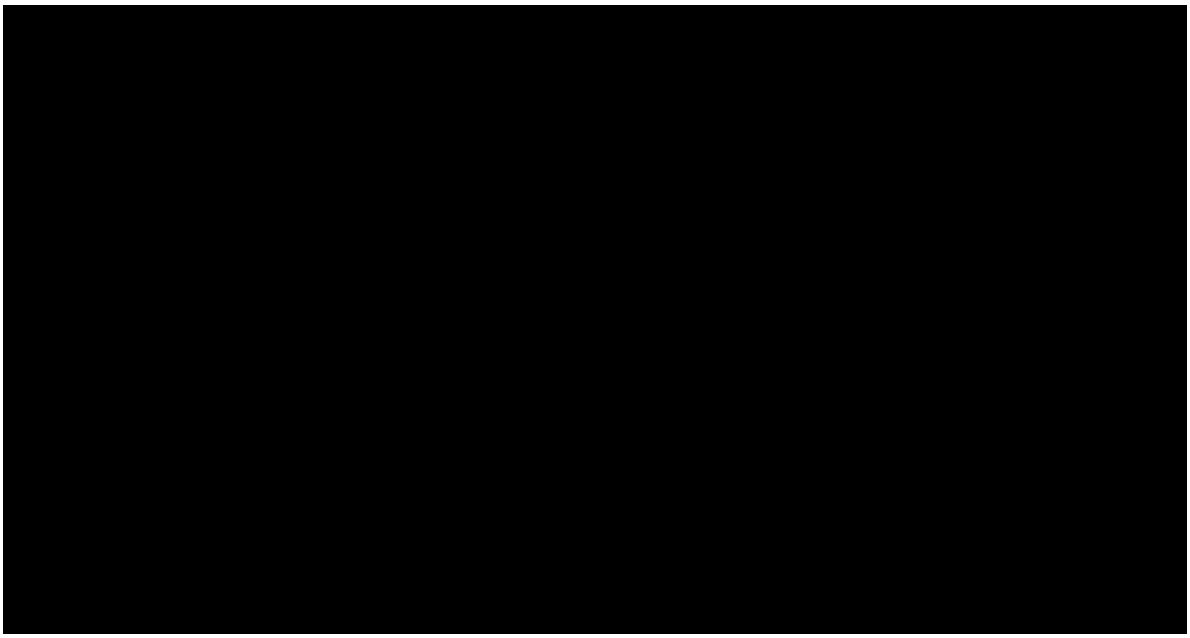
Concomitant medications will be coded using WHODrug coding dictionary, summarized, and listed. The summary of concomitant medications will show the number and percentage of subjects taking concomitant medications by Ingredient. Multi-ingredient products will be summarized by their separate ingredients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

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

In the summary of concomitant medications, the ingredients will be summarized by the base only, using CMBASECD and CMBASE.

A separate listing of prior and concomitant medications of subjects with diabetes at baseline (as reporting on the medical history page of the eCRF) will be produced.

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.



11. EFFICACY

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

Efficacy assessments are based on modified RECIST 1.1. Primary assessments will be based on imaging data. Investigator assessments will be considered as primary assessments. Independent Reviewer assessments, will be supplementary.

Note: If needed, the IRC charter will have further modifications to RECIST 1.1 because of additional instructions needed for the independent review. Specifically, instructions will be provided with respect to ascites, pleural effusion, and subjects with no lesions documented at baseline.

11.1. Primary Efficacy Analysis

Intracranial Response Rate (IRR) in Cohort A

The intracranial response rate (IRR) is defined as the percentage of subjects achieving a confirmed intracranial CR or PR from the start of treatment until disease progression or the start of new anti-cancer therapy. This will be based on investigator-assessed best intracranial response.

Stable intracranial disease requires meeting the SD criteria at least once after the first dose of study treatment at a minimum interval of 8 weeks. As a window of ± 7 days is allowed for scheduling, 7 weeks (or 49 days) will be used for analysis.

To be assigned a status of intracranial PR or CR, a confirmatory disease assessment for intracranial disease should be performed not less than 4 weeks after the criteria for response are first met.

The Independent Reviewer-assessed best intracranial response will also be summarized.

Subjects with Not Evaluable (NE) or missing intracranial response will be treated as non-responders; i.e., they will be included in the denominator when calculating the percentage.

The exact 95% CI for the intracranial response rate will be calculated for both the interim and final analysis.

All data relating to intracranial response from the investigator and, if done, the independent reviewer will be listed, including lesion measurements, response assessments and best response.

A plot of the maximum percent tumor reduction in intracranial target lesions from baseline will be provided. The plot will be color-coded for best intracranial response. The subject number will be indicated on the plot.

Intracranial response will be determined using only intracranial target, non-target, and new lesions, using the criteria specified in the protocol.

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

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

11.2. Secondary Efficacy Analyses

Intracranial Response (IR) in Cohorts B, C, and D

Intracranial response will be summarized for Cohorts B, C, and D as for Cohort A.

Extracranial Response (ER) in Cohorts A, B, C, and D

The extracranial response rate (ERR) is defined as the percentage of subjects achieving a confirmed extracranial CR or PR from the start of treatment until disease progression or the start of new anti-cancer therapy. This will be based on investigator-assessed best extracranial response.

Stable extracranial disease requires meeting the SD criteria at least once after the first dose of study treatment at a minimum interval of 8 weeks. To be assigned a status of extracranial PR or CR, a confirmatory disease assessment for extracranial disease should be performed not less than 4 weeks after the criteria for response are first met.

The Independent Reviewer-assessed best extracranial response will also be summarized.

Subjects with Not Evaluable (NE) or missing extracranial response will be treated as non-responders; i.e., they will be included in the denominator when calculating the percentage.

The exact 95% CI for the extracranial response rate will be calculated.

All data relating to extracranial response from the investigator and, if done, the independent reviewer will be listed, including lesion measurements, response assessments and best response.

A plot of the maximum percent tumor reduction in extracranial target lesions from baseline will be provided. The plot will be color-coded for best extracranial response. The subject number will be indicated on the plot.

Extracranial response will be determined using only extracranial target, non-target, and new lesions, using the criteria specified in the protocol.

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

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

Overall Response (OR) in Cohorts A, B, C, and D

The overall response rate (ORR) is defined as the percentage of subjects achieving a confirmed overall CR or PR from the start of treatment until disease progression or the start of new anti-cancer therapy. This will be based on investigator-assessed best overall response.

Stable disease requires meeting the SD criteria for both intracranial and extracranial disease at least once after the first dose of study treatment at a minimum interval of 8 weeks. To be assigned a status of overall PR or CR, a confirmatory disease assessment for both intracranial and extracranial disease should be performed not less than 4 weeks after the criteria for response are first met.

The Independent Reviewer-assessed best overall response will also be summarized.

Subjects with Not Evaluable (NE) or missing overall response will be treated as non-responders; i.e., they will be included in the denominator when calculating the percentage.

The exact 95% CI for the overall response rate will be calculated.

All data relating to overall response from the investigator and, if done, the independent reviewer will be listed, including lesion measurements, response assessments and best response.

A plot of the maximum percent tumor reduction in overall target lesions from baseline will be provided. The plot will be color-coded for best overall response. The subject number will be indicated on the plot.

Overall response will be determined using both extracranial and intracranial target, non-target, and new lesions, using the criteria specified in the protocol. Overall target lesion response is based on all (that is, intracranial and extracranial) target lesions, up to 10 total. The sum of longest diameters of all intracranial and extracranial target lesions will be used to determine overall response. Unequivocal new intracranial or extracranial (or both) lesions, or unequivocal intracranial or extracranial (or both) non-target lesion progression indicate overall progression. Target, non-target, and new lesion responses are combined as for intracranial and extracranial response to determine response at each disease assessment and best overall response.

- Complete Response (CR): Disappearance of all intracranial and extracranial target lesions. Any pathological lymph nodes must be <10mm in the short axis.
- Partial Response (PR): At least a 30% decrease in the sum of the diameters of intracranial and extracranial target lesions, taking as a reference, the baseline sum of the intracranial and extracranial diameters (e.g. percent change from baseline).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease.
- Progressive Disease (PD): At least a 20% increase in the sum of the diameters of intracranial and extracranial target lesions, taking as a reference, the smallest sum of intracranial and extracranial diameters recorded since the treatment started (e.g.,

percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5mm.

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

Intracranial, Extracranial, and Overall Disease Control in Cohorts A, B, C, and D

The intracranial disease control (IDC), extracranial disease control (EDC), and overall disease control (ODC) are defined as CR+PR+SD for intracranial, extracranial, and overall disease control, respectively. Disease control rates are defined as the percentage of subjects achieving a confirmed overall CR or PR, or SD for at least 8 weeks from the start of study treatment, from the start of treatment until disease progression or the start of new anti-cancer therapy. This will be based on investigator-assessed responses.

The Independent Reviewer-assessed disease control rate will also be summarized.

Subjects with Not Evaluable (NE) or missing intracranial, extracranial, or overall response will be treated as non-responders; i.e., they will be included in the denominator when calculating the percentage.

Exact 95% CIs for the disease control rates will be calculated.

Duration of Intracranial, Extracranial, and Overall Response in Cohorts A, B, C, and D

Duration of intracranial, extracranial, and overall response will be summarized separately for subjects with a confirmed of intracranial, extracranial, or overall CR or PR and is defined as the time (in months) from the initial response (CR/PR) to first documented disease progression or death due to any cause. This will be based on responses from the investigator assessment. Censoring rules will follow those of the primary PFS analysis defined in Section 11.1.

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.

Figures and listings of duration of response will also be provided.

The duration of intracranial, extracranial, and overall response per independent reviewer-assessment will also be summarized. Figures and listings of duration of independent reviewer-assessed response will also be provided.

Progression-Free Survival in Cohorts A, B, C, and D

Progression-Free survival (PFS) is defined as the interval of time (in months) between the date of first dose of study treatment and the earliest of the date of overall disease progression and the date of death due to any cause. Disease progression will be based on assessments by the investigator.

The date of documented disease progression will be defined as the date of overall disease progression based on imaging data. The date of death will be taken from the Record of Death page. Death on study due to any cause will be used.

Subjects who progressed or died after an extended period without adequate intracranial and extracranial assessment will be censored at their date of last adequate intracranial and extracranial assessment prior to progression or death even if subsequent information is available regarding intracranial or extracranial 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. Because the assessment schedule changes during study treatment, specific rules for identifying extended loss to follow-up or extended time without an adequate assessment are provided in Section 9.

[redacted]

If anti-cancer therapy is started without documented overall disease progression or is started prior to documented overall disease progression, then PFS will be censored at the date of the last adequate assessment that is on or before 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). 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 on or before the date of initiation of anti-cancer therapy, PFS will be censored at the date of first dose of study treatment.

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-assessed 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 Event (Progression/Death) or Censoring	Outcome Event (Progression/Death) Or Censored
No *(or inadequate)* baseline intracranial and extracranial tumor assessments and the subject has not died	First dose of study treatment	Censored

Situation	Date of Event (Progression/Death) or Censoring	Outcome Event (Progression/Death) Or Censored
No post-baseline intracranial or extracranial assessments and the subject has not died	First dose of study treatment	Censored
Progression documented between scheduled visits	Date of assessment of earliest source of progression[1]	Event
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 before starting new anti-cancer therapy	Censored
Death before first PD assessment (including death at baseline or prior to any adequate assessments)	Date of death	Event
Death between adequate assessment visits	Date of death	Event
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 intracranial or extracranial lesion (if progression is based on a new lesion); or (ii) date of radiological assessment showing unequivocal progression in intracranial or extracranial non target lesions, or (iii) date of last radiological assessment of measured intracranial and extracranial lesions (if progression is based on increase in sum of measured intracranial and extracranial 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 first dose of study treatment.

PFS will be summarized using Kaplan-Meier estimates. Frequency of patients with PFS events will be presented and also separately by types of PFS event, i.e. progression or death. If there are a sufficient number of progressions or deaths, median PFS, first and third quartiles, and 95% CIs will be estimated using the Brookmeyer-Crowley method [Brookmeyer, 1982]. A figure and listing of progression-free survival time will also be provided.

PFS per independent reviewer-assessment will be summarized. A figure and listing of progression-free survival time per independent reviewer will also be provided.

Overall Survival in Cohorts A, B, C, and D

Overall Survival (OS) is defined as the interval of time (in months) between the date of first dose of study treatment and the date of death due to any cause. For subjects who do not die, time of death will be censored at the date of last contact. The date of death should be taken from that recorded on the Record of Death page. Death on study due to any cause will be included.

The date of last contact will be assigned to the latest date of: Exposure, randomization, death date, follow-up contact, or any actual assessment/procedure date in any data set. The following dates will NOT be included in the date of last contact calculations:

- Date of birth, date of initial cancer diagnosis, date when metastatic disease was first diagnosed, and date of disease staging at screening: These dates are prior to randomization.
- Date of withdrawal from the study: This date may not be associated with an actual subject visit.
- Date of protocol deviation: This date may not be associated with an actual assessment.
- Date of when dispensed investigational product bottles were returned: This date may not be associated with an actual subject visit. For example, a relative could return un-used drugs.
- Date when a sample was analyzed for BRAF mutation: This date is not associated with an actual subject visit.

If there are no post baseline data then the date of randomization will be the last contact date.

Survival will be summarized using the Kaplan-Meier for each cohort. In addition to the Kaplan-Meier estimates for median overall survival time, the first and third quartiles will be presented, along with approximate 95% CIs if there are a sufficient number of deaths.

A graph of survival curves and a listing of survival times will also be provided.

Analyses will be conducted at the time of the primary endpoint analysis as well as at the end of the study.

11.3. Other Efficacy Analyses

Summaries of comparisons between Investigator assessment and Independent Reviewer assessment of the Best intracranial, extracranial and overall Response for each subject will be provided overall by cohort. Also, a summary of comparison between investigator assessment and independent reviewer assessment of progression free survival times will be provided.

Concordance Analysis of Intracranial, Extracranial, and Overall Response Rates

An assessment of the concordance between Independent Reviewer assessment and Investigator Assessment of the Best Intracranial, Extracranial, and Overall Response for each subject will be provided overall across all cohorts. The calculation will be based on the percent agreement (the proportion of response outcomes that agree or match across both Independent Reviewer and Investigator Assessments):

Percent Agreement = (Number of matched responders + Number of matched non-responders) / total number of subjects assessed.

12. SAFETY ANALYSES

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

The list of displays for safety analyses are shown in Section 14 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 months (from first day to last day of treatment) will be summarized. 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: <3 months, 3 months to 6 months, >6 months to 12 months and >12 months.

The subject's average daily dose, defined as the cumulative dose divided by the duration of exposure for each subject, will be summarized.

Dose reductions will be summarized by number of reductions and reasons for reductions for dabrafenib and trametinib separately. Dose interruptions will be summarized by number of interruptions, reasons for the interruptions, and interruption duration (days) for dabrafenib and trametinib separately. 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.

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

12.2. Adverse Events

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 Medical Dictionary for Regulatory Affairs (MedDRA dictionary).

AE summaries will use the following algorithms for counting subjects:

- **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.

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. The same overview summary will be produced by sex and age groups (<65 and ≥ 65 years old)

The frequency and percentage of AEs (all grades) will be summarized and displayed in two ways: 1) in descending order of total incidence by PT only and 2) in descending order of total incidence 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 summary of common (that is, that occurred in strictly 5% of the subjects or above) non-serious AEs 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 SOC and PT.

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.

The relationship between MedDRA SOC, PT, and Verbatim Text will be listed.

A separate summary for dabrafenib related, trametinib related, and dabrafenib and trametinib related AEs 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 by PT only for each drug.

All AEs will be listed. Additionally, a listing of subject IDs for each individual AE will be produced.

12.3. Adverse Events of Special Interest

A comprehensive list of MedDRA terms based on clinical review will be used to identify each type of events. Changes 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 terms to be used for each event of interest and the specific events of interest will be based on the safety review team (SRT) agreements in place at the time of reporting.

An overview summary of AEs of special interest, 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.

The events of special interest include

- Skin related toxicities
- Ocular events
- Cardiac related events
- Hepatic disorders
- Pneumonitis/Interstitial lung disease
- Bleeding events
- Diarrhea
- Hypertension
- Edema
- Hypersensitivity
- Pyrexia
- Cutaneous squamous cell carcinoma including Keratoacanthoma
- Non-Cutaneous Treatment-Emergent Malignancies
- New primary melanoma
- Pre-renal and Intrinsic Renal Failure
- Uveitis
- Hyperglycemia
- Deep vein thrombosis/pulmonary embolism
- Pancreatitis
- Neutropenia

Summaries of the characteristics of each AE of special interest, including the number and percentage of subjects with these events will be provided for each separately. All summaries of AEs of special interest will use the number of subjects with the event as the denominator when calculating percentages. The summary of event characteristics will also be provided, including number of subjects with any event, number of events, number of subjects with any event that is serious, number of subjects with any event that is related to study treatment, the outcome of the event, maximum grade and the action taken for the event. The percentage will be calculated using the number of subjects with the event as the denominator. 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 in response to an event, subjects will be counted once under each action, e.g., if a subject has an event leading to both study treatment discontinuation and dose reduction, the subject will be counted once under both actions.

Summaries of onset for cutaneous squamous cell carcinoma including keratoacanthoma, and new primary melanomas (that is, AEs of special interest for which duration is not meaningful) will be produced. All other AEs of special interest will have summaries of the onset and duration produced.

In addition, subjects with each AE of special interest will be listed separately by AE of special interest.

12.4. Deaths and Serious Adverse Events

Note that if any subject withdraws consent, no data after the date of withdrawing consent, including death, is supposed to appear in the database.

All deaths will be summarized 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). 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 dabrafenib- and trametinib-related SAEs, fatal SAEs and dabrafenib- and trametinib-related fatal SAEs. The summary tables will be displayed in descending order of total incidence by PT only.

A dabrafenib- or trametinib-related SAE is defined as an SAE for which the investigator classifies the relationship dabrafenib or trametinib 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.

12.5. Adverse Events Leading to Discontinuation of Study Treatment and Dose Modifications

The following categories of AEs will be summarized separately in descending order of total incidence by PT only and separate supportive listings will be generated with subject level details for those subjects:

- AEs Leading to Discontinuation of Study Treatment
- AEs Leading to Dose Interruptions
- AEs Leadings 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 or subjects' partner become pregnant while on the study, the information will be included in the 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: White Blood Cell (WBC) count (absolute), Absolute Neutrophil Count (ANC), Hemoglobin (HGB), Hemoglobin A1C, Hematocrit (HCT), Platelet count, Basophils, Eosinphils, Lymphocytes, Moncytes, and Neutrophils. Basophils, Eosinphils, Lymphocytes, Moncytes, and Neutrophils are expressed as percentages. Note that hematocrit is not gradable by CTCAE v4.0.

Clinical Chemistry: Albumin, Gamma-Glutamyl Transpeptidase (GGT), Urea/Blood Urea Nitrogen (BUN), Calcium, Creatinine, Glucose, Lactate Dehydrogenase (LDH), Magnesium, Phosphate, Potassium, and Sodium. BUN and LDH are not gradable by CTCAE v4.0. For Sodium, Potassium, Calcium, and Glucose there will be two bi-directional parameters (hyper and hypo) created, and the tests will be graded by CTCAE v4.0 in both directions.

Liver Function Tests: Aspartateamino transferase (AST), Alanine aminotransferase (ALT), Alkaline phosphatase, and Total bilirubin (total). All these tests are gradable by CTCAE v4.0.

Coagulation Tests: Prothrombin time (PT) or International Normalized Ratio (INR), and activated partial thromboplastin time (APTT). INR and PTT are gradable by CTCAE v4.0 and PT is not. Coagulation tests are only done at baseline.

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

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

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 post-baseline grade increases 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 and worst-case post-baseline. 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, and liver function laboratory tests will be produced. Coagulation test results at baseline will be summarized.

A listing of selected laboratory tests and grades will be provided. A supporting listing of laboratory data for subjects with values outside the normal range will be provided. A separate listing of laboratory data with character values will also be provided.

Detailed derivation of baseline assessment is specified in Section 9.2.7.

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.

Coagulation tests only collected at baseline. Therefore these tests will not appear in any summaries of changes from baseline.

12.7.1. Analyses of Liver Function Tests

Summaries of hepatobiliary laboratory abnormalities 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×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.

LFT patient profiles plots for subjects experiencing an ALT, AST or total bilirubin of toxicity grade 2 or above will be produced.

A plot of maximum total bilirubin versus maximum ALT will be generated.

12.8. Other Safety Measures

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.

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 values will be categorized as follows:

- Systolic 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 (beats/min): <60, 60-100, and >100
- Temperature (°C): <35, 35<= and <38, ≥38

Summaries of increase in vital signs 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 at each scheduled assessment time and in the worst case post-baseline.

A supportive listing will also be provided.

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.

A supporting listing will also be provided.

ECG

The summaries for the QTc will use the collected value only.

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's 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). A summary of grade shifts from baseline value for each scheduled assessment time and in the worst case post-baseline will be provided.

Summaries of grade increase will be provided. These summaries will display the number and percentage of subjects with any grade increase and increase to grade 3 at each scheduled assessment time and in the worst case post-baseline.

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 at each scheduled assessment time and in the worst case post-baseline. Subjects with missing baseline values will be excluded from this summary.

Listings of abnormal ECG findings and a listing of ECG values will be provided. In addition, a listing the QTc data for subjects in each cohort an absolute QTcB interval ≥501 (Grade 3) and an increase from baseline QTcB of >60 at any time in the on-therapy period (that is, these values do not have to be at the same assessment but the subject must be on study treatment or within 30 days of the last dose of study treatment) will be produced.

A figure plotting the baseline QTc and the worst-case post-baseline values will be produced. The figure will have reference lines at 450 and 500 msec for both the ordinate and the abscissa axes. There will be diagonal reference lines at equality (i.e., a 45 degree line), at equality plus 30 msec, and at equality plus 60 msec.

LVEF

Absolute change from baseline in LVEF will be summarized at each scheduled assessment time and in the worst case post-baseline. 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 ≥ LLN
- ≥10% decrease and < 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 RUCUM 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 and Week 4 data will be summarized based on the number and percentage of subjects who receive an ocular exam. Because post-baseline exams are only performed as clinically indicated, data beyond Week 4 will only be listed.

13. REFERENCES

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14. ATTACHMENTS

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Table	Efficacy	2.2010	Overall Response by Cohort Kaplan-Meier Estimates of Independent Reviewer-Assessed
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Table	Efficacy	2.7010	Summary of Concordance Between Investigator-Assessed and Independent Reviewer-Assessed Best Intracranial Response (with confirmation) (Modified RECIST 1.1 Criteria)
Table	Efficacy	2.7020	Summary of Concordance Between Investigator-Assessed and Independent Reviewer-Assessed Best Extracranial Response (with confirmation) (Modified RECIST 1.1 Criteria)
Table	Efficacy	2.7030	Summary of Concordance Between Investigator-Assessed and Independent Reviewer-Assessed Best Overal Response (with confirmation) (Modified RECIST 1.1 Criteria)
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Table	Safety	3.0040	Summary of Dose Reductions by Cohort (Dabrafenib)
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Table	Safety	3.1510	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment by Cohort
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Table	Safety	3.1614	Summary of Onset of the First Occurrence of New Primary Melanoma
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Table	Safety	3.1622	Summary of Characteristics of Hypertension
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Table	Safety	3.1625	Summary of Characteristics of Diarrhea
Table	Safety	3.1626	Summary of Onset and Duration of the First Occurrence of Diarrhea
Table	Safety	3.1628	Summary of Characteristics of Ocular Events
Table	Safety	3.1629	Summary of Onset and Duration of the First Occurrence of Ocular Events
Table	Safety	3.1631	Summary of Characteristics of Pneumonitis/Interstitial lung disease

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Table	Safety	3.1652	Summary of Characteristics of Hepatic Disorders
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Table	Safety	3.1655	Summary of Characteristics of Pyrexia
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Table	Safety	3.1661	Summary of Characteristics of Hyperglycemia
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Table	Safety	3.1664	Summary of Characteristics of Hypersensitivity
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Table	Safety	3.3020	Summary of Chemistry Grade Changes from Baseline Grade
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Table	Safety	3.4010	Summary of Vital Signs by Cohort
Table	Safety	3.4020	Summary of Vital Sign Changes from Baseline by Cohort
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Table	Safety	3.4110	Summary of ECOG performance Status by Cohort
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Table	Safety	3.6010	Summary of ECG Findings by Cohort
Table	Safety	3.6030	Summary of Increases in QTc (Bazett's) from Baseline by Cohort

Table	Safety	3.6040	Summary of Amount of Increase from Baseline Value in QTc (Bazett's) by Cohort
Table	Safety	3.6050	Summary of QTc (Bazett's) Shifts from Baseline Value by Cohort
Table	Safety	3.8010	Summary of Liver Chemistry Assessments for Subjects with Liver Signal/Event by Cohort
Table	Safety	3.8020	Summary of Hepatobiliary Laboratory Abnormalities by Cohort
Table	Safety	3.8030	Summary of Liver Event Information for RUCAM Score by Cohort
Table	Safety	3.9010	Summary of Ophthalmic Examinations by Cohort
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Figure	Efficacy	12.0020	Graph of Kaplan Meier Investigator-Assessed Duration of Intracranial Response Curve by Cohort
Figure	Efficacy	12.0021	Graph of Kaplan Meier Investigator-Assessed Duration of Extracranial Response Curve by Cohort
Figure	Efficacy	12.0022	Graph of Kaplan Meier Investigator-Assessed Duration of Overall Response Curve by Cohort
Figure	Efficacy	12.0011	Graph of Kaplan Meier Independent Reviewer-Assessed Progression Free Survival Curve by Cohort
Figure	Efficacy	12.0023	Graph of Kaplan Meier Independent Reviewer-Assessed Duration of Intracranial Response Curve by Cohort
Figure	Efficacy	12.0024	Graph of Kaplan Meier Independent Reviewer-Assessed Duration of Extracranial Response Curve by Cohort
Figure	Efficacy	12.0025	Graph of Kaplan Meier Independent Reviewer-Assessed Duration of Overall Response Curve by Cohort
Figure	Efficacy	12.0030	Graph of Kaplan Meier Overall Survival Curves by Cohort
Figure	Efficacy	12.0040	Investigator-Assessed Percent Change at Maximum Reduction from Baseline in Intracranial Tumour Measurement by Cohort
Figure	Efficacy	12.0041	Independent Reviewer-Assessed Percent Change at Maximum Reduction from Baseline in Intracranial Tumour Measurement by Cohort
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Figure	Safety	12.0070	Figure of Maximum Total Bilirubin vs Maximum ALT by Cohort – eDISH Plot
Listing	Study Pop	21.0010	Listing of Planned and Actual Treatments
Listing	Study Pop	21.0020	Listing of Subjects Excluded from Analysis Population
Listing	Study Pop	21.0030	Listing of Reasons for Study Withdrawal

Listing	Study Pop	21.0040	Listing of Dabrafenib Discontinuation Record
Listing	Study Pop	21.0041	Listing of Trametinib Discontinuation Record
Listing	Study Pop	21.0050	Listing of Subjects with Inclusion/Exclusion Criteria Deviations
Listing	Study Pop	21.0060	Listing of Protocol Deviations
Listing	Study Pop	21.0070	Listing of Demographic Characteristics
Listing	Study Pop	21.0080	Listing of Race
Listing	Study Pop	21.0090	Listing of Overall Compliance (Dabrafenib)
Listing	Study Pop	21.0091	Listing of Overall Compliance (Tramatinib)
Listing	Study Pop	21.0100	Listing of Drug Accountability (Dabrafenib)
Listing	Study Pop	21.0101	Listing of Drug Accountability (Tramatinib)
Listing	Efficacy	22.0010	Listing of Investigator-Assessed Progression-Free Survival
Listing	Efficacy	22.0011	Listing of Independent Reviewer-Assessed Progression-Free Survival
Listing	Efficacy	22.0020	Listing of Overall Survival
Listing	Efficacy	22.0030	Listing of Investigator-Assessed Duration of Response
Listing	Efficacy	22.0031	Listing of Independent Reviewer-Assessed Duration of Response
Listing	Efficacy	22.0040	Listing of Investigator-Assessed Target Lesion Assessments (modified RECIST 1.1 Criteria)
Listing	Efficacy	22.0050	Listing of Investigator.-Assessed Non-Target Lesion Assessments (modified RECIST 1.1 Criteria)
Listing	Efficacy	22.0060	Listing of Investigator-Assessed New Lesions (modified RECIST 1.1 Criteria)
Listing	Efficacy	22.0041	Listing of Independent Reviewer-Assessed Target Lesion Assessments (modified RECIST 1.1 Criteria)
Listing	Efficacy	22.0051	Listing of Independent Reviewer-Assessed Non-Target Lesion Assessments (modified RECIST 1.1 Criteria)
Listing	Efficacy	22.0061	Listing of Independent Reviewer-Assessed New Lesions (modified RECIST 1.1 Criteria)
Listing	Efficacy	22.0070	Listing of Investigator-Assessed Tumour Responses (with confirmation) (modified RECIST1.1 Criteria)
Listing	Efficacy	22.0071	Listing of Independent Reviewer.-Assessed Tumour Responses (with confirmation) (modified RECIST1.1 Criteria)

Listing	Safety	23.0010	Listing of Exposure to Dabrafenib
Listing	Safety	23.0011	Listing of Exposure to Trametinib
Listing	Safety	23.0020	Listing of Dose Reductions of Dabrafenib
Listing	Safety	23.0021	Listing of Dose Reductions of Trametinib
Listing	Safety	23.0030	Listing of Dose Interruptions of Dabrafenib
Listing	Safety	23.0031	Listing of Dose Interruptions of Trametinib
Listing	Safety	23.0090	Listing of Relationship Between System Organ Class, Preferred Term, and Verbatim Text
Listing	Safety	23.0100	Listing of Subject Numbers for Individual Adverse Events
Listing	Safety	23.0110	Listing of All Adverse Events
Listing	Safety	23.0120	Listing of Fatal Serious Adverse Events
Listing	Safety	23.0130	Listing of Non-Fatal Serious Adverse Events
Listing	Safety	23.0140	Listing of Adverse Events Leading to Permanent Discontinuation of Dabrafenib
Listing	Safety	23.0141	Listing of Adverse Events Leading to Permanent Discontinuation of Trametinib
Listing	Safety	23.0150	Listing of Adverse Events that Lead to Dose Interruptions of Dabrafenib
Listing	Safety	23.0151	Listing of Adverse Events that Lead to Dose Interruptions of Trametinib
Listing	Safety	23.0200	Listing of Non-Cutaneous Treatment Emergent Malignancies
Listing	Safety	23.0201	Listing of Cardiac-Related Events
Listing	Safety	23.0202	Listing of Hypertension
Listing	Safety	23.0203	Listing of Diarrhea
Listing	Safety	23.0204	Listing of Ocular Events
Listing	Safety	23.0205	Listing of Pneumonitis/Interstitial lung disease
Listing	Safety	23.0206	Listing of Skin-Related Toxicities
Listing	Safety	23.0207	Listing of Neutropenia

Listing	Safety	23.0208	Listing of Uveitis
Listing	Safety	23.0209	Listing of Deep Vein Thrombosis/Pulmonary Embolism
Listing	Safety	23.0210	Listing of Edema
Listing	Safety	23.0211	Listing of Pre-renal and Intrinsic Renal Failure
Listing	Safety	23.0212	Listing of Hepatic Disorders
Listing	Safety	23.0213	Listing of New Primary Melanoma
Listing	Safety	23.0214	Listing of Cutaneous Squamous Cell Carcinoma including Keratoacanthoma
Listing	Safety	23.0215	Listing of Pyrexia
Listing	Safety	23.0216	Listing of Pancreatitis
Listing	Safety	23.0217	Listing of Hyperglycemia
Listing	Safety	23.0218	Listing of Hypersensitivity
Listing	Safety	23.0219	Listing of Bleeding Events
Listing	Safety	23.0250	Listing of Deaths
Listing	Safety	23.0260	Listing of All Laboratory Data
Listing	Safety	23.0270	Listing of Laboratory Data for Subjects with Lab Values Outside of Normal Range
Listing	Safety	23.0280	Listing of ECOG Performance Status
Listing	Study Pop	30.0010	Listing of Tobacco Use
Listing	Study Pop	30.0011	Listing of Alcohol Consumption
Listing	Study Pop	30.0020	Listing of Past Medical Conditions
Listing	Study Pop	30.0021	Listing of Current Cancer-Related Medical Conditions
Listing	Study Pop	30.0030	Listing of Disease Characteristics at Initial Diagnosis
Listing	Study Pop	30.0040	Listing of Disease Characteristics at Screening
Listing	Study Pop	30.0050	Listing of Prior Anti-Cancer Therapy

Listing	Study Pop	30.0060	Listing of Prior Anti-Cancer Radiotherapy
Listing	Study Pop	30.0070	Listing of Prior Cancer-Cancer Related Surgical Procedures
[redacted]			
Listing	Study Pop	30.0090	Listing of Concomitant Medications
Listing	Efficacy	30.0130	Listing of Subjects with a Difference between Investigator-Assessed and Independent Reviewer-Assessed Tumour Response (with confirmation) (modified RECIST 1.1 Criteria)
Listing	Efficacy	30.0140	Listing of Subjects with a Difference between Investigator-Assessed and Independent Reviewer-Assessed Best Tumor Response
Listing	Safety	30.0220	Listing of Subject Numbers for Specific Causes of Deaths
Listing	Safety	30.0240	Listing of Abnormal ECG Findings
Listing	Safety	30.0250	Listing of ECG Values
Listing	Safety	30.0270	Listing of Vital Signs
Listing	Safety	30.0280	Listing of Left Ventricular Ejection Fraction Results
Listing	Safety	30.0290	Listing of Liver Chemistry Assessments for Subjects with Liver Signal/Events
Listing	Safety	30.0300	Listing of Liver Laboratory Tests and Grade
Listing	Safety	30.0330	Listing of Ophthalmic Examinations

14.1.1. Data Display Deliverables

All displays in Section 14.1 will be provided at the time of the primary endpoint analysis.

The following displays from Section 14.1 will be provided for the interim analysis:

Table No.	*Title*
1.0010	Summary of Study Populations by Cohort
1.1110	Summary of Subject Disposition by Cohort
1.1220	Summary of Study Treatment Status For Trametinib by Cohort

1.1221 Summary of Study Treatment Status For Dabrafenib by Cohort

1.2010 Summary of Demographic Characteristics by Cohort

1.2110 Summary of Extracranial Disease Burden at Baseline by Cohort

1.3220 Summary of Disease Characteristics at Screening By Cohort

1.4020 Summary of Prior Dictionary Coded Anti-Cancer Therapy by Cohort

1.4030 Summary of Number of Prior Anti-Cancer Therapy Regimens by Cohort

1.5010 Summary of Concomitant Medications by Cohort

2.1009 Investigator-Assessed Best Intracranial Response (with confirmation) (modified RECIST 1.1 Criteria) for Cohort A (Interim Analysis)

2.1010 Investigator-Assessed Best Intracranial Response (with confirmation) (modified RECIST 1.1 Criteria) for Cohort A (Primary Analysis)

2.1011 Investigator-Assessed Best Intracranial Response (with confirmation) (modified RECIST 1.1 Criteria) for Cohorts B, C, and D

2.1012 Investigator-Assessed Best Extracranial Response (with confirmation) (modified RECIST 1.1 Criteria) by Cohort

2.1013 Investigator-Assessed Best Overall Response (with confirmation) (modified RECIST 1.1 Criteria) by Cohort

3.0010 Summary of Exposure to Dabrafenib by Cohort

3.0011 Summary of Exposure to Trametinib by Cohort

3.1010 Adverse Event Overview by Cohort

3.1070 Summary of Adverse Events By Maximum Grade by Cohort

3.1090 Summary of Adverse Events of Special Interest by Maximum Grade and Cohort

3.1110 Summary of Adverse Events Related to Dabrafenib by Cohort

3.1111 Summary of Adverse Events Related to Trametinib by Cohort

3.1210 Summary of Serious Adverse Events by Cohort

3.1410 Summary of Fatal Adverse Events by Cohort

3.1510 Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment by Cohort

3.1520 Summary of Adverse Events Leading to Dose Reductions by Cohort

3.1530	Summary of Adverse Events Leading to Dose Interruptions by Cohort
3.1600	Adverse Events of Special Interest Overview by Cohort
3.2010	Summary of Deaths by Cohort
3.3020	Summary of Chemistry Grade Changes from Baseline Grade
3.3021	Summary of Hematology Grade Changes from Baseline Grade by Cohort
3.3020	Summary of Liver Function Test Grade Changes from Baseline Grade by Cohort
3.3030	Summary of Chemistry Changes from Baseline With Respect to the Normal Range
3.3031	Summary of Hematology Changes from Baseline With Respect to the Normal Range
3.3032	Summary of Liver Function Test Changes from Baseline With Respect to the Normal Range
3.4020	Summary of Vital Sign Changes from Baseline by Cohort
3.4040	Summary of Increases in Systolic Blood Pressure from Baseline by Cohort
3.4090	Summary of Left Ventricular Ejection Fraction Change from Baseline by Cohort
3.6010	Summary of ECG Findings by Cohort
3.6030	Summary of Increases in QTc (Bazett's) by Cohort
3.6040	Summary of Amount of Increase from Baseline Value in QTc (Bazett's) by Cohort
3.6050	Summary of QTc (Bazett's) Shifts from Baseline Value by Cohort
3.8010	Summary of Liver Chemistry Assessments for Subjects with Liver Signal/Event by Cohort
3.8020	Summary of Hepatobiliary Laboratory Abnormalities by Cohort
3.8030	Summary of Liver Event Information for RUCAM Score by Cohort

The displays for the **End of Study** analysis will be provided in a separate TFL document:

14.2. Data Display Specifications

The data display specifications are contained in a separate document. The display mock-ups are provided as a guideline. The final formats and layouts may be revised due to potential limitations of the programs and tools used to produce the displays.