Protocol C4221006 (ARRAY-818-201)

A Phase 2, Open-Label, Randomized, Multicenter Trial of Encorafenib + Binimetinib Evaluating a Standard-dose and a High-dose Regimen in Patients With *BRAF*V600-Mutant Melanoma Brain Metastasis

Statistical Analysis Plan
(SAP)

Version: **2.0**

Date: 18 September 2020

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1. VERSION HISTORY

Table 1: Summary of Change

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1.0/ 17 June 2020	2.0/ 13 March 2020	Not Applicable	Not Applicable
2.0/ 18 September 2020	3.0/ 07 August 2020	Updates per protocol amendment v3.0; Pfizer SAP template is used and the standard lanague and methods included in the Pfizer Oncology Statistics Rulebook are adopted	1. General – Added data analysis and summary to address COVID-19 related issues. 2. Section 2 – Added explanation that this version of SAP is based on the outcome of the Safety Lead-in that the high-dose treatment of encorafenib was not included in Phase 2. Therefore no randomization is used in Phase 2. 3. Section 4 – Deleted Per-protocol analysis set. CCI [redacted] Minor updates on Safety Set and PK Set. 4. Section 5.2 – Added additional information on general methods per Pfzier Oncology Statistics Rulebook. 5. Section 5.2.5 – Updated on-treatment period definition to include all subsequent anticancer therapies (not just anticancer drug therapy). 6. Section 6.2.5 – Updated PFS cenoring reasons and hierarchy per Pfizer Oncology Statistics Rulebook. 7. Section 6.3.1 – Revised the list of PK parameters to be estimated and reported, when feasible and appropriate. CCI [redacted] 9. Section 6.6 – Deleted body weight, ECOG PS, dermatologic, ECHO/MUGA and ophthalmic examination data descriptive summary per Pfizer TLFs reduction recommendation. Deleted listing of dermatological examination and physical examination as minimum data are collected for these parameters. CCI [redacted] 10. Section 6.6.1 – Added AE summary for patients escalating to 600 mg encorafenib in Phase 2.

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C4221006 (ARRAY-818-201). This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint and key secondary endpoint definition or corresponding analyses will also be reflected in a protocol amendment.

The study plans to have two parts with Safety Lead-in followed by Phase 2. At the time of this document development, 3 dose-limiting toxicities (DLTs) have been observed in 9 evaluable patients enrolled in the Safety Lead-in of the study. The protocol defines the high-dose regimen of 300mg BID encorafenib + 45mg QD binimetinib combination therapy deemed not safe if 3 DLTs or more (ie, ≥33%) are observed in 9 evaluable patients in the Safety Lead-in. Therefore the study continues to Phase 2 without the high-dose regimen. The SAP version 2.0 is developed based on this study design scenario, ie, if the high-dose treatment is determined not to be safe in the Safety Lead-in, no patients will be enrolled into the high-dose arm, up to 100 patients will be enrolled into 2 cohorts in the standard-dose arm and no randomization will be used in the Phase 2 part of the study.

2.1. Study Objectives, Endpoints, and Estimands

Primary Objective	Primary Endpoint
Safety Lead-in • Evaluate the safety of a high-dose regimen of encorafenib + binimetinib combination therapy in patients with *BRAF*V600-mutant melanoma who have asymptomatic brain metastasis.	**Safety Lead-in** • Incidence of DLTs. • Incidence and severity of AEs graded according to the NCI CTCAE version 4.03 and changes in clinical laboratory parameters, vital signs and ECGs. • Incidence of dose interruptions, dose modifications and discontinuations due to AEs.
Phase 2 If the high-dose regimen is determined to be safe based on the results of the Safety Lead-in phase, then • Evaluate the antitumor activity in brain metastases of the standard and high dose regimens of encorafenib + binimetinib combination therapy in patients with *BRAF*V600-mutant melanoma who have asymptomatic brain metastasis.	**Phase 2** • BMRR per mRECIST v1.1.

<u>If the high-dose regimen is determined **not** to be safe based on the results of the Safety Lead-in phase, then</u> • Evaluate the antitumor activity in brain metastases of the standard dosing regimen of encorafenib + binimetinib combination in patients with *BRAF*V600-mutant melanoma who have asymptomatic brain metastasis.	
Secondary Objectives	**Secondary Endpoints**

• Further evaluate the antitumor activity of encorafenib + binimetinib combination therapy in patients with *BRAF*V600-mutant melanoma who have asymptomatic brain metastasis.	• Extracranial response rate per RECIST v1.1.
	• Global response rate (brain metastasis response per mRECIST v1.1 and extracranial response per RECIST v1.1).
	• DCR:
	  • for brain metastasis response per mRECIST v1.1;
	  • for extracranial response per RECIST v1.1;
	  • for global response (brain metastasis per mRECIST v1.1 and extracranial per RECIST v1.1).
	• DOR:
	  • for brain metastasis response per mRECIST v1.1;
	  • for extracranial response per RECIST v1.1;
	  • for global response (brain metastasis per mRECIST v1.1 and extracranial per RECIST v1.1).
	• PFS:
	  • for brain metastasis per mRECIST v1.1;
	  • for global assessment (brain metastasis per mRECIST v1.1 and extracranial disease per RECIST v1.1).
	• BMRR per mRECIST v1.1 for Safety Lead-in only.

• Evaluate the efficacy of encorafenib + binimetinib combination therapy as measured by OS in patients with *BRAF*V600-mutant melanoma who have asymptomatic brain metastasis.	• OS.
• Further evaluate the safety profile of encorafenib + binimetinib combination therapy in patients with *BRAF*V600-mutant melanoma who have asymptomatic brain metastasis.	• Incidence and severity of AEs graded according to the NCI CTCAE version 4.03 and changes in clinical laboratory parameters, vital signs and ECGs.
• Characterize the PK of encorafenib and its metabolite LHY746, and binimetinib and its metabolite AR00426032.	• Plasma concentration-time profiles and PK parameter estimates for encorafenib and its metabolite LHY746, and binimetinib and its metabolite AR00426032.
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2.1.1. Primary Estimands

Phase 2

The primary estimand in Phase 2 is the treatment effect of encorafenib + binimetinib combination therapy in confirmed brain metastasis response rate (BMRR) by Investigator assessment per modified Response Evaluation Criteria in Solid Tumors version 1.1 (mRECIST v1.1). The estimand has the following attributes:

- Population: all patients as defined by the inclusion/exclusion criteria in Section 5.1 and Section 5.2 in the study protocol and with a central laboratory confirmed result of *BRAF*V600 to reflect the patients targeted by the clinical question.

- Variable: brain metastasis response defined as best overall response (BOR) of confirmed complete response (CR) or confirmed partial response (PR) in brain metastasis by Investigator assessment per mRECIST v1.1 from date of the first dose until disease progression, death due to any cause, or start of subsequent anticancer therapy, whichever occurs first.

- Intercurrent events: hypothetical strategy will be applied for the intercurrent event of starting new anticancer therapy. Any tumor assessments after starting subsequent anticancer therapy will be excluded in the calculation of BMRR.

- Population-level summary measure: BMRR defined as proportion of patients who have achieved a confirmed BOR of CR or PR in brain metastasis by Investigator assessment per mRECIST v1.1 and corresponding exact Clopper-Pearson 2-sided 90% confidence interval (CI) and 95% CI.

2.1.2. Additional Estimands

Supportive Estimand 1 (BMRR):

- Population: same as primary estimand of BMRR.

- Variable: confirmed + unconfirmed brain metastasis response defined as BOR of confirmed or unconfirmed CR or PR in brain metastasis by Investigator assessment per mRECIST v1.1 from date of the first dose until disease progression, death due to any cause, or start of subsequent anticancer therapy, whichever occurs first.

- Intercurrent events: same as primary estimand of BMRR.

- Population-level summary measure: confirmed + unconfirmed BMRR defined as proportion of patients who have achieved a BOR of confirmed or unconfirmed CR or PR in brain metastasis by Investigator assessment per mRECIST v1.1 and corresponding exact Clopper-Pearson 2-sided 95% CI.

Supportive Estimand 2 (BMRR):

- Population: all patients as defined by the inclusion/exclusion criteria in Section 5.1 and Section 5.2 in the study protocol to reflect the patients targeted by the clinical question.

- Variable: same as primary estimand of BMRR.

- Intercurrent events: same as primary estimand of BMRR.

- Population-level summary measure: BMRR and corresponding exact Clopper-Pearson 2-sided 95% CI.

2.2. Study Design

This is a multicenter, randomized open-label Phase 2 study to assess the safety, efficacy and PK of 2 dosing regimens of encorafenib + binimetinib combination therapy in patients with *BRAF*V600-mutant melanoma with asymptomatic brain metastasis. Approximately 110 eligible patients will be enrolled, including 9 patients in a single-arm Safety Lead-in. After a Screening Period, treatment will be administered in 28-day cycles and will continue until disease progression, unacceptable toxicity, withdrawal of consent, start of subsequent anticancer therapy, death. Once the patient discontinues study treatment, the Treatment Period will end, and the patient will enter the Follow-up Period.

The first 9 evaluable patients in the high-dose treatment will constitute the high-dose Safety Lead-in cohort.

As the high-dose treatment is determined not to be safe in the Safety Lead-in, no patients will be enrolled into Arm B, and up to 100 patients will be enrolled into 2 cohorts in the standard-dose Arm A:

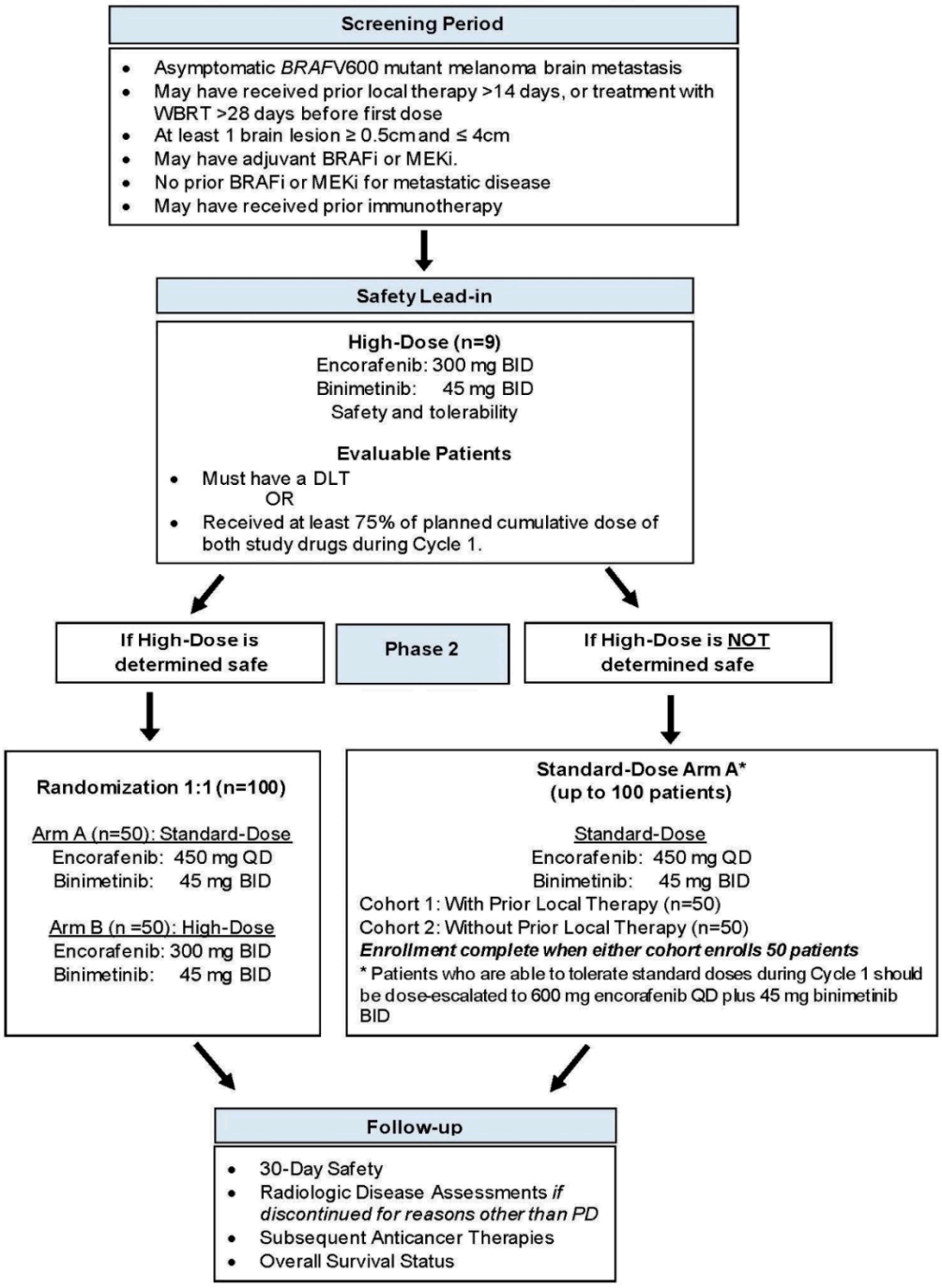
- **Cohort 1:** Up to 50 patients with *BRAF*V600 cutaneous melanoma with metastases to the brain confirmed by MRI, asymptomatic, and with prior local therapy (eg, stereotactic radiosurgery [SRS] or stereotactic radiotherapy [SRT]).

- **Cohort 2:** Up to 50 patients with *BRAF*V600 cutaneous melanoma with metastases to the brain confirmed by MRI, asymptomatic, without prior local therapy (eg, SRS or SRT). Phase 2 enrollment will close when either Cohort 1 or 2 reaches approximately 50 patients.

Patients who are able to tolerate the standard dose of encorafenib (450 mg QD) plus binimetinib (45 mg BID) during the first 4 weeks of treatment (Cycle 1) should be dose-escalated to 600 mg encorafenib QD plus 45 mg binimetinib BID provided they meet the criteria defined in Section 6.7.2 in the protocol.

A schematic of the study design is presented in Figure 1

Figure 1: Study Schema



3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Safety Lead-in

3.1.1. Primary Endpoint

The primary endpoint for the Safety Lead-in is incidence of DLTs estimated based on data from DLT-evaluable patients during Cycle 1. A DLT is defined as any AE or laboratory abnormality (unexplained by underlying disease, disease progression, intercurrent illness, or concomitant therapies) that either meets the criteria described in the study protocol (Table 7) or results in the inability to tolerate at least 75% of the planned dose of binimetinib or encorafenib during Cycle 1.

3.2. Phase 2

3.2.1. Primary Endpoint

Confirmed BMRR is defined as the proportion of patients who have achieved a BOR of confirmed CR or confirmed PR by Investigator assessment in brain metastasis per mRECIST v1.1.

The definition of BOR is described in Section 6.1.2.

3.2.2. Efficacy Secondary Endpoints

3.2.2.1. Extracranial Response Rate

Extracranial response rate is defined as the proportion of patients with a BOR of confirmed CR or confirmed PR in extracranial lesions by Investigator assessment per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1).

3.2.2.2. Global Response Rate

Global response rate is defined as the proportion of patients with a BOR of confirmed CR or confirmed PR by Investigator assessment in brain metastasis and extracranial lesions per mRECIST v1.1 and RECIST v1.1, respectively.

3.2.2.3. Disease Control Rate

Disease control rate (DCR) is defined as the proportion of patients with a BOR of CR, PR or SD by Investigator assessment.

3.2.2.4. Duration of Response

Duration of response (DOR) is defined as the time from date of the first radiographic response (CR or PR) to the earliest documented disease progression or death due to any cause.

3.2.2.5. Progression-free Survival

Progression-free survival (PFS) is defined as the time from date of the first dose of study treatment to the earliest documented disease progression by Investigator assessment, or death due to any cause, whichever occurs first. If a patient has not had a PFS event at the time of the analysis cutoff or at the start of any new anticancer therapy, PFS is censored at the date of last adequate tumor assessment.

3.2.2.6. Overall Survival

Overall survival (OS) is defined as the time from date of the first dose of study treatment to the date of death due to any cause. If a death has not been observed by the date of the analysis cutoff, OS will be censored at the date of last contact.

3.2.3. Other Secondary Endpoints

3.2.3.1. Pharmacokinetic Endpoints

- Plasma concentration-time profiles and PK parameter estimates for encorafenib and its metabolite LHY746, and binimetinib and its metabolite AR00426032.

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3.3. Baseline Variables

The date of first dose of study treatment is the earliest date of non-zero dosing of any study drug. The date of last dose of study treatment is the latest date of non-zero dosing of any study drug.

Baseline is defined as the last completed assessment performed prior to the first dose date/time. If an assessment that is planned to be performed prior to the first dose of study treatment per the protocol is performed on the same day as the first dose of study drug and the time is unknown, it will be assumed that it was performed prior to study treatment administration and will be considered as baseline assessment.

Unscheduled assessments may be considered baseline assessment if they meet the criteria above. Data reported at the End of Treatment (EOT) visit are not eligible for baseline selection. The ECG baseline will be the average of triplicate ECG measurements obtained before the start of treatment on cycle 1 day 1.

3.4. Safety Endpoints

Safety endpoints will be summarized based on the on-treatment period unless otherwise specified. Safety data collected outside the on-treatment period will be listed but not summarized.

3.4.1. Adverse Events

An AE is considered a treatment-emergent adverse event (TEAE) if the event starts on or after the first dosing day and time/start time, if collected, but before the last dose +30 days, or start of subsequent anticancer *drug* therapy minus 1 day, whichever occurs first. Any events that started prior to date of the first dose are not considered TEAEs. If an AE starts on the same day as date of the first dose, it will be considered treatment emergent unless the CRF data indicates otherwise via explicitly recording time for AE onset and treatment dosing.

Adverse events will be coded using current Medical Dictionary for Regulatory Activities (MedDRA). Severity of AEs will be graded using the NCI-CTCAE v 4.03 toxicity grading scale.

3.4.2. Laboratory Data

Hematology, chemistry and coagulation tests results will be programmatically graded according to the NCI CTCAE version 4.03 for relevant parameters. Additional details are provided in Section 6.6.3.

3.4.3. Vital Signs Data

Vital signs data includes weight, pulse, systolic blood pressure (BP), and diastolic BP will be summarized. Additional details are provided in Section 6.6.4.

3.4.4. Electrocardiograms Data

Clinically notable ECG values during the on-treatment period will be summarized. Additional details are provided in Section 6.6.5.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all patients will be assessed to determine if patients meet the criteria for inclusion in each analysis population prior to releasing the database and classifications will be documented per standard operating procedures.

Patient Analysis Set	Description
Enrolled	All patients who sign the informed consent form (ICF). Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled.
Dose-determining Set	All patients enrolled in the high-dose treatment arm in the Safety Lead-in who complete one 28-day cycle of treatment and receive at least 75% of the planned cumulative dose of both study drugs or discontinue treatment because of DLT.
Full Analysis Set (FAS)	The FAS includes all patients who receive at least 1 dose of any study drug in the Phase 2 portion of the study.
Efficacy Set	The Efficacy Set includes all FAS patients who receive at least 1 dose of any study drug in the Phase 2 portion of the study and have their *BRAF*V600 mutation status confirmed by central laboratory. Unless otherwise specified, the Efficacy Set will be the default analysis set used for all efficacy analyses.
Safety Set	The Safety Set includes all patients who receive at least 1 dose of any study drug. Unless otherwise specified, the Safety Set will be the default analysis set used for all safety analyses.
PK Set	The PK Set includes all patients who receive at least 1 dose of any study drug and have at least 1 PK blood collection after the first dose of study drug with associated bioanalytical results. The PKS will be used for summaries and listings of PK data.
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5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

5.1.1. Hypotheses and Sample Size Calculation

The planned sample size of the study is approximately 110 patients including approximately 9 patients in the Safety Lead-in, and approximately 100 patients in the Phase 2 portion of the study.

5.1.1.1. Safety Lead-in

There is no statistical hypothesis for the Safety Lead-in.

The primary endpoint of the Safety Lead-in is incidence of DLTs. Up to 9 evaluable patients will be enrolled to receive the high-dose encorafenib + binimetinib combination therapy. The safety and PK data will be evaluated by the Steering Committee after these 9 evaluable patients have been followed for a minimum of 28 days.

5.1.1.2. Phase 2

The sample size calculation is based on the primary endpoint of BMRR per mRECIST v1.1 by Investigator assessment. The study is designed to test the null hypothesis of BMRR ≤30% for patients with *BRAF*V600-mutant melanoma brain metastasis, which is considered not sufficiently clinically meaningful to warrant further study. The alternative hypothesis is BMRR >30% with the assumption that the true BMRR is at least 50%.

If the high-dose treatment is determined not to be safe in the Safety Lead-in, no patients will be enrolled into the high-dose treatment arm. Up to 100 eligible patients will be enrolled into 2 cohorts in the standard-dose treatment arm. Phase 2 enrollment will close when either Cohort 1 or 2 reaches the enrollment of 50 patients. The sample size consideration is based on an exact binomial test with a 1-sided alpha of 0.05 for each cohort.

- **Cohort 1:** Patients with locally confirmed *BRAF*V600 cutaneous melanoma with metastases to the brain confirmed by MRI, asymptomatic, and *with* prior local therapy (eg, SRS or SRT).

- **Cohort 2:** Patients with locally confirmed *BRAF*V600 cutaneous melanoma with metastases to the brain confirmed by MRI, asymptomatic, *without* prior local therapy (eg, SRS or SRT).

No formal statistical comparison will be conducted between the 2 cohorts.

5.1.2. Decision Rules

5.1.2.1. Safety Lead-in

The target DLT rate during Cycle 1 in the Safety Lead-in is <33% (ie, <3 out of 9 evaluable patients with DLTs). The high-dose treatment will be considered tolerable if the observed Cycle 1 DLT rate is <33%. Table 2 provides a comparison of the characteristics of this DLT evaluation rule and the traditional 3 + 3 rules based on 9 patients.

Table 2: Characteristics of DLT Probability During the DLT Evaluation Period

True DLT Rate During DLT Evaluation Period	Probability of Dose Declared Toxic Using 3 + 3 Rules	Probability of Observed DLT Rate ≥33% in 9 Patients During DLT Evaluation Period
10%	0.094	0.053
20%	0.291	0.262
30%	0.506	0.537
40%	0.691	0.768
50%	0.828	0.910

5.1.2.2. Phase 2

Under the assumption that the true BMRR ≥50%, the null hypothesis of BMRR ≤30% will be rejected if at least 21 brain metastasis responses per mRECIST v1.1 are observed in a cohort of 50 patients. With approximately 50 eligible patients, the study will provide approximately 90% power with a 1-sided type I error rate of 5%.

5.2. General Methods

Unless otherwise specified, all analyses will be performed separately for the Safety Lead-in and for the Phase 2 portion of the study.

Qualitative/categorical data will be summarized by frequency counts and percentages. Percentages will be calculated using the number of patients in the relevant treatment arm or subgroup as the denominator. Continuous data will be summarized using appropriate descriptive statistics (eg, mean, standard deviation, median, minimum, and maximum) by treatment arm.

For reporting conventions, minimum and maximum values will be presented with the same decimal precision as collected in the raw data; mean, median, and quartiles should generally be presented to one more decimal place than the raw data; standard deviation should be displayed to two more decimal places than the raw data. Percentages will be reported to one decimal place. Unless otherwise noted, for all percentages, the number of patients in the analysis set for the treatment arm who have an observation will be the denominator.

Table summaries will be presented as follows. For Phase 2 portion of the study, patients in a cohort escalating to 600 mg encorafenib QD may also be summarized separately.

For Phase 2, the following analyses will be performed by cohort and overall (Cohort 1 + Cohort 2):

- Demographics and other baseline disase characteristics summary.
- Patient disposition.
- Protocol deviations.

- Efficacy analysis.
- Safety analysis.

The following analyses will be performed by cohort only:

- Study treatment exposure.
- Concomitant medication.
- Subsequent anticancer therapies/procesures.

Data listings will be sorted by cohort, patient identifier, parameter and the corresponding date of assessment. The listing source will be included in the footer of the listings.

Statistical analyses detailed in this SAP will be conducted using SAS®, version 9.4 or higher (SAS Institute, Inc.). Noncompartmental PK analyses will be performed with Phoenix® WinNonlin® version 6.4 or higher (Certara USA, Inc., Princeton, NJ).

5.2.1. Data Handling After the Cut-off Date

Data after the cut-off date may not undergo the cleaning process and will not be displayed in any listings or used for summary statistics, statistical analyses or imputations.

All events with a start date before or on the cutoff date and an end date after the cutoff date will be considered as continuing at the cutoff date. The same rule will be applied to events starting before or on the cutoff date and not having a documented end date.

5.2.2. Analyses to Assess the Impact of COVID-19 Pandemic

The study enrollment occurs during the COVID-19 pandemic period. Therefore, the following data summaries and analyses may be performed to assess the impact of COVID-19 on the trial population and study data. Additional analyses may be added in a SAP amendment if they are considered necessary to evaluate the outcome of the trial. Details of these summaries and analyses are included in the respective sections.

- A listing of all patients affected by COVID-19 related study disruption.
- A listing of protocol deviations related to COVID-19.
- COVID-19 related AEs and deaths.
- Summary of missing tumor assessments due to COVID-19.

5.2.3. COVID-19 Anchor Date

If additional analyses are needed to assess the impact of COVID-19 on the trial population and the study data, an anchor date will be used as a start date for COVID-19 pandemic related periods based on Pfizer guidance and standard operating procesure (SOP):

- For global pandemic reference date: Use the date the World Health Organization designated COVID-19 as a global pandemic - March 11, 2020.
- For China reference date: Use the date COVID-19 was identified as the causative agent of outbreak in Wuhan by the China Center for Disease Control and Prevention - January 9, 2020.

When producing data summaries intended to show the potential impacts of COVID-19 on the study, data will be presented as "before" and "during," where the anchor date is included in the "during" group.

A different anchor date may be used for purposes of regulatory submission should the regulatory authority requests.

5.2.4. Definition of Study Day

The study day for assessments occurring on or after the first dose of study treatment (eg, adverse event onset, laboratory date) will be calculated as:

Study day = Date of the assessment/event - start date of study treatment +1.

The study day for assessments occurring prior to the first dose of study treatment (eg, baseline characteristics, medical history) will be negative and calculated as:

Study day = Date of the assessment/event -start date of study treatment.

The study day will be displayed in all relevant data listings.

5.2.5. On-treatment Period

On-treatment period is defined as the time from the first dose date of any study drug through (minimum of last dose of study treatment +30 days, start day of subsequent anticancer therapy - 1 day).

5.2.6. Date of Last Contact

The date of last contact will be derived for patients not known to have died at the data cutoff date using the latest complete date (ie, imputed dates will not be used in the derivation) among the following:

- All patient assessment dates (eg, blood draws (laboratory, Pharmacokinetics (PK)), vital signs, performance status, ECG, tumor assessments, hemodynamic assessment);
- Start and stop dates of concomitant therapies including non-drug treatments or procedures;

- Start and end dates of anticancer therapies administered after study treatment discontinuation including systemic therapy, radiation, and surgeries;
- AE start and end dates;
- Last date of contact collected on the survival follow-up electronic case report form (eCRF) (do not use date of survival follow-up assessment unless status is 'alive');
- Study treatment start and end dates;
- Date of discontinuation on disposition eCRF pages (do not use if reason for discontinuation is lost to follow-up or death).

Only dates associated with actual examinations of the patient will be used in the derivation. Dates associated with a technical operation unrelated to patient status such as the date a blood sample was processed or dates data were entered into the eCRF will not be used. Assessment dates after the data cutoff date will not be applied to derive the last contact date.

5.2.7. Unscheduled Assessments

Unless otherwise specified, unscheduled assessments will not be displayed in summary tables by nominal visit/timepoint. Unscheduled assessments will be used when deriving baseline and worst case on-treatment for safety analyses (except where noted for baseline ECGs). Additionally, unscheduled tumor assessments will be used for efficacy analyses (eg, defining date of progression/censoring, best overall response, date of last contact).

5.2.8. Tumor Assessment Date

If there are multiple scan dates associated with a tumor evaluation, ie, radiological assessments occur over a series of days rather than the same day, the earliest scan date associated with the evaluation will be used as the date of the assessment.

5.2.9. Adequate Baseline Tumor Assessment

An adequate baseline tumor assessment is defined as follows:

- Baseline assessments of all lesions (target, and non-target) must be within 28 days prior to or on the same day as date of first dose.
- All lesions (target and non-target) must have non-missing assessments.

  Note: for target lesions, an actual measurement should be recorded and it should meet the criteria for being measurable and for non-target lesions the actual status at baseline should indicate that the lesion was present).

5.2.10. Adequate Post-baseline Tumor Assessment

An adequate post-baseline tumor assessment is defined as an assessment where a response of CR, PR, SD, non-CR/non-PD, or PD can be determined. Time points where the response is NE or no assessment was performed will not be used for determining the censoring date.

5.2.11. Standard Derivations and Reporting Conventions

The following conversion factors will be used to convert days into weeks, months or years:

1 week = 7 days, 1 month = 30.4375 days, 1 year = 365.25 days.

Percentages will be reported to one decimal place. The rounding will be performed to closest integer/first decimal using the common mid-point between the two consecutive values. Eg, 5.1 to 5.4 will be rounded to an integer of 5, and 5.5 to 5.9 will be rounded to an integer of 6.

5.2.12. Analyses for Binary and Categorical Endpoints

Binary and categorical endpoints will be summarized by frequency counts and percentages along with corresponding exact 2-sided Clopper-Pearson 95% CI. Unless otherwise specified, the calculation of proportions will include the missing category. Therefore counts of missing observations will be included in the denominator and presented as a separate category.

In case the analysis refers only to certain visits, percentages will be based on the number of patients with an assessment at that visit, unless otherwise specified.

5.2.13. Analyses for Continuous Endpoints

Continuous endpoints will be summarized using descriptive statistics ie, number of non-missing values and number of missing values [ie, n (missing)], mean, median, standard deviation, minimum, maximum and first and third quartile (Q1 and Q3). PK summaries will also include coefficient of variation percent (%CV).

In case the analysis refers only to certain visits, percentages will be based on the number of patients with an assessment at that visit, unless otherwise specified.

5.2.14. Analyses for Time-to-Event Endpoints

Time to event endpoints will be summarized using the Kaplan-Meier method[1] and estimated survival curves will be displayed graphically when appropriate. Graphs will describe the number of patients at risk over time. The median, quartiles, and probabilities of an event at particular points in time will be estimated by the Kaplan-Meier method. Confidence intervals for medians and quartiles are based on the Brookmeyer-Crowley method.[2] Confidence intervals for the estimated probability of event at a particular timepoint will be generated using the log(-log) method with back transformation to a confidence interval on the untransformed scale. Summaries of the number and percentages of patients with an event and reason for censoring will also be provided on summary tables and/or figures.

5.3. Methods to Manage Missing Data

Unless otherwise specified, all data will be evaluated as observed, and no imputation method for missing values will be used.

Any imputations will occur at the analysis dataset level. Additionally, in all patient data listings imputed values will be presented and flagged as imputed.

Missing statistics, eg, when they cannot be calculated, should be presented as 'ND' for not done, 'NR' for not reached or 'NA' for not applicable. For example, if N=1, the measure of variability cannot be computed and should be presented as 'ND' or 'NA'.

5.3.1. Missing Dates

For purposes of data listings, dates will reflect only the information provided by the Investigator on the eCRF.

If start dates for adverse events or concomitant medications are completely missing a worst case approach will be taken whereby the events will be considered treatment emergent and the medications will be considered concomitant. If only partial information are available (eg, only a month and year or only a year) and the partial information provide sufficient information to indicate the dates are prior to the start of study treatment (eg, month/year less than month/year of first dose) then these will be considered to have started prior to treatment; otherwise a similar worst case approach will apply and these will be considered to have started after treatment.

Missing or Partial Death Dates

Missing or partial death dates will be imputed based on the last contact date:

- If the entire date is missing it will be imputed as the day after the date of last contact (see derivation of date of last contact in Section 5.2.6).
- If the day or month is missing, death will be imputed to the maximum of the full (non-imputed) day after the date of last contact and the following:
  - Missing day: 1st day of the month and year of death, or
  - Missing day and month: January 1st of the year of death.

Date of First and Last Dose of Study Treatment

No imputation will be done for first dose date.

Date of last dose of study drug, if unknown or partially unknown, will be imputed as follows:

- If the last date of study drug is completely missing and there is no End of Treatment eCRF page and no death date, the patient should be considered to be ongoing and use the cutoff date for the analysis as the last dosing date. **Note:** the study team should confirm that the patient is actively receiving dose at the time of the data cutoff.

- If the last date of study drug is completely or partially missing and there is EITHER an End of Treatment eCRF page OR a death date available (within the data cutoff date), then impute as follows:

  - If only Year is available and Year < Year of min (EOT date, death date), impute the date as 31DECYYYY.

  - If both Year and Month are available and Year = Year of min (EOT date, death date) and Month < Month of min (EOT date, death date), impute as last day of the month.

  - For all other cases, impute as min (EOT date, death date).

Date of Start of New Anticancer Therapy

Incomplete dates for start date of new anticancer therapy will be imputed as follows and will be used for determining censoring dates for efficacy analyses. PD date below refers to PD date by Investigator assessment. If the imputation results in an end date prior to the imputed start date then the imputed start date should be set to the end date.

- The end date of new anticancer therapy will be included in the imputations for start date of new anticancer therapy. If the end date of new anticancer therapy is:

  - completely missing then it will be ignored in the imputations below;

  - partially missing with only year (YYYY) available then the imputations below will consider 31DECYYYY as the end date of the new anticancer therapy;

  - partially missing with only month and year available then the imputations below will consider the last day of the month for MMMYYYY as the end date of the new anticancer therapy.

- For patients who have not discontinued study treatment at the analysis cut-off date, last dose of study treatment is set to the analysis cut-off date in the imputations below.

- If the start date of new anticancer therapy is completely or partially missing then the imputed start date of new anticancer therapy is derived as follows:

  - Start date of new anticancer therapy is completely missing.

    Imputed start date = min [max(PD date +1, last dose of study treatment +1), end date of new anticancer therapy].

  - Only year (YYYY) for start of anticancer therapy is available.

IF YYYY < Year of min [max(PD date +1, last dose of study treatment +1), end date of new anticancer therapy] HEN imputed start date = 31DECYYYY;

ELSE IF YYYY = Year of min [max(PD date +1, last dose of study treatment +1), end date of new anticancer therapy];

THEN imputed start date = min [max(PD date +1, last dose of study treatment +1), end date of new anticancer therapy];

ELSE IF YYYY > Year of min [max(PD date +1, last dose of study treatment +1), end date of new anticancer therapy];

THEN imputed start date = 01JANYYYY.

- Both Year (YYYY) and Month (MMM) for start of anticancer therapy are available

IF

YYYY = Year of min [max(PD date +1, last dose of study treatment +1), end date of new anticancer therapy], AND

MMM < Month of min [max(PD date +1 day, last dose of study treatment +1 day), end date of new anticancer therapy].

THEN

imputed start date = DAY (Last day of MMM) MMM YYYY;

ELSE IF

YYYY = Year of min [max(PD date +1, last dose of study treatment +1), end date of new anticancer therapy], AND

MMM = Month of min [max(PD date +1 day, last dose of study treatment +1 day), end date of new anticancer therapy]

THEN

imputed start date = min [max(PD date +1 day, last dose of study treatment +1 day), end date of new anticancer therapy]);

ELSE IF

YYYY = Year of min [max(PD date +1, last dose of study treatment +1), end date of new anticancer therapy], AND

MMM > Month of min [max(PD date + 1 day, last dose of study treatment +1 day), end date of new anticancer therapy].

THEN

imputed start date = 01 MMM YYYY;

ELSE IF

YYYY < Year of min [max(PD date +1, last dose of study treatment +1), end date of new anticancer therapy].

THEN

imputed start date = DAY (Last day of MMM) MMM YYYY;

ELSE IF

YYYY > Year of min [max(PD date +1, last dose of study treatment +1), end date of new anticancer therapy].

THEN

imputed start date = 01 MMM YYYY.

AE Dates

AE Onset Date:

If completely missing, the onset date will be set to first dose date if date of the first dose is less than AE stop date. Otherwise if date of the first dose is after AE stop date, then set the onset date to the earliest of non-missing AE stop date or informed consent date.

AE Stop Date:

If completely missing, the stop date will be imputed as the latest of the end of study date, death date, last dose date of the study treatment, or onset date.

Partial AE Date:

Partial AE date will be imputed bases on the imputation rule for "Other Missing or Partial Dates". If the AE onset date is imputed from a partial AE date and date of the first dose falls in the same month as the AE onset date, the following will be done:

- The AE onset date is reset to date of the first dose.

If AE stop date is imputed, and less than date of the first dose, set the AE stop date to date of the first dose.

Other Missing or Partial Dates

Imputation methods for other partial dates are as follows:

- If the day of the month is missing for a start date used in a calculation, the 1st of the month will be used to replace the missing date.
- If both the day and month are missing, the first day of the year is used.

- For stop dates, the last day of the month, or last day of the year is used if the day or day and month are missing, respectively.

These rules are used unless the calculations result in negative time durations (eg, date of resolution cannot be prior to date of onset). In these case, the resolution and onset dates will be the same and the duration will be set to 1 day.

5.3.2. Missing Pharmacokinetic Data

Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of geometric mean profiles, concentrations will be set to missing if one of the following cases is true:

- A concentration has been reported as ND (ie, not done) or NS (ie, no sample);
- A deviation in sampling time is of sufficient concern or a concentration has been flagged as anomalous by the clinical pharmacologist.

Summary statistics will not be presented at a particular timepoint if more than 50% of the data are missing. For analysis of pharmacokinetic concentrations, no values will be imputed for missing data.

5.3.3. Missing Biomarker Data

No missing data will be imputed.

6. ANALYSES AND SUMMARIES

The primary analysis will take place after all patients in the Efficacy Set meet the following criteria:

- had at least 2 post-baseline tumor assessments, or discontinued from the study or had disease progression/death at any time on the study;
- all patients with an initial brain metastasis response have been followed up for at least 6 months.

Efficacy analyses will be performed using the Efficacy Set. Key efficacy analyses will also be repeated using the FAS. All safety analyses will be performed using the Safety Set.

6.1. Primary Endpoints

6.1.1. Safety Lead-in

The number and proportion of patients experiencing DLTs during Cycle 1 will be summarized by SOC and PT based on maximum toxicity grade. Analyses of DLT will be performed on Dose-determining Set.

All DLTs and their attributes will be presented in data listings sorted by patient identifier, AE and date of onset of the AE.

6.1.2. Phase 2

Main Analysis:

BMRR will be calculated by dividing the number of patients with a BOR of confirmed CR or confirmed PR in brain metastasis by the number of patients in the Efficacy Set in the respective cohort. The corresponding exact Clopper-Pearson 2-sided 90% CI and 95% CI will be calculated.

BOR is defined as the best response recorded from date of the first dose of study treatment until progression by Investigator assessment at each time point. Only tumor assessments performed before the start of any subsequent anticancer therapies will be considered in the assessment of BOR. Clinical deterioration or clinical progression noted on the End of Study completion eCRF will not be considered as documented disease progression. BOR will be determined according to the following rules:

- CR = at least two determinations of CR at least 4 weeks apart and documented before progression and start of new anticancer therapy.
- PR = at least two determinations of PR or better (and not qualifying for a CR) at least 4 weeks apart and documented before progression and start of new anticancer therapy.
- SD (for patients with at least one measurable lesion at baseline)= at least one SD assessment (or better and not qualifying for CR or PR) ≥6 weeks after date of the first dose and before progression and start of new anticancer.
- Non-CR/Non-PD (for patients with only non-target disease at baseline) = at least one Non-CR/Non-PD assessment (or better and not qualifying for CR or PR) ≥6 weeks after date of the first dose and before progression and the start of new anticancer therapy.
- PD = progression ≤16 weeks after date of the first dose (and not qualifying for CR, PR or SD.
- Not Evaluable (NE) = all other cases.

The frequency (number and percentage) of patients with BOR in brain metastatis of CR, PR, SD, PD, non-CR/non-PD (applicable only to patients with non-measurable disease at baseline), and NE will be tabulated.

Patients with a BOR in brain metastatis of "Not Evaluable" based on confirmed responses will be summarized by reason for having unknown status. The following reasons will be used:

- No adequate baseline assessment.

- No post-baseline assessments due to early death (ie, death ≤16 weeks after the start date).
- No post-baseline assessments due to COVID-19 (ie, patients miss tumor assessment visits due to COVID-19 pandemic).
- No post-baseline assessments due to other reasons.
- All post-baseline assessments have overall response NE.
- New anticancer therapy started before first post-baseline assessment.
- SD of insufficient duration (<6 weeks after date of the first dose without further evaluable tumor assessments).
- PD >16 weeks after date of the first dose (ie, tumor assessment of PD was >16 weeks after date of the first dose and there was no tumor assessment in between).

Special and rare cases where BOR is NE due to both SD of insufficient duration (SD <6 weeks after date of the first dose) and late PD (PD >16 weeks after date of the first dose) will be classified as "SD of insufficient duration".

A figure for duration of exposure and BOR in brain metastasis (confirmed) per mRECIST v1.1 will be created.

A waterfall plot will be created to show the best percentage change from baseline in the sum of longest diameters of all target brain metastases. Patients with baseline and at least one post-baseline brain metastasis assessment will be included in the waterfall plot.

Individual brain metastasis measurements, overall brain metastasis response assessments per mRECIST v1.1 and target and non-target response by timepoint per mRECIST v1.1 will be listed by patient and assessment date.

Sensitivity/Supplementary Analyses

- BMRR based on confirmed + unconfirmed response (CR or PR) in brain metastasis will be calculated along with corresponding exact Clopper-Pearson 2-sided 95% CI.
- BMRR based on confirmed response (CR or PR) in brain metastasis will be calculated using the FAS.

6.2. Efficacy Secondary Endpoints

6.2.1. Extracranial Response Rate

Extracranial response rate will be calculated by dividing the number of patients with a BOR of CR or PR in extracranial lesions by the number of patients in the Efficacy Set in the respective cohort. The corresponding exact Clopper-Pearson 2-sided 95% CI will be calculated.

Details for the determination of BOR are provided in Section 6.1.2.

Two sets of extracranial response rates will be summarized, one based on confirmed responses and one based on confirmed + unconfirmed responses in extracranial lesions.

Patients with extracranial response rate 'Not Evaluable' will be summarized by reason for having unknown status (see Section 6.1.2 for reasons).

A figure for duration of exposure and best overall extracranial response (confirmed) per RECIST v1.1 will be created.

A waterfall plot will be created to show the best percentage change from baseline in the sum of longest diameters of target extracranial lesions. Patients with baseline and at least one post-baseline extracranial tumor assessment will be included in the waterfall plot.

Individual extracranial lesion measurements, overall extracranial response assessments, and target and non-target response by timepoint per RECIST v1.1 will be listed.

6.2.2. Global Response Rate

Global response rate will be calculated by dividing the number of patients with a BOR of CR or PR in both brain and extracranial lesions by the number of patients in the Efficacy Set in the respective cohort. The corresponding exact Clopper-Pearson 2-sided 95% CI will be calculated.

Details for the determination of BOR are provided in Section 6.1.2.

Two sets of global response rates will be summarized, one based on confirmed responses and one based on confirmed + unconfirmed responses in global (brain and extracranial) lesions.

Patients with global response rate 'Not Evaluable' will be summarized by reason for having unknown status (see Section 6.1.2 for reasons).

A figure for duration of exposure and best overall global response (confirmed) will be created.

A waterfall plot will be created to show the best percentage change from baseline in the sum of longest diameters of all target lesions (brain and extracranial). Patients with baseline and at least one post-baseline tumor assessment will be included in the waterfall plot.

Overall global response assessments and timepoint response will be listed by patient and assessment date.

6.2.3. Disease Control Rate

DCR will be calculated for brain metastasis per mRECIST v1.1, extracranial lesion response per RECIST v1.1 and global response along with corresponding exact Clopper-Pearson 2-sided 95% CI.

6.2.4. Duration of Response

DOR will be calculated for patients with a confirmed response (CR or PR) for brain metastasis per mRECIST v1.1, extracranial per RECIST v1.1 and global response (brain metastasis and extracranial lesions) as follows:

DOR (months) = (date of event or censoring – date of first CR or PR + 1)/30.4375

If a patient with a CR or PR did not have an event at the time of the analysis cutoff or with an event more than 16 weeks (for the first 11 cycles after treatment start date) or 24 weeks (after Cycle 11) after the last adequate tumor assessment, the patient will be censored on the date of the last adequate tumor assessment that documented no progression. In addition, if a new anticancer therapy is started prior to an event, the patient will be censored on the date of the last adequate tumor assessment that documented no progression prior to the start of the new anticancer therapy.

Adequate post-baseline assessment are defined in Section 5.2.10.

The censoring and event date options to be considered for DOR analysis are presented in Table 3.

Kaplan-Meier estimates will be presented together with a summary of associated statistics including the median DOR time with 2-sided 95% CI. Details are provided in Section 5.2.14. DOR rates at 3, 6, 9, 12 and 15 months will be estimated with corresponding 2-sided 95% CIs.

In addition, a plot of time to and duration of response for patients with a confirmed response (swimmer plot) will be created.

Table 3: PFS and DOR Outcome and Event Dates

Situation	Date of Progression/Censoring	Outcome
No adequate baseline assessment[a]	Date of first dose[a]	Censored [a]
PD or death - after at most one missing or inadequate post-baseline tumor assessment, or - ≤8 weeks ((±3-day window) after date of first dose	Date of PD or death	Event
PD or death - after >=2 missing or inadequate post-baseline tumor assessment, or	Date of last adequate tumor assessment[b] documenting no PD prior to new anticancer therapy, or missed tumor assessments	Censored
No PD		
New anticancer therapy given prior to PD or death		

[a] This criterion only applies to PFS censoring. If the participant dies ≤8 weeks after date of first dose and and did not initiate new anticancer therapy, the death is an event with date on death date (8 weeks is 2 times the length of the first 2 tumor assessment intervals).

[b] If there are no adequate post-baseline assessments prior to the PD or death, then the time without adequate assessment should be measured from the date of fist dose; if the criteria is met, the censoring will be on the date of first dose.

6.2.5. Progression-free Survival

PFS will be calculated for brain metastasis per mRECIST v1.1 and global assessment (brain metastasis and extracranial lesions) as follows:

PFS (months) = (date of event or censoring – date of first dose +1)/30.4375

The algorithm to derive the outcome, event dates and reasons for censoring for PFS will be the same as that to derive those for the analysis of DOR (Section 6.2.4). The censoring and event date options to be considered for PFS analysis are presented in Table 3.

PFS time will be estimated using the same Kaplan-Meier method as described for DOR in Section 6.2.4. The PFS rate at 3, 6, 9, 12, 15 and 18 months will be estimated with corresponding 2-sided 95% CIs.

Frequency (number and percentage) of participants with each event type (PD or death) and censoring reasons will be presented along with the overall event and censor rates. Reasons for censoring will be summarized according to the categories in Table 4.

In addition, time to progression/censoring, event, and censoring reasons will be listed.

Table 4: PFS Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	No adequate baseline assessment	No adequate baseline assessment
2	Start of new anticancer therapy before event	Start of new anticancer therapy
3	Event after 2 or more missing or inadequate post-baseline tumor assessment/start date	Event after missing or inadequate assessments
4	No event and [withdrawal of consent date ≥ date of first dose OR End of study (EOS) = Subject refused further follow-up]	Withdrawal of consent
5	No event and lost to follow-up in any disposition page	Lost to follow-up
6	No event and [EOS present OR disposition page for any phase after screening says participant will not continue into any subsequent phase of the study] and no adequate post-baseline tumor assessment	No adequate post-baseline tumor assessment
7	No event and none of the conditions in the prior hierarchy are met	Ongoing without an event

6.2.6. Overall Survival

OS will be calculated in months as follows:

OS (months) = (date of death or censoring – date of first dose +1)/30.4375

OS time will be estimated using the same Kaplan-Meier method as described for DOR in Section 6.2.4. The OS rate at 6, 12, 18, 24, 30 and 36 months will be estimated with corresponding 2-sided 95% CIs.

Frequency (number and percentage) of patients with death events and censoring reasons will be presented by cohor along with the overall event and censor rates. The event and ensoring reasons are as follows:

- Death:
  - Death due to COVID-19.
- Ongoing and no death.
- Withdrawal of consent.
- Lost to follow-up.

The OS time or censoring time and the reasons for censoring will also be presented in a patient listing.

6.2.7. Brain Metastasis Response Rate for Safety Lead-in

BMRR per mRECIST v1.1 will also be calculated for Dose-determining Set patients in the Safety Lead-in portion of the study. An exact two-sided 95% CI of BMRR will be reported.

6.3. Other Secondary Endpoints

6.3.1. Pharmacokinetic Analysis

Plasma concentrations and PK parameters will be determined for encorafenib and its metabolite (LHY746) and binimetinib and its metabolite (AR00426032). PK summaries will be presented by treatment arm for patients in the PK set. In the following, Day y of Cycle x will be abbreviated as CxDy. C1D1 is defined as single dose (ie, first dose) and C1D15 is defined as multiple dose.

If a patient experiences emesis after dosing on C1D15, a full PK sampling schedule will be implemented on C2D1. In this situation, the C2D1 data will be summarized in PK tables and summary figures along with other patients' C1D15 data, and the C1D15 data for the affected patient will only be listed for information. Throughout the following text, all references to C1D15 includes C2D1 records in patients experiencing emesis on C1D15 rather than their C1D15 data.

6.3.1.1. Plasma Concentrations of Encorafenib, LHY746, Binimetinib and AR00426032

Plasma concentrations of encorafenib, LHY746, binimetinib and AR00426032 will be quantitated at the time points indicated in Table 5:

Table 5: Pharmacokinetic Blood Sampling Times

Study Visit	Timing of Sample	Allowed Window[a]
C1D1	0.5 hours postdose	±5 min
	1.5 hours postdose	±5 min
	3 hours postdose	±10 min
	6 hours postdose	±20 min
C1D15	Predose	-30 min
	0.5 hours postdose	±5 min
	1.5 hours postdose	±5 min
	3 hours postdose	±10 min
	6 hours postdose	±20 min
C2D1[b]	Predose	-30 min
C3D1	Predose	-30 min

[a] Predose samples must be within 30 minutes of, but before, the following dose.
[b] When more sampling is performed on C2D1 due to emesis on C1D15, the sample times and windows will be the same as for C1D15.

All plasma concentration values of each analyte for each patient in the PK set will be included in the bioanalytical plasma concentration listings. Individual concentration records will be flagged for the affected visit if any of the following occur on the day of PK sampling:

a. Patient had vomiting:

   - within 4 hours following study drug administration on the day of PK sampling for post-dose samples (C1D1, C1D15 and C2D1 when more sampling is performed on that day due to emesis on C1D15); or

   - at any time over the preceding 24 hours for pre-dose samples (C1D15, C2D1 and C3D1).

b. Prescription dosing was not performed for at least 4 consecutive days prior to C1D15, C2D1 or C3D1).

c. Patient received a higher or lower dose compared to planned treatment

d. PK sampling time was outside the allowed window (as shown in Table 5) or the elapsed time was not calculable.

The plasma concentrations of encorafenib, LHY746, binimetinib and AR00426032 will be summarized by dose, treatment cohort or arm and combined arms as applicable for all nominal time points, including predose (trough) concentrations for C2D1 and C3D1, using the following descriptive statistics: n (number of patients with non-missing values), m (number of non-zero [ie, > below the limit of quantification (BLQ)] concentrations), arithmetic mean, standard deviation, coefficient of variation (CV), geometric mean, geometric CV, minimum, median and maximum. An individual concentration-time data point may be excluded from the calculation of summary statistics if any of the above flags [a-d] apply. Concentrations below the BLQ will be set to zero for calculation of all summary statistics; geometric mean and geometric CV will set to missing if at least one BLQ value is included in the data being summarized. The arithmetic mean with standard deviation plasma concentration-versus-time profiles will be presented graphically for each analyte using both linear and semi-logarithmic scales by treatment arm on C1D1 and C1D15. Individual plasma concentration-time profiles (with median overlaid) will also be presented graphically using linear and semi-logarithmic scales by treatment arm and study day. For ease of presentation, nominal times will be used to present results in summary figures; for individual figures, actual times will be used.

6.3.1.2. Plasma Pharmacokinetic Parameters for Encorafenib, LHY746, Binimetinib and AR00426032

Pharmacokinetic parameters for patients in the PK set will be determined by treatment arm for encorafenib, LHY746, binimetinib and AR00426032 when possible and appropriate.

The individual plasma concentration-time data for each analyte will be evaluated with noncompartmental analysis (NCA) using Phoenix WinNonlin®, version 8.0 or higher. Actual blood collection times and doses on the day of PK sampling will be used for PK calculations. All BLQ values before the observed maximum plasma concentration (Cmax) will be set to 0; all BLQ values after Cmax will be considered as missing.

The following parameters will be calculated for encorafenib, LHY746, binimetinib and AR00426032 on C1D1 and C1D15:

PK Parameter	Definition
AUC_{0-6}	Area under the plasma concentration-time curve from zero to 6 hours after drug administration
AUC_{last}	Area under the plasma concentration-time curve from zero to the last measurable time point
AUC_{tau}	Area under the plasma concentration-time curve over a dosing interval (C1D15 only) To estimate AUCtau,ss, the concentration measured at predose on C1D15 will be imputed as the concentration at the end of the dosing interval (ie, 12 or 24 hours, as appropriate) assuming steady-state has been attained
C_{max}	Maximum observed plasma concentration after drug administration
C_{min}	Minimum observed plasma concentration after drug administration
C_{trough}	Measured concentration at the end of a dosing interval
T_{max}	Time to reach C_{max}
T_{last}	Time of last PK sample
MR_{Cmax}	Ratio of C_{max} values of the metabolite compared to parent, corrected for molecular weight, for AR00426032/ binimetinib and LHY746/Encorafenib
$MR_{AUClast}$	Ratio of AUC_{last} values of the metabolite compared to parent, corrected for molecular weight, for AR00426032/ binimetinib and LHY746/Encorafenib
R_{AUC}	Accumulation ratio, calculated as: C1D15 AUC_{0-6}/C1D1 AUC_{0-6}
R_{Cmax}	Accumulation ratio, calculated as: C1D15 C_{max}/C1D1 C_{max}

C1D15 parameters will also be determined for C2D1 when more sampling is performed on that day due to emesis on C1D15.

The area under the curve (AUC) parameters will be calculated according to the linear-up log-down trapezoidal rule. All AUC, Cmax, Cmin, and Ctrough values (AUClast/D, AUC0-6/D, AUCtau, /D, Cmax/D, Cmin/D and Ctrough/D) will also be provided as dose-normalized values. Additional PK parameters may be calculated at the discretion of the pharmacokineticist.

All PK parameter values of each analyte will be presented in data listings by dose, treatment cohort or arm, cycle and study day. Individual PK records will be flagged for the affected visit and/or parameter if any of the following occur:

a. Patient had vomiting:

   - within 4 hours following study drug administration on the day of PK sampling for post-dose samples (C1D1, C1D15 and C2D1 when more sampling is performed on that day due to emesis on C1D15); or

   - at any time over the preceding 24 hours for pre-dose samples (C1D15, C2D1 and C3D1).

b. Prescription dosing was not performed for at least 4 consecutive days prior to C1D15, C2D1 or C3D1).

c. Patient received a higher or lower dose compared to planned treatment for the related analytes.

Each parameter for each analyte will be summarized in tables by dose, treatment cohort or arm and combined arms as appreciate, cycle and study day using the following descriptive statistics: n, arithmetic mean, standard deviation, CV, geometric mean, geometric CV, minimum, median and maximum. Summary descriptive statistics for in-text summary tables will include geometric mean with geometric CV for AUC, AUC/D, Cmax, Cmax/D, and RAUC. For Tlast and Tmax values, median, minimum and maximum will be presented. Pharmacokinetic parameters will be excluded from the calculation of summary statistics if any of the above flags [a-c] apply.

6.3.1.3. Other PK Analysis

A separate population PK analysis with exposure-response analyses, if appropriate, will be conducted to further establish the PK for high daily dose encorafenib in BID administration. Details of the analyses will be included in a PK analysis plan and results will be presented separately from the main clinical study report (CSR).

CCI [redacted]

[redacted]

[redacted]

[redacted]

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

The following analyses will be performed overall on the Dose-determining Set for the Safety Lead-in, and on the FAS by cohort and overall for the Phase 2.

6.5.1.1. Demographic Summary

The following demographic will be summarized by number and percentage:

- Gender (male, female).
- Age (<65, ≥65).
- Race (White, Black or Afriacan American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Other, Not Reported).
- Ethnicity (Hispanic/Latino, not-Hispanic/Latino).

Age (continuous) will be summarized with descriptive statistics (mean, median, standard deviation, minimum, and maximum).

6.5.1.2. Baseline and Disease Characteristics

The following baseline and disease characteristics will be summarized:

- Location of primary tumor.
- Stage at initial diagnosis.
- Stage at study entry.
- Tumor histology.
- Time since initial diagnosis, defined as [date of first dose – date of initial diagnosis]/30.4375.
- Baseline tumor burden in the brain (1 to 2 brain lesions vs. ≥3 brain lesions).
- Lactate dehydrogenase (LDH) level at baseline.
- ECOG performance status.
- Local and central laboratory assessments of *BRAF* status. Local assessment results will be based on the data collected on the "Local BRAF Results" eCRF page.

6.5.1.3. Medical History

Medical history reported at the time of the Screening will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) terminology available at the time of reporting. Medical history will be summarized by primary system organ class (SOC) and preferred term (PT). Each patient will be counted only once within each PT or SOC.

6.5.1.4. Prior Anticancer Treatments

Prior anticancer treatments include systemic therapy, radiation and surgery.

The number and percentage of patients who received, separately, any prior anticancer systemic treatment, radiotherapy, or surgery will be summarized.

Prior anticancer systemic treatment will be summarized as follows:

- Total number of regimens (there can be more than one medication per regimen),
- Number of regimens for checkpoint inhibitor. The final list of checkpoint inhibitors will be provided upon medical review of all prior anticancer therapies.
- Setting at last medication.
- Best response at last medication (defined as the best response during the last treatment regimen recorded).
- Reason for discontinuation at last medication.
- Time (in months) from end of last medication to study start date.
- Time (in months) from start of last medication to disease progression. The last medication is defined based on the last end date of all prior regimen components.

Prior anticancer systemic treatment will also be summarized by Anatomical Therapeutic Chemical (ATC) class and preferred term.

For prior anticancer radiotherapy, information about the last radiotherapy (based on end date) will be summarized: time (in months) between radiotherapy and start of study treatment, location and best response. In addition, prior local brain radiotherapy will be summarized (location = "Brain" in the Prior Cancer Treatment Radiation CRF page).

For prior anticancer surgery, the time (months) between last surgery and start of study treatment, site, location, whether the surgery was palliative, and the result will be summarized. In addition, prior local brain surgery will be summarized (location = "Brain" in the Prior Cancer Treatment Surgery CRF page).

All prior anticancer therapies will be presented in a data listing separately for systemic treatment, radiotherapy, and surgery.

Incomplete dates will be handled as described in Section 5.3.1.

6.5.2. Study Conduct and Patient Disposition

6.5.2.1. Patient Disposition

The disposition summary will be created for the Safety Lead-in and the Phase 2 portion of the study separately.

The following disposition categories will be summarized:

- Number (%) of patients who received at least one dose of study drug.

- Number (%) of patients who are still on treatment.
- Number (%) of patients who discontinued the treatment:
  - Primary reasons for treatment discontinuation.
- Number (%) of patients who discontinued the treatment but are still in long-term follow-up.
- Number (%) of patients who discontinued the study:
  - Primary reasons for study discontinuation.

The number and percent of participants enrolled by region, country and site, and the number and percent of participants in each analysis set as described in Section 4 will also be summarized.

Screen failure patients are those who were screened, but never started the study treatment for any reason. The data collected on these patients will not be included in any analyses.

COVID-19 Related Disposition

A listing of all patients affected by COVID-19 related study disruption will be created. The listing will present subject number identifier by investigational site, and a description of COVID-19 related events including:

- Protocol deviations.
- Adverse events treatment.
- Treatment discontinuation.
- Study discontinuation.
- Death.

6.5.2.2. Protocol Deviations

Potentially important protocol deviations (PIPDs) will be compiled prior to database closure and will be summarized by category and also presented in a listing. Categories will be assigned by the study Clinician.

In addition, PIPDs related to COVID-19 will be presented in a separate listing.

6.5.3. Study Treatment Exposure

Duration of Exposure

- **Intended treatment duration** (days) = end of treatment date – date of first dose of study drug +1.
    - If a patient permanently discontinues both binimetinib and encorafenib, end of treatment date is the date of last dose of the study drug;
    - If a patient permanently discontinues binimetinib but is still on single-agent encorafenib treatment, end of treatment date is the date of last dose of encorafenib treatment.
- **Actual treatment duration** (days) = date of last non-zero dose of the study drug - date of first dose of study drug +1

Cumulative Dose

Cumulative dose is defined as:

- **Intended cumulative dose** (mg) = sum of all protocol specified doses across intended treatment duration.
- **Actual cumulative dose** (mg) = sum of all actual doses that the patient received across actual treatment duration.

For patients who did not take any drug the actual cumulative dose is by definition equal to zero.

Dose Intensity

- **Intended dose intensity** (mg/day) = intended cumulative dose / intended treatment duration.
- **Actual dose intensity** (mg/day) = actual cumulative dose / intended treatment duration.
- **Relative dose intensity** (%) = 100* (actual dose intensity / intended dose intensity).

A summary of exposure, including duration of exposure, cumulative dose, actual dose intensity, and relative dose intensity (including categories <50%, 50%-<75%, 75%-<90%, 90%-<110%, and ≥110%, if applicable), will be presented for each study drug.

Actual treatment duration will be summarized in months including descriptive statistics (n, mean, median, minimum, maximum) and will also be categorized by time intervals (eg, <1 months, 1-3 months, etc. as appropriate for the protocol) for which frequency counts and percentages of patients will be provided.

Actual treatment duration, cumulative dose, actual dose intensity, and relative dose intensity will also be listed for each patient by treatment arm.

6.5.3.1. Dose Modification

Dose modification will be summarized based on the the dosing data collected on the study treatment CRF page.

Dose Reduction

Dose reductions are permitted for encorafenib and binimetinib and will be summarized based on the dose modification data collected on the respective study medication eCRF page.

The number and percentage of patients with at least one dose reduction as well as a breakdown of dose reductions (1/2/≥3) will be summarized.

Reasons for dose reductions will also be summarized. Patients can contribute to more than one reason if multiple dose reductions occurred for different reasons, but will only be counted once per reason. Percentages will be calculated based on the total number of patients in the safety analysis set.

Dose Interruption

A dose interruption will be indicated in the study medication eCRF. For encorafenib (Safety Lead-in) and binimetinib, a total dose of 0 mg in the morning and/or in the evening indicates a dose interruption. If a patient had a total dose of 0 mg both in the morning and in the evening, it is counted as one dose interruption for this patient. For encorafenib (Phase 2), a dosing record with a total daily dose of 0 mg for one or more days indicates a dose interruption. If the start and stop date of two dose interruption records are consecutive, it will be counted as one dose interruption.

Dose interruption will be summarized based on the dose modification data collected on the eCRF page. However, in order not to over count interruptions, dosing records with 0 mg entered as last dosing record will not be counted as interruptions. Those represent the reason for permanent discontinuation and will therefore be presented in the reason for treatment discontinuation analysis.

The number and percentage of patients with dose interruptions and the corresponding reasons will be summarized. Patients can contribute to more than one reason if multiple dose interruptions occurred for different reasons, but will only be counted once per reason. Percentages will be calculated based on the total number of patients in the safety analysis set.

6.5.4. Concomitant Medications

Concomitant medications are medications, other than study medications, which started prior to first dose of study treatment and continued during the on-treatment period (see Section 5.2.5) as well as those started during the on-treatment period. Concomitant

medications will be coded in the WHO Drug coding dictionary and will be tabulated by ATC classification level 2 and PT (level 4) by decreasing frequency. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used. A patient will be counted only once within a given drug name, even if he/she received the same medication at different times.

All concomitant medications will be presented in a data listing.

Incomplete dates will be handled as described in Section 5.3.1.

6.5.5. Subsequent Anticancer Therapies/Procedures

Number of patients with any anticancer treatment after discontinuation of study treatment will be summarized by type of therapy (systemic treatment, radiotherapy, and surgery).

Summary statistics will be created for the data collected on the "Subsequent Cancer Treatment Systemic" eCRF page.

Subsequent anticancer systemic treatment will be summarized by ATC class and preferred term and will also be presented in a listing.

Incomplete dates will be handled as described in Section 5.3.1.

6.6. Safety Summaries and Analyses

Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

6.6.1. Adverse Events

All analyses will be based on TEAEs as defined in Section 3.4.1 unless otherwise specified. AEs not considered treatment emergent will be flagged in data listings.

Seriousness, toxicity grade, action taken (interruption, reduction, and withdraw) of AEs are as reported by the Investigator on the "Adverse Events" CRF.

A high level summary of AEs will include the number and percent of patients with:

- Any TEAEs.
- Serious TEAEs.
- TEAEs with CTCAE Grade ≥3.
- Related TEAEs to:
  - Encorafenib;

    - Binimetinib;
    - Both encorafenib and binimetinib.
- Related serious TEAEs:
    - Encorafenib;
    - Binimetinib;
    - Both encorafenib and binimetinib.
- TEAEs leading to dose interruption of:
    - Encorafenib;
    - Binimetinib;
    - Both encorafenib and binimetinib.
- TEAEs leading to dose reduction of:
    - Encorafenib;
    - Binimetinib;
    - Both encorafenib and binimetinib.
- TEAEs leading to permanent discontinuation from:
    - Encorafenib;
    - Binimetinib;
    - Both encorafenib and binimetinib.
- TEAEs leading to dose reduction of any study drug due to COVID-19.
- TEAEs leading to permanent discontinuation from any study drug due to COVID-19.

Each unique AE at the PT level in each treatment arm of the study for a patient is included in the count.

Adverse Events by SOC and PT

The following summaries will be created by SOC and PT by decreasing frequency:

- TEAEs by maximum toxicity grade (all causality).
- TEAEs by maximum toxicity grade (treatment related).
- COVID-19 related TEAEs (all causality).
- Serious TEAEs by maximum toxicity grade (all causality).
- Serious TEAEs by maximum toxicity grade (treatment related).
- TEAEs leading to dose reduction of any study drug due to COVID-19.
- TEAEs leading to permanent discontinuation from any study drug due to COVID-19.

An event will be considered treatment related if the Investigator considered the event related to the study drug or this information is unknown.

Adverse Events by PT Only

The following summaries will be created by AE PT by decreasing frequency:

- TEAEs (all causality) experienced by ≥10% of patients in Safety Lead-in and in at least one cohort for Phase 2.
- Treatment related TEAEs experienced by ≥10% of patients in at least one cohort (Phase 2).
- TEAEs with CTCAE Grade ≥3 (all causality) by PT and maximum toxicity grade.
- Serious TEAEs (all causality).
- COVID-19 related serious TEAEs (all causality).

Adverse Events Leading to Dose Modification by PT

The following summaries will be created by PT by decreasing frequency:

- TEAEs leading to dose interruptions by maximum toxicity grade (all causality).
- TEAEs leading to dose reductions by maximum toxicity grade (all causality).
- TEAEs leading to permanent discontinuation by maximum toxicity grade (all causality).

The AE by PT summary will be created separately for:

- Encorafenib;

- Binimetinib.

Each patient will be counted only once within each PT.

Adverse Events in Patients with Dose Escalation in Phase 2

TEAEs leading to dose interruptions, dose reductions and permanent discontinuation will also be summarized by PT for patients who escalate to encorafenib 600 mg QD in Phase 2.

All AEs and their attributes will be presented in data listings sorted by patient identifier, AE and date of onset of the AE.

6.6.2. Deaths

All deaths, deaths within 30 days after last dose of study drug, deaths within 30 days after first dose of study drug as well as the primary reason for death, will be tabulated based on information from the "Death Details" and "Disposition Long-term Follow-Up" eCRFs.

- Number of deaths.
- Number of deaths within 30 days after *last* dose of study treatment.
- Number of deaths within 30 days after *first* dose of study treatment.
- Primary cause of death.

In addition, if there are ≥5 deaths due to COVID-19, a separate death summary will be created.

Date and cause of death will be provided in patient data listing together with selected dosing information (study treatment received, date of first/last administration, dose).

6.6.3. Laboratory Data

Laboratory results will be converted to International System of Units (SI) units which will be used for applying toxicity grades and for all summaries.

As described in Section 3.3, baseline is defined as the last completed assessment prior to date of first dose for the safety assessments. If there are multiple assessments that meet the baseline definition on the same day without the ability to determine which was truly last, then the worst grade will be assigned as the baseline grade.

Laboratory results will be programmatically classified according to NCI-CTCAE version 4.03. Non-numerical qualifiers will not be taken into consideration in the derivation of grade (eg, hypokalemia Grade 1 and Grade 2 are only distinguished by a non-numerical qualifier and therefore Grade 2 will not be derived). In summary statistics the number and percentage of patients corresponding to grades that only include non-quantitative criteria will be displayed as a blank or NA (not assessed) rather than 0. If there is any overlap between

grade criteria (eg, CTCAE grading criteria for Creatinine Increased – a value can fall into one range based on comparison to ULN and another range based on comparison to baseline), the highest (worst) grade would be assigned to that record. Grade 5 is defined in the CTCAE criteria guidance as an event with an outcome of death. Since laboratory data does not collect an outcome, Grade 5 is not used when programmatically grading laboratory data.

Grade 0 or Outside Toxicity Reference (OTR) is not defined specifically in the CTCAE guidance. However, programmatically this is used as a category to represent those patients who did not meet any of the Grades 1 to 4 criteria. If the laboratory value is evaluable for CTCAE criteria grading (numeric value is present, valid units and ranges are present as required to allow conversion to standard units and grading), and does not qualify for any of the Grade 1-4 criteria for a given lab test, then the value is assigned as Grade 0 or OTR.

Abnormalities will be described using the worst grade post-baseline. When determining the maximum post-baseline grade for a given patient and CTCAE test, the maximum across all analytes and assessments contributing to that CTCAE test will be used. Several laboratory tests have bi-directional grading criteria defined so that both low (hypo) and high (hyper) values can be graded separately. Each criterion will be summarized separately. In the cases where a value is graded as a Grade 1, 2, 3, or 4 for one of the directions, that value will also be assigned as a Grade 0 for the opposite direction for that test. For example, a value meeting the criteria for Grade 3 Hypercalcemia will be classified as a Grade 0 Hypocalcemia. For CTCAE terms that can be derived using one of several laboratory tests, the maximum post-baseline grade for a given patient and CTCAE term will be the maximum across all possible laboratory tests.

For **WBC differential counts** (total neutrophil [including bands], lymphocyte, monocyte, eosinophil, and basophil counts), the absolute value will be used when reported by the lab. When only percentages are available (this is mainly applicable for neutrophils and lymphocytes, because the CTCAE grading is based on the absolute counts), the absolute value is derived as follows:

$$\text{Derived differential absolute count} = (\text{WBC count}) \times (\text{Differential \%value}/100)$$

If the investigator reports both the absolute and % value for Neutrophils or Lymphocytes from the same laboratory sample date and patient, ONLY the absolute value will be graded. The % value will not be graded in this scenario.

If the % value is converted to the differential absolute count for grading and the LLN for the differential absolute count is not available (only LLN for % is available) then Grade 1 will be assigned if the following conditions are met:

- Lymphocyte count decreased:
    - derived absolute count does not meet Grade 2-4 criteria, and
    - % value < % LLN value, and

  - derived absolute count ≥800/mm^3.

- Neutrophil count decreased:

  - derived absolute count does not meet Grade 2-4 criteria, and

  - % value < % LLN value, and

  - derived absolute count ≥1500/mm^3.

For **calcium**, CTCAE grading is based on Corrected Calcium and Ionized Calcium. Corrected Calcium is calculated from Albumin and Calcium as follows:

- Corrected Calcium (mg/dL) = measured total calcium (mg/dL) – 0.8 × [serum albumin (g/dL)-4].

Laboratory toxicities will be tabulated using descriptive statistics (number of patients and percentages). If both central and local labs are collected for a subject, summaries of worst on-treatment abnormalities will be based on both local and central lab data.

Additional laboratory results that are not part of NCI-CTCAE will be presented according to the categories: below normal limit, within normal limits and above normal limit (according to the laboratory normal ranges). The following summary tables will be created:

- Shift summary of laboratory parameters during the on-treatment period by maximum CTCAE grade.

- Shift summary of laboratory parameters from ≤ Grade 2 at baseline to ≥ Grade 3 post-baseline.

- Shift summary of laboratory test results with no CTCAE criteria by worst on-treatment assessment.

All laboratory test results will be presented in a data listing sorted by patient identifier, laboratory test, and date/time of collection. The CTCAE grades and the classifications relative to the laboratory reference ranges will be presented. Values outside laboratory normal ranges will be flagged where appropriate and the central laboratory data and local laboratory data will be flagged accordingly.

Drug Induced Liver Toxicity

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), Alkaline Phosphatase (ALP), and total bilirubin (TBILI) are used to assess possible drug induced liver toxicity. The ratios of test result over the ULN will be calculated and classified for these three parameters during the on-treatment period.

Summary of liver function tests will include the following categories. The number and percentage of patients with each of the following during the on-treatment period will be summarized:

- ALT ≥3×ULN, ALT ≥5xULN, ALT ≥10×ULN, ALT ≥20×ULN.
- AST ≥3×ULN, AST ≥5xULN, AST ≥10×ULN, AST ≥20×ULN.
- (ALT or AST) ≥3×ULN, (ALT or AST) ≥5×ULN, (ALT or AST) ≥10×ULN, (ALT or AST) ≥20×ULN.
- TBILI ≥2×ULN.
- Concurrent ALT ≥3×ULN and TBILI ≥2×ULN.
- Concurrent AST ≥3×ULN and TBILI ≥2×ULN.
- Concurrent (ALT or AST) ≥3×ULN and TBILI ≥2×ULN.
- Concurrent (ALT or AST) ≥3×ULN and TBILI ≥2×ULN and ALP >2×ULN.
- Concurrent (ALT or AST) ≥3×ULN and TBILI ≥2×ULN and ALP ≤2×ULN or missing.

Concurrent measurements are those occurring on the same date.

Categories will be cumulative, ie, a patient with an elevation of AST ≥10×ULN will also appear in the categories ≥5×ULN and ≥3×ULN. Liver function elevation and possible Hy's Law cases will be summarized using frequency counts and percentages.

An evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot will also be created, with different symbols for different treatment arms, by graphically displaying:

- Peak serum ALT(/ULN) vs peak total bilirubin (/ULN) including reference lines at ALT=3×ULN and total bilirubin=2×ULN.
- Peak serum AST(/ULN) vs peak total bilirubin (/ULN) including reference lines at AST=3×ULN and total bilirubin=2×ULN.

In addition, a listing of all TBILI, ALT, AST and ALP values for patients with a post-baseline TBILI ≥2×ULN, ALT≥3×ULN or AST ≥3×ULN will be provided.

6.6.4. Vital Signs

Vital signs data includes weight, pulse, systolic blood pressure (BP), and diastolic BP. Measurements were only to be provided once per timepoint. If multiple assessments are provided per timepoint, the maximum value will be used for reporting.

The following criteria define clinically notable vital sign abnormalities:

- Clinically notable elevated values:
  - Systolic BP: ≥160 mmHg and an increase ≥20 mmHg from baseline;
  - Diastolic BP: ≥100 mmHg and an increase ≥15 mmHg from baseline;
  - Heart rate (collected as pulse rate in the vital signs eCRF): ≥120 bpm with increase from baseline of ≥15 bpm;
  - Weight: increase from baseline of ≥10%;
  - Body temperature [C]: ≥37.5 C.
- Clinically notable low values
  - Systolic BP: ≤90 mmHg with decrease from baseline of ≥20 mmHg;
  - Diastolic BP: ≤50 mmHg with decrease from baseline of ≥15 mmHg;
  - Heart rate (collected as pulse rate in the vital signs eCRF): ≤50 bpm with decrease from baseline of ≥15 bpm;
  - Weight: ≥20% decrease from baseline;
  - Body temperature [C]: ≤36 C.

All assessments, including unscheduled assessments will be considered. A patient can be included in multiple categories if different criteria are met at different timepoints.

Number and percentage of patients with at least one post-baseline vital sign abnormality will be summarized.

Patients with clinically notable vital sign abnormalities will be presented in a data listing. Clinically notable values will also be flagged in this listing.

6.6.5. Electrocardiograms

Potential effects of treatment with study drug on ECG parameters will be assessed by ECG interval analysis of heart rate, pulse rate, QRS, QT, and QT interval corrected for heart rate (QTc). Triplicate measurements will be obtained at screening and pre-dose on Cycle 1 Day 1 according to the schedule of assessments in the protocol.

The average of the machine-read triplicate ECG measurements collected closest to but prior to the first dose of study drug will serve as each patient's baseline QT, QTcF, and heart rate value for all post-dose comparisons. The QT, QTcF, and heart rate data collected on the eCRF page will be used in the summary.

Number and percentages of patients with clinically notable ECG values during the on-treatment period will be summarized. The clinically notable ECG values are defined in Table 6.

Patients with clinically notable ECG values will be presented in a data listing. Clinically notable values will also be flagged in this listing.

Table 6: Clinical Notable ECG Criteria

Parameter	Criterion
QT, QTcF	increase from baseline >30 ms increase from baseline >60 ms new >450 ms new >480 ms new >500 ms
Heart rate	Increase from baseline >25% and to a value >100 bpm Decrease from baseline >25% and to a value <50 bpm

6.6.6. Neurological Symptoms

Neurological symptom data will be presented in a data listing.

6.6.7. ECOG Performance Status

ECOG performance status at each time point will be presented in a data listing.

6.6.8. Echocardiogram/Multi-gated Acquisition

Left ventricular ejection fraction (LVEF) abnormalities are defined according to CTCAE grade version 4.03. Patients will be considered as having a LVEF abnormality if the worst post value is grade 2, 3 or 4 according to the following classification:

- Grade 0: Non-missing value below Grade 2.
- Grade 2: LVEF between 40% and 50% or absolute change from baseline between -10% and < -20%.
- Grade 3: LVEF between 20% and 39% or absolute change from baseline lower than or equal to -20%.
- Grade 4: LVEF lower than 20%.

A shift table using CTCAE grades to compare baseline to the worst post-baseline LVEF value will be produced.

Different modalities to assess LVEF might be used for the same patient. The shift table will be provided regardless of the modality.

All LVEF assessments will be presented in a data listing.

6.6.9. Ophthalmic Examination

All ophthalmic examinations, ie, tonometry, visual acuity, fundoscopy, slit lamp, optical coherence tomography, and fluorescein angiography, will be presented in a data listing.

6.6.10. Pregnancy Tests

Results of all pregnancy tests will be presented in a data listing.

6.6.11. Comments

All comments entered into the electronic data capture (EDC) system by personnel at the study sites will be presented in a data listing.

6.6.12. Procedures

Results of all procedures collected on the Procedures eCRF will be presented in a data listing.

7. INTERIM ANALYSES

No formal interim analysis is planned for this study.

8. REFERENCES

1. Kaplan EL, Meier P. (1958). Nonparametric Estimation from Incomplete Observations. Journal of the American Statistical Association 53:457-481.

2. Brookmeyer R and Crowley J (1982). A Confidence Interval for the Median Survival Time, Biometrics 38, 29 - 41.

9. APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
AUC	area under the curve
BID	twice a day
BP	blood pressure
BLQ	below the limit of quantification
BMRR	brain metastasis response rate
BOR	best overall response
BRAF	B-RAF proto-oncogene, serine/threonine-protein kinase
CI	confidence interval
C_{max}	maximum observed concentration
CR	complete response
CSR	clinical study report
CV	coefficient of variation
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
FAS	full analysis set
LDH	lactate dehydrogenase
LLN	Lower limit of normal
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
ms	millisecond(s)
mRECIST	modified Response Evaluation Criteria in Solid Tumors
NA	not applicable
NCI	National Cancer Institute
NE	non-evaluable
OS	overall survival
OTR	outside toxicity reference
PD	progressive disease
PFS	progression-free survival
PIPDs	potentially important protocol deviations

Abbreviation	Term
PK	pharmacokinetic(s)
PR	partial response
PT	preferred term
Q1	first quartile
Q3	third quartile
QD	once daily
QT	QT interval
QTcF	corrected QT (Fridericia method)
RANO-BM	Response Assessment in Neuro-Oncology Brain Metastases
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SOC	system organ class
SOP	standard operating procedure
SRS	stereotactic radiosurgery
SRT	stereotactic radiotherapy
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization