STATISTICAL ANALYSIS PLAN

A Phase 2, Open-Label Study of Encorafenib + Binimetinib in Patients with *BRAF*^{V600}-mutant Non-small Cell Lung Cancer

STUDY DRUG:	Encorafenib + Binimetinib
PROTOCOL NUMBER:	C4221008 (ARRAY-818-202)
VERSION:	3.0
DATE:	26 May 2022

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LIST OF ABBREVIATIONS

Abbreviation or Special Term	Explanation
AE	adverse event
AESI	adverse event of special interest
AJCC	American Joint Committee on Cancer
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the plasma concentration-time curve
AUC_{0-6}	area under the plasma concentration-time curve from zero to 6 hours
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 the dosing interval
BLQ	below the limit of quantification
BOR	best overall response
BP	blood pressure
BRAF	B-RAF proto-oncogene, serine/threonine-protein kinase
C1D1	Day 1 of Cycle 1
CXDY	Day Y of Cycle X
CI	confidence interval
CK	creatine kinase
C_{max}	observed maximum plasma concentration
CR	complete response
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
C_{trough}	trough (predose) concentration at steady state
CV	coefficient of variation
DCR	disease control rate
DOR	duration of response
DRL	Drug Reference Listing
ECG	electrocardiogram
ECHO	echocardiogram

Abbreviation or Special Term	Explanation
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOS	end of study
EOT	end of treatment
FDA	United States Food and Drug Administration
ICF	informed consent form
IRR	Independent radiology review
KM	Kaplan-Meier
LDH	lactate dehydrogenase
LFT	liver function test
LLOQ	Lower limit of quantification
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MR_{Cmax}	ratio of C_{max} values of the metabolite compared to parent, corrected for molecular weight
$MR_{AUClast}$	ratio of AUC_{last} values of the metabolite compared to parent, corrected for molecular weight
ms	millisecond(s)
MUGA	multi-gated acquisition
NAE	not all evaluated
NE	not evaluable
NCA	noncompartmental analysis
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death protein ligand 1
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PT	preferred term
PTT	partial thromboplastin time
QT	QT interval

Abbreviation or Special Term	Explanation
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fredericia's formula
R_{AUC}	accumulation ratio based on AUC values
RBC	red blood cell(s)
RE	response evaluable set
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SI units	International System of Units
SOC	system organ class
SOD	sum of diameters
SRL	safety risk lead
SS	safety analysis set
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TLF	table, listing, figure
T_{last}	observed time of last measured concentration
T_{max}	observed time of C_{max}
TPS	tumor proportion score
TTR	time to tumor response
ULN	upper limit of normal
WBC	white blood cell(s)
WHO	World Health Organization

1. VERSION HISTORY

This SAP for study PHAROS (C4221008, ARRAY-818-202) is based on the protocol amendment 5 dated 24 Sep 2021.

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
Version 1.0 18 June 2020	Version 2 03 Oct 2019	N/A	N/A
Version 2.0 03 May 2021	Version 4 16 Feb 2021	Following consultation with the FDA, the design of the study has been revised to allow for registration of a treatment naïve population and a previously treated population, either separate or together	• Primary endpoint will be confirmed tumor response by independent radiology for treatment naïve participants and previously treated participants with $BRAF^{V600E}$ mutant NSCLC. • Sample size has been calculated for the 2 populations (treatment naïve participants and previously treated participants). • Two interim analyses included. • A sensitivity analysis for ORR by IRR will be performed in RE set. • AESI analyses added. • Substituted the term patient with participant per new Pfizer standard. • Signature page will be an external document.

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
Version 3.0 26 May 2022	Version 5 24 Sep 2021	Following consultation with the FDA after first interim analysis, the second interim analysis was removed and PCD was defined	• Removed the second interim analysis. • Specified the timing of final ORR analysis (PCD) for treatment-naïve participants. • Specified the RE set will be used at the time of interim analysis. Aligned TTR (secondary endpoint) to protocol amendment 5. • Modified the description of some AE tables. • Added evaluation of differences between treatment-naïve and previously treated participants for log-transformed PK parameter estimates (AUC_{0-6}, AUC_{tau}, and C_{max}) for analytes (encorafenib, LHY746, and binimetinib) by visit day (C1D1 and C1D15).

2. INTRODUCTION

This document describes the statistical analyses and data presentations to be performed for the clinical protocol ARRAY-818-202 entitled "A Phase 2, Open-label Study of Encorafenib + Binimetinib in Patients with *BRAF*^{V600}-Mutant Non-small Cell Lung Cancer (NSCLC)."

This SAP should be read in conjunction with the study protocol and eCRFs. This document has been developed using the protocol Version 5 dated 24 September 2021 and eCRFs dated 18 October 2021. Any further changes to the protocol or eCRFs may necessitate updates to the SAP.

This SAP provides a comprehensive and detailed description of the strategy, rationale, and statistical techniques to be used to assess the efficacy, safety, PK, and biomarker analyses of encorafenib + binimetinib in participants with *BRAF*^{V600}-Mutant NSCLC as outlined in the protocol.

Statistical analyses detailed in this SAP will be conducted using SAS®, Version 9.4 or higher (SAS Institute, Inc., Cary, NC USA). Noncompartmental PK analyses will be performed with Phoenix® WinNonlin® Version 8.0 or higher (Certara USA, Inc., Princeton, NJ). Data displays will adhere generally, if not specifically, to the standard mock tables, listings, and figures and can be found in a separate SAP shell document.

2.1. Responsibilities

A Sponsor or CRO-designated Biostatistician or Statistical Programmer will perform any statistical analyses required for participant disposition, protocol deviations, participant characteristics, efficacy, and safety and is responsible for the production and quality control of all tables, figures, and listings associated with these analyses. A Sponsor or CRO-designated Clinical Pharmacology representative will perform any PK statistical analyses and is responsible for the production and quality control of all tables, figures, and listings associated with these analyses. A Sponsor Translational Science representative will perform any biomarker statistical analyses and is responsible for the production and quality control of all tables, figures, and listings associated with these analyses.

3. STUDY OBJECTIVES, ENDPOINTS AND ESTIMANDS

3.1. Study Objective and Endpoints

Table 2. Objectives and Endpoints

Primary Objective	**Primary Endpoint**
• To evaluate the efficacy of encorafenib + binimetinib in treatment-naïve and previously treated participants with *BRAF*^{V600E}-mutant NSCLC as measured by ORR	• ORR defined as the proportion of participants who have achieved a confirmed best overall response (CR or PR) as determined by IRR per RECIST v1.1 in the treatment-naïve setting • ORR defined as the proportion of participants who have achieved a confirmed best overall response (CR or PR) as determined by IRR per RECIST v1.1 in the previously treated setting
Secondary Objectives	**Secondary Endpoints**
• To evaluate the efficacy of encorafenib + binimetinib in treatment-naïve and previously treated participants with *BRAF*^{V600E}-mutant NSCLC as measured by DOR, DCR, PFS, and TTR	• Confirmed ORR by investigator per RECIST v1.1 • DOR (by IRR and investigator) defined as the time from the date of the first documented response (CR or PR) that is subsequently confirmed to the earliest date of disease progression, per RECIST v1.1, or death due to any cause • DCR (by IRR and by investigator) defined as the proportion of participants who have achieved a confirmed CR, confirmed PR or SD per RECIST v1.1

Table 2. Objectives and Endpoints

	• PFS (by IRR and by investigator) defined as the time from the date of first dose of study drug to the earliest date of disease progression, per RECIST v1.1, or death due to any cause • TTR (by IRR and by investigator), defined as the time from the date of first dose to the first documentation of objective response (CR or PR) which is subsequently confirmed (by IRR and by Investigator)
• To evaluate the efficacy of encorafenib + binimetinib in treatment-naïve and previously treated participants with *BRAF*^{V600E}-mutant NSCLC with respect to OS	• OS defined as the time from the date of first dose of study drug to the date of death due to any cause
• To evaluate the safety and tolerability of encorafenib + binimetinib in treatment-naïve and previously treated participants with *BRAF*^{V600E}-mutant NSCLC	• Incidence and severity of AEs graded according to the NCI CTCAE v4.03 and changes in clinical laboratory parameters, vital signs, ECGs and ECHO/MUGA scans
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate the PK of encorafenib, its metabolite LHY746, and binimetinib in participants with *BRAF*^{V600}-mutant NSCLC	• Plasma concentration-time profiles and PK parameter estimates for encorafenib, its metabolite LHY746, and binimetinib
• To assess blood ctDNA mutation status	• Genomic analysis of ctDNA in blood samples

3.2. Primary Estimand

The primary estimand of the study will be Objective Response defined as follows:

- Analysis Population: all participants with *BRAF*^{V600E}-mutant (based on local test) NSCLC who receive at least 1 dose of study drug.

- Variable: Objective response defined as CR or PR according to RECIST v1.1 based on IRR assessment, from the date of first dose of study treatment until the date of the first documentation of PD, death or start of new anticancer therapy. Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met.

- Population-level summary measure: proportion of participants who have achieved a confirmed BOR of CR or PR as determined by IRR per RECIST v1.1 and corresponding exact two-sided 95% CI.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is an open-label, multicenter, non-randomized, Phase 2 study to determine the safety, tolerability, and efficacy of encorafenib given in combination with binimetinib in treatment-naïve and previously treated participants with *BRAF*^{V600}-mutant metastatic NSCLC. Participants who are either treatment-naïve, or who have received 1) first-line treatment with standard platinum-based chemotherapy, or 2) first-line treatment with an anti-PD-1/PD-L1 inhibitor given alone or in combination with platinum-based chemotherapy will be enrolled. Treatment will be administered in 28-day (± 3 days) cycles and will continue until disease progression, unacceptable toxicity, withdrawal of consent, start of subsequent anticancer therapy, or death. Once the participant discontinues study treatment, the treatment period will end, and the participant will enter the follow-up period for safety, subsequent anticancer therapy, disease status, and survival status; participants who discontinue treatment for reasons other than PD will continue to have radiographic assessments every 8 or 12 weeks until PD or subsequent anticancer therapy.

Additional information regarding eligibility criteria, planned dose levels, schedules of assessments, and other study design details and procedures are detailed in the clinical study protocol.

4.2. Statistical Hypotheses

The primary endpoint of the study is ORR for treatment-naïve and previously treated participants as determined by IRR per RECIST v1.1.

The study is designed to test the null hypothesis of ORR ≤ 39% for treatment-naïve participants with *BRAF*^{V600E} NSCLC, which is considered not sufficiently clinically meaningful to warrant further study on encorafenib and binimetinib in this indication where similar therapies are already available. The alternative hypothesis is ORR >39% with the assumption that the true ORR is ≥ 65%. Hypotheses are based on the results observed in the dabrafenib plus trametinib study in *BRAF*^{V600E}-mutant NSCLC participants, in which the ORR per investigator assessment was 64% (95% CI: 46, 79) for treatment-naïve participants (Planchard et al 2017[5]), and the results observed in participants with NSCLC whose tumors expressed PD-L1 levels with a TPS ≥ 50% and received pembrolizumab as a single agent (Keynote-042) in which ORR per IRR was 39% (95% CI: 34, 45) (Mok et al 2019[4]).

For previously treated participants with *BRAF*^{V600E} NSCLC, the null hypothesis of ORR ≤ 20% will be tested. The alternative hypothesis is ORR >20% with the assumption that the true ORR is ≥ 45%. This hypothesis is based on the ORR of 18% (95% CI: 14, 23) observed in previously treated participants with NSCLC whose tumors expressed PD-L1 levels with a TPS ≥ 1% and who received pembrolizumab as a single agent (Keynote-010; Herbst et al 2016[2]).

4.3. Sample Size Considerations

The sample size calculation is based on the primary endpoint of ORR as determined by IRR per RECIST v1.1. The hypotheses to be tested are described in Section 4.2.

At least 60 treatment-naïve and 37 previously treated *BRAF*^{V600E} NSCLC participants will be enrolled and treated. It is not expected that more than 107 participants with any *BRAF*^{V600} mutation will be enrolled and treated.

With 60 evaluable treatment-naïve participants with *BRAF*^{V600E} NSCLC, the power is greater than 95% to test the null hypothesis that the ORR ≤ 39% versus the alternative hypothesis that it is > 39% assuming an alternative target rate of 65% with a one-sided $\alpha \leq 0.025$ based on a single-stage design using exact test. The null hypothesis will be rejected if ≥ 32 confirmed objective responses are observed out of 60 participants.

With 37 evaluable previously treated participants with *BRAF*^{V600E} NSCLC, there is at least 90% power to test the null hypothesis that the ORR ≤ 20% versus the alternative hypothesis that it is > 20% assuming an alternative target rate of 45% with a one-sided $\alpha \leq 0.025$ based on a single stage design using exact test. The null hypothesis will be rejected if ≥ 13 confirmed objective responses are observed out of 37 participants.

5. ANALYSIS SETS

5.1. Screened

Screened participants include all participants who sign the ICF.

5.2. Safety Analysis Set

The SS includes all participants who receive at least 1 dose of study treatment.

Unless otherwise specified, the safety analysis set will be the default analysis set used for all efficacy and safety analyses.

5.3. Response Evaluable Set

The RE set will be used for a sensitivity analysis of ORR by IRR at the time of the interim analysis. RE is defined as all participants in the SS who have an adequate baseline disease assessment and meet at least 1 of the following 2 criteria:

- Had at least one post-baseline disease assessment at least 6 weeks from first dose;
- Withdrew from the study or experienced progressive disease/death at any time on study.

5.4. PK Analysis Set

The PK analysis set includes all participants in the SS who have at least 1 postdose PK blood collection after the first dose of study treatment with associated bioanalytical results. The PK analysis set will be used for summaries of PK data.

6. CHANGES FROM THE STUDY PROTOCOL

This SAP incorporates the following changes from the statistical analyses described in the study protocol:

- Removed the second interim analysis and defined the time of final ORR analysis (Primary Completion Date) for treatment-naïve participants;
- Included RE set for a sensitivity analysis of ORR by IRR to be conducted at the time of the interim analysis;
- Substituted the term patient with participant per new Pfizer standard;
- Section 8.4.3 Safety Analysis: clinically notable measurements will not be summarized for laboratory data. No descriptive summary will be created for ECOG performance status.

7. STATISTICAL METHODS

7.1. Reporting Conventions and Definitions

All tables will include 3 columns/groups: “Treatment Naïve”, “Previously Treated”, “Total”.

7.1.1. Baseline

Baseline is defined as the last available and valid assessment before or on the start date of study treatment. If an assessment is planned to be performed prior to the first dose of study treatment in the protocol and the assessment is performed on the same day as the first administration of study treatment and the time is unknown, it will be assumed that it was performed prior to study treatment administration unless the protocol specifies it otherwise. Unscheduled assessments will be used in the determination of baseline. 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 Day 1 of Cycle 1 (C1D1), or on screening, if baseline assessment is missing.

7.1.2. Last Contact Date

Last contact date will be derived for participants not known to have died on or before the analysis cutoff date. Imputed dates will not be considered for the determination of last contact date. Only dates associated with participant visits or the actual assessment of the participant will be used in the derivation. Dates associated with a technical operation unrelated to participant status (e.g., the date a blood sample was processed) will not be used. Last contact date will only be derived using the latest complete date among the following:

- Study drug start and end dates with non-missing dose (doses of 0 are allowed)
- RECIST assessment date with evaluation marked as done
- Laboratory/PK collection date with sample collection marked as done

- Vital sign, ECG, physical exam, dermatologic exam, and ophthalmic exam assessment dates with non-missing parameter value
- ECOG performance status date with non-missing performance status
- Start/end date of AEs with non-missing verbatim term
- Start/end date of anticancer therapies administered after study treatment; discontinuation with non-missing medication/procedure term
- Start/end date of concomitant medications/non-drug treatments/procedures
- Date of contact for most recent post-treatment survival assessment with the status as "Alive"
- Cardiac imaging assessment date
- Biomarker collection date.

7.1.3. Study Day

Study day is defined in the following manner:

- On or after the start date of study treatment: (date of assessment/event) – (treatment start date) + 1. Day 1 will therefore be the first day of study treatment.
- Before the start date of study treatment: (date of assessment/event) – (treatment start date).

7.1.4. On-treatment Period

On-treatment period is defined as the time from the first dose date of study treatment to the last dose of study drug administration date (when both drugs are permanently discontinued) + 30 days or the earliest date of subsequent anti-cancer drug therapy minus 1 day, whichever occurs first.

7.1.5. Adequate Baseline Tumor Assessment

Adequate baseline is defined using the following criteria:

- All baseline assessments must be within 28 days prior to and including the date of first dose.
- All documented lesions must have non-missing assessments (ie, non-missing measurements for target lesions and meeting criteria for measurable lesions, and non-missing lesions status at baseline for non-target lesions).
- Baseline lesions must be assessed with an acceptable method of tumor assessment as specified in the protocol (eg, Chest, abdomen, and pelvis CT scans [or CT without contrast or MRI if CT is contraindicated], an MRI of the brain, CT scan of the brain,

preferably with IV contrast, may be performed if MRI is contraindicated. Localized CT, MRI, or X-ray for skeletal lesions). Chest X-ray or ultrasound should not be used for tumor response assessments in this study. While FDG-PET scans are not required for this study, sites may perform combined PET/CT scans per their local standard of care, provided the CT is of similar diagnostic quality as CT performed without PET, including the use of oral and IV contrast media. If acquired according to local standard of care, FDG-PET may be relied upon to document PD in accordance with RECIST.

7.1.6. Adequate Postbaseline Tumor Assessment

An adequate assessment is defined as an assessment where a response of CR, PR, Stable Disease (SD), non-CR/non-PD (to be used if only non-measurable disease is present), or PD has been provided by IRR or the investigator for the analyses by IRR or investigator, respectively. Time points where the response is not evaluable or no assessment was performed will not be used for determining the censoring date for time to event endpoints.

7.1.7. Definition of Start of New Anticancer Therapy

Start date of new anticancer therapy (drug, radiation, surgery) is used for censoring in efficacy analyses (see Section 7.5).

The start date of new anticancer therapy is the earliest date after first dose date among the following:

- Start date of anticancer drug therapy recorded in the 'Subsequent Cancer Treatment Systemic' eCRF pages;
- Start date of radiation therapy recorded in 'Subsequent Cancer Treatment Radiation' eCRF pages;
- Surgery date recorded in 'Subsequent Cancer Treatment Surgery' eCRF pages;

When start date of anticancer therapy is missing or partially missing, the imputation rules described in Section 7.1.11 should be applied using 'Subsequent Cancer Treatment Systemic', 'Subsequent Cancer Treatment Radiation', and 'Subsequent Cancer Treatment Surgery' eCRF pages.

7.1.8. Tumor assessment dates

Tumor assessment dates will be assigned differently for IRR assessment and for investigator's assessment of tumor data.

For analyses of IRR assessments, the date of tumor assessments will be provided by IRR and identified as the earliest scan/assessment date at each nominal timepoint. These dates, together with the determined overall tumor response at each timepoint, will be used to programmatically identify the response/progression date and for censoring in time to event analyses.

For analyses based on investigator's assessment, response/progression are derived programmatically from the target lesions measurements, non-target lesions status, and new lesions recorded on the eCRF, and the date of tumor assessment will be derived as the earliest scan/assessment date.

7.1.9. Reporting Conventions

Unless specified otherwise, durations of events (e.g., duration of treatment) will be calculated in days as (stop date – start date + 1).

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.

Demographics and physical measurements:

- Age (years):
  - (date of given informed consent - date of birth + 1) / 365.25
  - In case of only year and month given: (year/month of given informed consent – year/month of birth)
  - In case only year of birth is given: (year of given informed consent – year of birth)
  - The integer part of the calculated age will be used for reporting purposes.

For each analysis, a data cutoff date will be determined. Only data with an assessment/finding dates (eg, vital sign assessment date, tumor scan date, laboratory collection date, etc) or event/intervention start date (eg, AE start date, concomitant medication start date) before or on the cutoff date will be included in the analysis.

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. Participants with a last contact date or a date of death after the data cutoff date will be considered alive at the data cutoff date. Participants known to be on treatment or discontinued the treatment after the cutoff date will be considered on treatment at the time of data cutoff date.

In general, missing values will be handled as follows unless otherwise specified. For continuous variables at baseline, missing values will be excluded from calculation of summary statistics, and the number and percent of participants with missing values will be displayed. For categorical values at baseline, the number and percent of participants with a missing value will be displayed. For missing post-baseline values, the method for reporting missing values will depend on the summary table.

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

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 participants in the analysis set who have an observation will be the denominator.

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

7.1.10. Unscheduled Visits

Generally, data collected at unscheduled visits will be included and analyzed for both safety and non-safety analyses in the same fashion as the data collected at scheduled visits except where otherwise noted in the sections that follow. Descriptive statistics (mean, standard deviation, median, minimum, maximum, quartiles) by nominal visit or time point for safety endpoints such as laboratory test measurements, ECGs, and vital signs will not display data from unscheduled visits/assessments.

7.1.11. Imputation Rules for Partial or 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 is available (e.g., only a month and year or only a year) and the partial information provides sufficient information to indicate the dates are prior to the start of study treatment (e.g., 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.

Death Date

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

- If the date is completely missing, it will be imputed as the day after last contact date (Section 7.1.2).
  - 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.

Exposure Date

No imputation will be done for first dose date. Date of last dose of study drugs, if unknown or partially unknown, will be imputed as follows:

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

- If the last date of study drugs 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 this date as the last dose date:

  = 31DECYYYY, if only Year is available and Year < Year of min (EOT date, death date)

  = Last day of the month, 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)

  = min (EOT date, death date), for all other cases.

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 participants 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 anti-cancer therapy is available

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 = 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 the first dose date is less than AE stop date. Otherwise if the first dose date 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 based on the imputation rule for "Other Missing or Partial Dates". If the AE onset date is imputed from a partial AE date and the first dose date falls in the same month as the AE onset date, the following will be done:

  - The AE onset date is reset to the first dose date.
  - If AE stop date is imputed, and less than the first dose date, set the AE stop date to the first dose date.

Other Missing or Partial Dates

Imputation methods for other partial dates as follows:

- If the day of the month is missing for a start date used in a calculation, the first day of the month will be used to replace the missing date.
- If both the day and month are missing for a start date, 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 (e.g., date of resolution cannot be prior to date of onset). In these cases, the resolution and onset dates will be the same and the duration will be set to 1 day.

7.2. Participant Disposition

Participant disposition analyses will use the SS unless otherwise stated.

The following disposition categories will be summarized:

- Number (%) of participants who received at least one dose of study treatment
- Number (%) of participants who are still on treatment
- Number (%) of participants who discontinued the treatment
- Primary reasons for treatment discontinuation
- Number (%) of participants who discontinued the treatment but are still in follow-up for disease or for survival
- Number (%) of participants who discontinued the study
- Primary reasons for study discontinuation

Inclusion and exclusion criteria for each of the analysis sets will also be summarized.

Participant disposition data will also be listed.

Screen failure participants are those who were screened, but never started the study treatment for any reason. The data collected on these participants will not be included in any analyses. A listing of reasons for screen failure will be presented.

A separate listing will describe each participant's inclusion or exclusion status for each of the analysis sets defined in Section 5.

7.3. Protocol Deviations

Protocol deviations will be determined and documented prior to database lock as outlined in the *Specifications of Protocol Deviations*. Categories and significance of protocol deviations will be assigned according to the deviation rules document. The number and percentage of participants in the SS with any significant protocol deviations will be tabulated by the deviation category.

Significant protocol deviations will be presented in a data listing by participant. In addition, protocol deviations due to COVID-19 will be presented in a separate table and listing.

7.4. Participant Characteristics

Participant characteristic analyses will be performed using the SS.

7.4.1. Demographics and Pretreatment Characteristics

Demographic and other pretreatment characteristics including age, gender, race, ethnicity, height, weight, and ECOG performance status at baseline will be summarized.

In addition, the tobacco use status collected on the Tobacco Use eCRF page will be summarized (current smoker, former smoker, and non-smoker), considering cigarette, cigar, pipe, e-cigarette, and vape.

A demographics listing by participant will be presented.

7.4.2. Medical and Disease History

Medical history reported at screening will be coded using the latest MedDRA terminology available at the time of reporting. Medical history will be summarized by primary SOC and PT for ongoing and past disease. Each participant will be counted only once within each PT and SOC.

The summary of disease history will include time since initial diagnosis (months), TNM (AJCC staging) at diagnosis, TNM (AJCC staging) at study entry, tumor histology, and presence of brain metastases.

7.4.3. BRAF Status

BRAF status will be summarized based on the data collected in the "BRAF Status" eCRF page for local testing results and data from the central laboratory for central testing results, if data available. The following information will be included in the summary: BRAF status (including tissue sample status [fresh or archive], site [primary or metastatic], irradiation status of site, method of testing, and testing results).

Concordance between BRAF status from local and central laboratory at screening will be summarized, if data from central laboratory will be available. Additional analyses and details will be included in a statistical analysis plan for companion diagnostic development.

BRAF status data for local test will also be listed for each participant.

7.4.4. Prior Anticancer Therapy

Prior anticancer therapy will be summarized for three distinct subtypes (systemic treatment, radiotherapy, and surgery). The number (%) of participants who received, separately, any prior systemic treatment, radiotherapy, or surgery will be summarized.

For prior systemic treatment, the following data will be summarized including for all setting and for drugs received for metastatic disease only:

- Number and percentage of participants with at least one prior systemic treatment
    - Number of participants who received prior immune therapy (monotherapy or combination therapy)
    - Number of participants who received monotherapy PD1/L1
    - Number of participants who received combination PD1/L1 therapy (with chemotherapy or other immune therapies)
    - Number of participants received chemotherapy without immune therapy
- Total number of regimens (there can be more than one medication per regimen) and total number of regimens for metastatic disease.
- Setting (adjuvant, neoadjuvant, locally advanced, metastatic) at last medication
- Best response by type of therapy (monotherapy PD1/L1, combination PD1/L1 therapy, chemotherapy without immune therapy) at last medication (defined as the best response during the last treatment regimen recorded)
- Time (in months) from start of last regimen for metastatic disease to disease progression. The last regimen is defined based on the last number of all prior regimens with a setting equal to metastatic, locally advanced, maintenance, palliative.

Prior systemic treatments for metastatic disease will also be summarized by ATC class and PT.

For prior anticancer radiotherapy, the following information about the last radiotherapy (based on end date) will be summarized: time (in months) between radiotherapy and start of study treatment, location, best response, radiation therapy type, setting (adjuvant, neoadjuvant, palliative, metastatic), and whether radiation was given with chemotherapy.

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.

All prior anticancer therapies will be listed separately for systemic treatment, radiotherapy, and surgery.

Incomplete dates will be handled as described in Section 7.1.11.

7.4.5. Other Prior Medications

Prior medications are any medications (excluding study drug and prior anticancer treatments) which started before first dose of study drug. Prior medications will be summarized based on the Prior and Concomitant Medications eCRF. These medications will be coded using the WHO DRL dictionary that employs the WHO ATC classification system.

The number and percentage of participants with prior medications will be summarized by ATC classification level 2 and preferred term (level 4).

Incomplete dates will be handled as described in Section 7.1.11.

7.5. Efficacy Analysis

SS will be the primary population for the analysis of all efficacy endpoints. Depending on the recruitment rate for previously treated participants, a primary analysis may be performed separately for the treatment-naïve participant population. In any case, data will be summarized for treatment-naïve participants, previously treated participants, and overall.

The final analysis for ORR (Primary Completion Date) for treatment-naïve participants will take place after 14 months from the enrollment of the last treatment-naïve participant.

All efficacy endpoints, except OS, will be evaluated by IRR and by derived investigator-assessment in participants with *BRAF*^{V600E} mutant NSCLC, as determined by local test. Endpoints for derived investigator (hereafter referred to as investigator) will be derived programmatically from the target lesion measurements, non-target lesion status, and new lesions recorded on the eCRF, see details in Section 10 (Appendix 1).

7.5.1. Objective Response Rate

Objective Response (OR) based on IRR is the primary endpoint and is defined as CR or PR according to RECIST version 1.1 from date of first dose of study treatment until documented PD or start of new anticancer therapy. Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met.

Clinical deterioration or clinical progression noted on the End of Treatment Disposition eCRF will not be considered as documented disease progression for the purposes of the ORR calculation.

The confirmed BOR for each participant is determined from the sequence of overall time point (lesion responses) according to the following rules below:

- CR = at least 2 determinations of CR at least 4 weeks apart before progression.
- PR = at least 2 determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR).
- SD = an assessment of SD or better ≥6 weeks after start of treatment (and not qualifying for PD, PR or CR).
- PD = progression ≤ 16 weeks after start of treatment (and not qualifying for CR, PR, or SD).
- NE (Not Evaluable) = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 16 weeks).

Participants with a BOR of 'Not Evaluable' will be summarized by reason for having unknown status. The following reasons will be used:

- No adequate baseline assessment
- No evidence of disease at baseline
- No post-baseline assessments due to early death (defined as death prior to 6 weeks after date of first dose
- No post-baseline assessment due to other reason
- All post-baseline assessments have overall response of "NE"
- New anticancer therapy started before first post-baseline assessment
- SD occurred < 6 weeks after the start of treatment and no subsequent tumor assessments

- Progression >16 weeks after the start of treatment (i.e., tumor assessment of PD was >16 weeks after start of treatment and there was no tumor assessment in between).

Special (and rare) cases where BOR is 'Not evaluable' due to both SD occurring < 6 weeks after start of treatment and progression > 16 weeks after the start of treatment will be classified as "SD occurred < 6 weeks after the start of treatment".

The ORR will be calculated with the exact 2-sided Clopper-Pearson 95% CI.

A sensitivity analysis will be performed for ORR by IRR in RE set at the time of interim analysis.

An additional analysis of ORR by IRR will be performed if participants with *BRAF*^{V600} mutant NSCLC other than V600E will be treated.

The impact of tumor assessments missing due to COVID19 will be evaluated and, if needed, a sensitivity analysis of ORR by IRR may be performed excluding participants with tumor assessments missing due to COVID19 from SS.

ORR by investigator assessment will be calculated with the exact 2-sided Clopper-Pearson 95% CI.

For ORR by IRR and investigator assessment additional subgroup analyses may be performed to explore the influence of various baseline characteristics [age group (<65 years and ≥65 years), gender, race group (Asian and non-Asian), and ECOG performance status (0 and 1)].

The total event disagreement rate for IRR and investigator responses will be presented.

Table 3. Definition of Agreement Used to Determine Total Event Agreement and Disagreement Rates in Response

	Investigator	**IRR**	**Variable Name**
Agreement	No response	No response	a
	Response	Response	b
Disagreement	No response	Response	c
	Response	No response	d

N = (a + b + c + d)

The total event disagreement rate measures the proportion of participants for whom there is a discrepancy between the IRR and investigator as to whether the participant was a responder

with either the IRR or the investigator, but not both, among all participants who are evaluated by both IRR and investigator.

Total Event Disagreement Rate = [(c+d) / N] x 100%.

The total event agreement rate measures the proportion of participants for whom there is a concordance between the IRR and investigator as to whether the participant was a responder or a non-responder with both the IRR and the investigator, among all participants who are evaluated by both IRR and investigator.

Total Event Agreement Rate = [(a+b) / N] × 100%.

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

A waterfall plot based on investigator will be created to show the best percentage change in target lesions from the baseline in the sum of longest diameters. Participants with baseline and at least one post-baseline tumor assessment will be included in the waterfall plot. The best percentage change in target lesions from baseline will be derived across all the post-baseline assessments until documented disease progression, excluding assessments after start of subsequent anticancer therapy, as follows:

Minimum of ((sum of target lesions at week XX – sum of target lesions at baseline)/sum of target lesions at baseline) * 100

Individual lesion measurements and overall response assessments per RECIST v1.1 will be listed by participant and assessment date by IRR and investigator.

7.5.2. Duration of Response

DOR is defined as the time from the date of the first documented response (CR or PR) that is subsequently confirmed, to the earliest date of disease progression, as determined by IRR and investigator per RECIST v1.1, or death due to any cause. If a participant with a CR or PR has neither progressed nor died at the time of the analysis cutoff or at the start of any new anticancer therapy, the participant will be censored at the date of last adequate tumor assessment. The same rules used for censoring of PFS will be applied, see Section 7.5.5 for more details. DOR will be calculated for participants who have achieved a confirmed response (i.e., CR or PR).

An estimate of the DOR survival function will be constructed using the KM method (Kaplan & Meier, 1958[3]) as implemented in PROC LIFETEST. The 25%, median, and 75% DOR (in months) will be summarized along with 95% confidence intervals as calculated from the PROC LIFETEST output (using method of [Brookmeyer & Crowley, 1982[1]]).

Frequency distribution (<3 months, ≥3 months, ≥6 months, ≥9 months, ≥12 months, ≥24 months) will be provided.

7.5.3. Time to Response

Time to Response (TTR) based on IRR and investigator assessments is defined, for participants with a confirmed objective response, as the time, in months, from the date of first dose to the first documentation of objective response (CR or PR) which is subsequently confirmed. Time to response will be calculated for the subgroup of participants with a confirmed objective tumor response.

TTR will be summarized using descriptive statistics. In addition, the number and percent of participants with TTR in the following time intervals may be provided: 0 to <2 months, 2 to <4 months, 4 to <6 months, and ≥6 months.

7.5.4. Disease Control Rate

DCR is defined as the proportion of participants who have achieved a confirmed CR, confirmed PR or SD, as determined by IRR and investigator per RECIST v1.1 after 24 weeks (>= 168 days) from the date of first dose of study drug.

DCR will be calculated along with the exact two-sided Clopper-Pearson 95% CI.

7.5.5. Progression-free Survival

Progression-free survival is defined as the time from the date of first dose of study drug to the earliest date of disease progression, as determined by IRR and investigator per RECIST v1.1, or death due to any cause, whichever occurs first, and will be summarized in months:

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

Participants without an event or with an event more than 16 weeks (for the first 12 months after treatment start date) or 24 weeks (after the first 12 months of treatment start date) after the last adequate tumor assessment 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 participant 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. Note: if date of progression occurs on the same date as the start of new anticancer therapy, the progression will be counted as an event.

An adequate post-baseline 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.

Participants with no baseline tumor assessment (including participants with an inadequate baseline assessment) or with no adequate post-baseline tumor assessments within 16 weeks after treatment start date will be censored on the day of treatment start date, unless the participant dies within 16 weeks of treatment start date, in which case, death will be an event on date of death.

The censoring and event date options to be considered for the PFS analysis are presented in Table 4.

Table 4. PFS Outcome and Event Dates

Situation	Date of Progression/Censoring	Outcome
No adequate baseline assessment	Date of treatment start date [a]	Censored [a]
PD or death ≤ 16 (or 24) [b] weeks after last adequate tumor assessment or ≤ 16 weeks after treatment start date	Date of PD or death	Event
PD or death > 16 (or 24) [b] weeks after the last adequate tumor assessment [c]	Date of last adequate tumor assessment [c] documenting no PD prior to new anticancer therapy or missed assessments	Censored
No PD		
New anticancer therapy given		

a If the participant dies ≤16 weeks after treatment start date, the death is an event with date on death date.

b Durations are equal to 2 times the length of the tumor assessment interval, which is 16 weeks for the first 12 months after treatment start date, and 24 weeks thereafter.

c If there are no adequate post-baseline assessments prior to the PD or death, then the time without adequate assessment should be measured from treatment start date; if the criteria is met, the censoring will be on treatment start date.

An estimate of the PFS survival function will be constructed using the KM method (Kaplan & Meier, 1958[3]) as implemented in PROC LIFETEST. The 25%, median, and 75% DOR (in months) will be summarized along with 95% confidence intervals as calculated from the PROC LIFETEST output (using method of [Brookmeyer & Crowley, 1982[1]]).

Frequency counts and percentages of participants with each event type (PD or death) and censoring reasons will be summarized. Censoring reasons are as follows:

- Ongoing in the study without an event
- No adequate baseline assessment
- No adequate post-baseline assessment
- New anticancer therapy was given
- Progression or death after 2 or more missed assessments
- Withdrawal of consent
- Lost to follow-up

If a participant meets multiple definitions for censoring the list below will be used to define the hierarchy.

Table 5. 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 postbaseline tumor assessment	Event after missing or inadequate assessments[a]
4	No event and [withdrawal of consent date ≥, date of first dose OR End of study (EOS) = Participant 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 any disposition page after screening says participant will not continue into any subsequent phase of the study] and no adequate postbaseline tumor assessment	No adequate postbaseline tumor assessment
7	No event and none of the conditions in the prior hierarchy are met	Ongoing without an event

a .More than 16 weeks after last adequate tumor assessment.

A graph of the estimated KM curve will be presented.

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

7.5.6. Overall Survival

OS is defined as the time from the date of 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, unless death or last contact date occurs after the data cutoff date in which case OS will be censored at the data cutoff date.

The survival distribution function for OS will be estimated using the KM method as described for PFS in Section 7.5.5. A graph of the estimated KM curve will be presented.

Frequency counts and percentages of participants with an event (death) and censoring reasons will be summarized. Censoring reasons are as follows:

- Ongoing and no death
- Withdrawal of consent
- Lost to follow-up

- No longer follow for survival (alive participant who discontinued from the study for reason different from withdrawal consent and lost to follow-up).

7.6. Safety Analysis

All safety analyses will be performed using the appropriate data for all participants in the SS unless otherwise stated.

7.6.1. Extent of Study Drug Exposure

Duration of exposure will be evaluated separately for encorafenib and binimetinib. It is defined as (date of last (non-zero) dose of study drug – date of first dose of study drug) + 1 and will be summarized in months including descriptive statistics (n, mean, standard deviation, median, minimum, maximum) and a frequency distribution (≤ 1 month, >1 to ≤ 3 months, > 3 to ≤ 6 months, >6 to ≤ 12 months, >12 to ≤ 24 months, > 24 months).

Cumulative dose is defined as:

- **Actual cumulative dose** (mg) = sum of all actual doses taken during the dosing period

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

Dose intensity and relative dose intensity are defined as follows:

- **Actual dose intensity** (mg/day) = actual cumulative dose (mg) / [duration of exposure (days)]

- **Relative dose intensity** = 100*[actual dose intensity (mg/day) / intended dose intensity (mg/day)]

A summary of exposure, including duration, 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. Duration of exposure, cumulative dose, actual dose intensity, and relative dose intensity will also be listed for each participant.

7.6.1.1. Dose Modifications

Dose reduction:

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

Dosing interruption:

A dosing interruption will be indicated in the study treatment eCRF by a dosing record with a total daily dose of 0 mg for one or more days.

Dosing 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.

Frequency counts and percentages of participants who have dose reductions or any study drug interruptions, and the corresponding reasons, will be provided. The number of dosing interruptions per participant, and the duration of dosing interruptions (days) will also be summarized for each study drug.

7.6.2. Concomitant Medications

Concomitant medications are any medications (excluding study drug and prior anticancer treatments) which started prior to first dose date of study treatment and continued during the on-treatment period as well as those that started during the on-treatment period. Concomitant medications will be summarized based on the Prior and Concomitant Medications eCRF.

Concomitant medications will be coded using the latest version of WHO DRL dictionary available at the time of reporting and will be summarized by ATC classification level 2 and preferred term (level 4).

All concomitant medications will be listed.

Incomplete dates will be handled as described in Section 7.1.11.

7.6.3. Subsequent Anticancer Treatments

Number of participants with any anti-cancer treatment after discontinuation of study treatment will be summarized by type of therapy (systemic treatment, radiotherapy, and surgery). In addition, number of participants who received PD1/L1 therapy after treatment discontinuation will also be summarized. The final list of subsequent PD1/L1 therapy will be provided upon medical review of all subsequent anti-cancer systemic treatment before database lock for analysis.

Summary statistics will be created for the data collected on the Subsequent Cancer Treatment Systemic eCRF page. The best overall response on the subsequent anti-cancer systemic treatments will be summarized by the first and secondary subsequent treatment, and by medication class. The final list of medication class will be provided upon medical review of all subsequent anti-cancer systemic treatment before database lock for analysis.

Anticancer systemic treatments initiated since discontinuation of study treatment will be summarized by ATC class and preferred term.

Incomplete dates will be handled as described in Section 7.1.11.

7.6.4. Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as AEs with onset date during the on-treatment period.

Unless otherwise stated, only TEAEs will be presented in summary tables. However, all AEs will be presented in listings. AEs and SAEs will be coded by PT and SOC using the latest available MedDRA version.

The severity of an AE will be assessed by the investigator using the NCI CTCAE, Version 4.03. For participants with more than 1 AE within a SOC or PT, only the highest grade will be included in by-severity summaries.

The investigator will also assess whether the AE is related to study drugs (i.e., a treatment-related AE). For participants with more than 1 AE within a SOC or PT, the highest level of relationship (related is higher than not related) will be included in the by relationship summaries. AEs will be considered treatment related if they are related to encorafenib and/or binimetinib.

For summaries by SOC and PT, each participant will be counted at most once per SOC and at most once per PT. For summaries by PT, each participant will be counted at most once per PT.

Overall summary of safety table will include numbers and percentages of the following:

- Participants with at least 1 TEAE regardless of causality
- Participants with at least 1 treatment-related TEAE
- Participants with Grade 3 or 4 TEAEs
- Participants with Grade 3 or 4 treatment-related TEAEs
- Participants with Grade 5 TEAEs
- Participants with Grade 5 treatment- related TEAEs
- Participants with at least 1 treatment-emergent SAE
- Participants with at least 1 treatment-related SAE
- Participants who discontinued study drug due to a TEAE regardless of causality
    - TEAE leading to encorafenib discontinuation
    - TEAE leading to binimetinib discontinuation
- Participants with a dose reduction due to a TEAE
    - TEAE requiring encorafenib dose reduction
    - TEAE requiring binimetinib dose reduction
- Participants with a dosing interruption due to a TEAE
    - TEAE requiring encorafenib dosing interruption
    - TEAE requiring binimetinib dosing interruption

All TEAE summaries will be displayed (frequency counts and percentages) alphabetically by system organ class (SOC) and preferred term (PT) by descending frequency within SOC

based on "Total" group, if not otherwise noted. Individual summary tables showing the incidence of participants with the following subsets of TEAEs will be generated:

- TEAEs, regardless of causality, by SOC and PT (All Grades and maximum severity)
- TEAEs, regardless of causality, by PT (All Grades and maximum severity) ordered by decreasing frequency based on "Total" group
- TEAEs, regardless of causality, by PT (Grade 3 and Grade 4) ordered by decreasing frequency based on "Total" group
- Treatment-related TEAEs by PT (All Grades and maximum severity) ordered by decreasing frequency based on "Total" group
- Treatment-related TEAEs, by PT (Grade 3 and Grade 4) ordered by decreasing frequency based on "Total" group
- SAEs, regardless of causality, by PT (All Grades) ordered by decreasing frequency based on "Total" group
- Treatment-related SAEs by PT (All Grades) ordered by decreasing frequency based on "Total" group
- TEAEs, regardless of causality, that led to permanent discontinuation of study drug by PT (All Grades) ordered by decreasing frequency based on "Total" group
    - TEAE that led to permanent encorafenib discontinuation
    - TEAE that led to permanent binimetinib discontinuation
    - TEAE that led to both encorafenib and binimetinib permanent discontinuation
- Treatment-related TEAEs that led to permanent discontinuation of study drug by PT (All Grades) ordered by decreasing frequency based on "Total" group
    - TEAE that led to permanent encorafenib discontinuation
    - TEAE that led to permanent binimetinib discontinuation
    - TEAE that led to both encorafenib and binimetinib permanent discontinuation
- TEAEs that led to reduction in dose of study drug by PT (All Grades) ordered by decreasing frequency based on "Total" group
    - TEAE that led to encorafenib dose reduction
    - TEAE that led to binimetinib dose reduction
    - TEAE that led to both encorafenib and binimetinib dose reduction

- Treatment-related TEAEs that led to reduction in dose of study drug by PT (All Grades) ordered by decreasing frequency based on "Total" group
    - TEAE that led to encorafenib dose reduction
    - TEAE that led to binimetinib dose reduction
    - TEAE that led to both encorafenib and binimetinib dose reduction
- TEAEs that led to interruption of study drug administration by PT (All Grades) ordered by decreasing frequency based on "Total" group
    - TEAE that led to encorafenib dosing interruption
    - TEAE that led to binimetinib dosing interruption
    - TEAE that led to both encorafenib and binimetinib dosing interruption
- Treatment-related TEAEs that led to interruption of study drug administration by PT (All Grades) ordered by decreasing frequency based on "Total" group
    - TEAE that led to encorafenib dosing interruption
    - TEAE that led to binimetinib dosing interruption
    - TEAE that led to both encorafenib and binimetinib dosing interruption.
- The following additional tables will be produced for AESIs. A list of AESIs used for this study will be maintained by the SRL and provided to programming in a different document.
- Summary table of binimetinib and encorafenib treatment-emergent AESIs (any AESI, any treatment-related AESI, SAE, treatment-related SAE, Grade 3 or 4 AESI, treatment-related Grade 3 or 4 AESI, Grade 5 AESI, Grade 5 treatment-related AESI)
- AESIs for binimetinib and encorafenib regardless of causality, by AESI grouping (all grades, Grade 3, Grade 4, Grade 5) ordered by decreasing frequency of all grades
- Treatment-related AESIs for binimetinib and encorafenib, by AESI grouping (all grades, Grade 3, Grade 4, Grade 5) ordered by decreasing frequency of all grades
- Time to First Onset of treatment-emergent AESIs for binimetinib and encorafenib regardless of causality (by AESI grouping)
- Time to First Onset of treatment-related treatment-emergent AESIs for binimetinib and encorafenib (by AESI grouping)
- Serious treatment-emergent AESIs for binimetinib and encorafenib by AESI grouping (all grades) ordered by decreasing frequency of "Total" (all-causality and treatment-related)

Time to AE Onset (in days) is defined as the time from the date of the first dose to the onset date of the AE, regardless of grade. If a participant has multiple episodes of an AE, the date of the first occurrence is used. Time to AE onset (in days) will be calculated as (AE start date – first dose date +1). Time to onset is calculated for the subgroup of participants who had the specific AE.

Descriptive statistics will be presented for time to AE onset (days) for the subgroup of participants with the AESI.

All deaths, deaths within 30 days after last dose of study drug, and deaths > 30 days after last dose of study drug will be summarized. The primary reason for death will be summarized for all deaths and deaths within 30 days after last dose of study drug based on the data collected on the Death eCRF page.

Deaths recorded during the study will be provided in a listing.

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

Incomplete dates will be handled as described in Section 7.1.11.

7.6.5. Clinical Laboratory Evaluations

Required hematology, coagulation, urinalysis and clinical chemistry tests are described in Table 11 of the protocol. Hematology, coagulation, urinalysis and clinical chemistry test results will be presented using the International System of Units (SI units) and, where appropriate, will be graded using NCI CTCAE, Version 4.03.

For laboratory data, baseline is the last available assessment performed prior to the treatment start date/time. If more than one value is available, priority is given to the central assessment versus the local assessment. If more than one central sample is available, priority is given to the assessment marked as Unscheduled or Repeat assessment. Participants who start treatment and discontinue from the study on the same day may have 2 different sets of data collected on study day 1, one being reported to the cycle 1 day 1 visit, the other reported to the EOT visit. Data reported at the EOT visit are not eligible for baseline selection.

The following laboratory parameters will be summarized by CTCAE grade:

- Hematology: Hemoglobin (anemia/hemoglobin increased), Platelets (platelet count decreased), WBC (white blood cell decreased/increased), Neutrophils (neutrophil count decreased), Lymphocytes (lymphocyte count increased/decreased).

- Chemistry: Albumin (hypoalbuminemia), Alkaline phosphatase (ALP) (alkaline phosphatase increased), Alanine aminotransferase (ALT) (ALT increased), Aspartate aminotransferase (AST) (AST increased), Total bilirubin (TBL) (blood bilirubin increased), Creatinine (creatinine increased), Corrected calcium, CK, Amylase (serum amylase increased), Lipase (lipase increased), Phosphate (hypophosphatemia),

Magnesium (hypomagnesemia/hypermagnesemia), Potassium (hypokalemia/hyperkalemia), Sodium (hyponatremia/hypernatremia).

- Coagulation: INR (INR increased), PTT or aPTT (Activated partial thromboplastin, time prolonged)

The following laboratory parameters will be summarized by normal range:

- Hematology: Hematocrit, RBC, Monocytes (absolute), Eosinophils (absolute), Basophils (absolute).

- Chemistry: Bicarbonate (CO2), BUN or urea, Chloride, Glucose, LDH, Total protein, Direct bilirubin.

- Coagulation: Prothrombin Time

The Corrected Calcium will be derived from calcium and albumin results as per the following formula:

Corrected Calcium (mmol/L) = [4*calcium(mmol/L) – 0.8*(0.1*albumin(g/L) – 4)]/4

The normal range of Calcium will be used as normal range for Corrected Calcium.

The following summaries will be produced for the hematology and chemistry laboratory data (by laboratory parameter) including central and local laboratory:

- Shift tables using CTCAE grades to compare baseline to the worst post-baseline value for laboratory parameters with CTCAE grades. For the laboratory parameters like blood sodium where participants can be graded for decreased or increased values, the worst post-baseline CTCAE grade will be presented for decrease and increase separately (e.g. hyponatremia and hypernatremia).

- Shift tables using CTCAE grades to compare baseline to the worst post-baseline value for laboratory parameters with CTCAE grades showing participants with Grade ≤ 2 at baseline and worst post baseline Grade 3 or 4.

- Tables reporting the worst post-baseline CTCAE grades for laboratory parameters.

- Shift tables using low, normal, high (as well as low and high combined) classifications to compare baseline to the worst post-baseline value for laboratory parameters where CTCAE grades are not defined.

The following listing will be produced for the laboratory data for all laboratory parameters are defined:

- All laboratory test results will be presented in listings sorted by participant identifier, laboratory test, and date/time of collection with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory

reference ranges. Values outside laboratory normal ranges will be flagged where appropriate.

Hepatic Toxicity

Hepatic toxicity will be assessed based on the following Liver Function Tests (LFTs): ALT, AST, ALP, TBL, and INR. Frequency counts and percentages of participants having a newly occurring value in the categories in Table 6 will be provided.

An evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot will also be created 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 LFTs values for participants having a newly occurring value in the categories presented in Table 6 will be provided.

Table 6. Hepatic Toxicity Criteria

Parameter	Criterion
ALT	>3xULN; >5xULN; >8xULN;>10xULN;>20 ULN
AST	>3xULN; >5xULN; >8xULN >10xULN;>20 ULN
AT (ALT or AST)	>3xULN; >5xULN; >8xULN >10xULN;>20 ULN
TBL	>1.5xULN, >2xULN
ALP	>2xULN, >3xULN
AT & TBL	AT >3xULN & TBL >2xULN; AT >5xULN & TBL >2xULN; AT >10xULN & TBL >2xULN
ALP & TBL	ALP >3xULN & TBL >2xULN
AT & TBL & ALP	AT >3xULN & TBL >2xULN & ALP <2xULN
AT & TBL & INR	AT >3xULN & (TBL >2xULN or INR >1.5)

7.6.6. Vital Signs and Body Measurements

The following criteria define clinically notable vital sign abnormalities:

Clinically notable elevated values

- Systolic Blood Pressure (BP): ≥ 160 mmHg and an increase ≥ 20 mmHg from baseline
- Diastolic BP: ≥ 100 mmHg and an increase ≥ 15 mmHg from baseline
- Pulse rate: ≥ 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
- Pulse rate: ≤ 50 bpm with decrease from baseline of ≥ 15 bpm
- Weight: ≥ 20% decrease from baseline
- Body temperature [C]: ≤ 36 °C

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

In addition, a table reporting the worst post baseline CTCAE grade for temperature will be produced showing: Grade 0 (≤ 38.0 °C), Grade 1 (> 38.0 ≤ 39.0 °C), Grade 2 (> 39.0 ≤ 40.0 °C), Grade 3 or 4 (> 40.0 °C).

7.6.7. ECG

Potential effects of treatment with study drug on ECG parameters will be assessed by ECG interval analysis of heart rate, QRS, QT, and QT interval corrected for heart rate using Fredericia's formula (QTcF). 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 participant's baseline QTcF value for all post-dose comparisons. The QTcF data collected on the eCRF page will be used in the summary.

Data from ECGs will be listed, notable values will be flagged, and any other information collected will be listed as appropriate. Frequency counts and percentages of participants having clinically notable ECG values according to Table 7 will be provided.

Table 7. Criteria for Clinically Notable ECG Criteria

Parameter	Criterion
QTcF	increase from baseline > 30 ms
	increase from baseline > 60 ms
	new > 450 ms
	new > 480 ms
	new > 500 ms

7.6.8. MUGA/Echocardiogram

LVEF abnormalities are defined according to CTCAE grade version 4.03. Participants 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%, inclusive, or absolute change from baseline between -10% and < -20%
- Grade 3: LVEF between 20% and 39%, inclusive, or absolute change from baseline ≤ -20%
- Grade 4: LVEF lower than 20%.

A table reporting the worst post-baseline LVEF value using CTCAE grades will be produced. Different modalities to assess LVEF might be used for the same participant. The CTCAE grades will be provided regardless of the modality.

7.6.9. Ophthalmic Examination

Visual Acuity

Visual acuity will be measured using the Snellen visual acuity. This is determined by establishing the smallest optotypes that can be identified correctly by the participant at a given observation distance. Snellen visual acuity can be reported as a Snellen fraction (m/M) in which the numerator (m) indicates the test distance and the denominator (M) indicates the distance at which the gap of the equivalent Landolt ring subtends 1 minute of arc.

For each timepoint, the LogMAR score will be calculated as –log(m/M).

Total visual acuity score will also be assessed identifying clinically meaningful deterioration in LogMAR. The number of participants reporting a change in score of <=0, 0 to <0.1, 0.1 to <0.2, 0.2 to <0.3 and ≥0.3 LogMAR will be summarized in shift table.

Maximum number of loss lines should be tabulated for post baseline assessment.
The change from baseline will be classified as:

- if change from baseline in terms of logmar is >0.26 then "≥ 3 line loss";
- if change from baseline in terms of logmar is > 0.16 and ≤ 0.26 then "2 line loss";
- if change from baseline in terms of logmar is ≥ -0.16 and ≤ 0.16 then "± 1 line loss";
- if change from baseline in terms of logmar is .< and <-0.16 then ">1 line increase".

7.7. Pharmacokinetic Analysis

Plasma concentrations and PK parameters will be determined for encorafenib, its metabolite (LHY746) and binimetinib. PK summaries will be presented for treatment naïve participants, previously treated participants and for all participants combined (overall) in the PK set. C1D1 is defined as single dose (i.e., first dose) and C1D15 is defined as steady state.

7.7.1. Plasma Concentrations of Encorafenib, LHY746, and Binimetinib

Plasma concentrations of encorafenib, its metabolite (LHY746), and binimetinib will be quantified at the time points indicated in Table 8:

Table 8. Pharmacokinetic Blood Sampling Times

Schedule[1]	Study Visit	Timing of Sample	Allowed Window
Serial	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	Predose	-30 min
Sparse	C1D1	Predose	-30 min
	C2D1	Predose	-30 min
	C3D1	Predose	-30 min
	C4D1	Predose	-30 min
	C5D1	Predose	-30 min
	C6D1	Predose	-30 min

1 Serial blood sampling in participants enrolled under Protocol Version 0 through 3.0; sparse blood sampling for all participants enrolled from Protocol Version 4.0 onwards.

Protocol Amendment 4 implemented a change to the PK sampling schedule. All participants enrolled under the original protocol and up to and including Protocol Amendment 3 were subjected to serial PK blood sampling; however, all participants enrolled under Protocol Amendment 4 and later versions were subjected to sparse PK sampling assessments only (see

Table 8). Since there is only one common time point between the serial and sparse PK sampling schedules, separate PK TLFs will be presented for each sampling schedule.

All plasma concentration values for each participant in the safety set will be included in the bioanalytical plasma concentration listings, and participants will be identified as being in the PK set, as applicable. Individual concentration records will be flagged for the affected visit if any of the following occur:

a. Participant had vomiting within 4 hours following study drug administration on the day of PK sampling (C1D1 and C1D15) or at any time over the preceding 24 hours.
b. Plasma levels were not considered to be at steady-state (i.e. dosing was not performed for at least 4 consecutive days prior to C1D15 or C2D1).
c. Subject received a higher or lower dose compared to planned treatment.
d. PK sampling time was outside the allowed window or the elapsed time was not calculable.

The plasma concentrations of encorafenib, its metabolite (LHY746), and binimetinib will be summarized for all nominal time points, including predose (trough) concentrations, using the following descriptive statistics: N (number of participants in the population), n (number of participants with non-missing values), m (number of non-zero concentrations), arithmetic mean, standard deviation, coefficient of variation (CV), geometric mean, geometric standard deviation, geometric CV, minimum, median and maximum. An individual concentration-time data point will be excluded from the calculation of summary statistics if any of the above flags [a-d] apply. Concentrations reported as below the limit of quantification (BLQ) will be set to zero for the calculation of arithmetic mean, standard deviation, CV, minimum, median and maximum. For the calculation of geometric mean and geometric CV, BLQ values will be replaced by ½LLOQ. All summary statistics below the limit of quantification will be presented as "< X.XX" where X.XX represents the lower limit of quantification.

Concentration data, PK parameters, summary statistics and statistical analyses values will be presented to 3 significant figures.

The geometric mean with standard deviation* plasma concentration-versus-time profiles will be presented graphically for each analyte using both linear and semi-logarithmic scales on C1D1 and C1D15 and for trough concentrations of Day 1 of Cycles 1 through 6.

* Note: ± (Standard Deviation) in this context represents the standard deviation calculated on a log scale; therefore, geometric standard deviation would be used as a multiplicative factor:

+Geometric Standard Deviation = $\exp^{(\text{Mean\_ln} + \text{Standard Deviation\_ln})} = \exp^{(\text{Mean\_ln})} * \exp^{(\text{Standard Deviation\_ln})}$ = Geometric Mean * Geometric Standard Deviation.

-Geometric Standard Deviation = $\exp^{(\text{Mean\_ln} - \text{Standard Deviation\_ln})} = \exp^{(\text{Mean\_ln})} / \exp^{(\text{Standard Deviation\_ln})}$ = Geometric Mean / Geometric Standard Deviation .

7.7.2. Plasma Pharmacokinetic Parameters for Encorafenib, LHY746, and Binimetinib

PK parameters for participants in the PK set will be determined for encorafenib, its metabolite (LHY746), and binimetinib, when possible and appropriate. Only participants assigned to the serial PK blood sampling schedule will be included in the PK parameter assessment.

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 will be used for PK calculations. If actual times are not recorded/available, nominal times will be used. All BLQ values before the observed maximum plasma concentration (Cmax) will be set to 0; all BLQ values after Cmax or embedded between two measurable values will be considered as missing.

The PK parameters that will be calculated for encorafenib, its metabolite (LHY746), and binimetinib on C1D1 and C1D15 are defined in Table 9.

The AUC parameters will be calculated according to the linear-up log-down trapezoidal rule. Additional PK parameters may be calculated at the discretion of the pharmacokineticist.

All PK parameter values will be presented in data listings by analyte, cycle and study day. Each parameter will be summarized in tables by line of therapy (treatment naive, previously treated, and overall), analyte, cycle and study day using the following descriptive statistics: N, n, arithmetic mean, standard deviation, CV, geometric mean, geometric CV, minimum, median and maximum. Descriptive statistics for in-text summary tables will include geometric mean with geometric CV for AUC, Cmax, and RAUC. For 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.

Table 9. Definitions of Pharmacokinetic Parameters

PK Parameter	Definition
AUC_{0-6}	Area under the plasma concentration-time curve from zero to 6 hours
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 at steady-state (C1D15 only) To estimate AUC_{tau}, the concentration measured at predose on C1D15 will be imputed as the concentration at the end of the dosing interval (i.e., 12 or 24 hours, as appropriate) assuming steady-state has been attained
C_{max}	Observed maximum plasma concentration
C_{trough}	Trough (predose) concentration at steady state
T_{max}	Observed time of C_{max}
T_{last}	Observed time of last measured concentration

Table 9. Definitions of Pharmacokinetic Parameters

PK Parameter	Definition
MR_{Cmax}	Ratio of C_{max} values of the metabolite compared to parent, corrected for molecular weight, for LHY746/ Encorafenib only
$MR_{AUClast}$	Ratio of AUC_{last} values of the metabolite compared to parent, corrected for molecular weight, for LHY746/ Encorafenib only

7.7.3. Statistical Assessment of Accumulation

For statistical analysis of accumulation of encorafenib, its metabolite (LHY746), and binimetinib, the accumulation ratio will be estimated for serial PK sampling participants by making comparisons of $AUC_{0-6,}$ AUC_{last} and C_{max} on C1D15 with corresponding estimates on C1D1; a mixed-effects model will be fitted to log-transformed $AUC_{0-6,}$ AUC_{last} and C_{max} including day as a fixed effect and subject as a random effect. This model will be used to estimate the accumulation ratio (C1D15 / C1D1) with 90% CIs. The geometric least square means and ratio with 90% CIs will be tabulated.

7.7.4. Statistical Assessment of Cigarette Smoking on PK Exposure

The impact of cigarette smoking on encorafenib and binimetinib metabolism will be explored. Smoking history collected will be used to calculate the median number of cigarettes smoked by the participant population per day, and the exposure of encorafenib, its metabolite (LHY746), and binimetinib (AUC_{0-6} and C_{max}) will be summarized with participants stratified based on this: zero, less than the median, or, greater than or equal to the median number of cigarettes, using the following descriptive statistics: N, n, arithmetic mean, standard deviation, CV, geometric mean, geometric CV, minimum, median and maximum. If the median is zero, the participants will be stratified by zero and non-zero cigarettes.

7.7.5. Statistical Assessment of Line of Therapy on PK Exposure

The impact of line of therapy on PK exposures will be assessed between treatment-naïve and previously treated participants in the PK Analysis Set. Welch's 2-sided t-test for unequal variances will be used to assess the statistical significance of the differences for log-transformed PK parameter estimates (AUC_{0-6}, AUC_{tau}, and C_{max}), by analytes (encorafenib, LHY746, and binimetinib) on C1D1 and C1D15. The p-values will not be adjusted for multiplicity.

7.8. Interim Analysis

An interim analysis may be performed for treatment-naïve participants after about 90% [n=54] of the planned treatment-naïve participants [n=60] will be enrolled.

At the time of the interim analysis, if the posterior probability that the true ORR exceeds 39% is ≥80%, assuming a non- informative Beta (0.5,0.5) prior, then the data will be considered for discussions with regulatory authorities.

The Table 10 includes posterior probability for the expected number of participants and the observed responses at the first look.

Table 10. Posterior Probabilities

Enrolled Participants	Observed Responses	Posterior Probability for True ORR >39%
54	24	79.5
54	25	86.4
54	26	91.5
54	27	95.0
54	28	97.2
54	29	98.6

8. DATA AND ANALYSIS QUALITY ASSURANCE

This protocol was conducted under the sponsorship of Pfizer Inc. Personnel within Pfizer or CRO designee provided statistical and data management input for the design of the clinical trial protocol; data management, statistical analysis and generation of tables, listings and figures; and medical writing support for the clinical study report.
All parties mentioned above will work diligently and collaboratively to ensure that data collection and analysis for this study are of the highest quality. This will be accomplished through programmed edit checks, quality control processes, and clinical and statistical review of data displays. Quality and accuracy of statistical analyses will be verified though established statistical programming validation processes.

9. REFERENCES

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4. Mok TSK, Wu YL, Kudaba I et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet. 2019;393(10183):1819-30.

5. Planchard D, Smit EF, Groen HJM et al. Dabrafenib plus trametinib in participants with previously untreated BRAFV600E-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. Lancet Oncol 2017;18(10):1307-16.

10. APPENDIX 1: EVALUATION OF RECIST (VERSION 1.1) TUMOR ASSESSMENT CRITERIA

The primary efficacy analysis is based on IRR assessment per RECIST 1.1. The secondary efficacy analysis is based on derived investigator assessment of tumor data and confirmation of response is required.

This section describes the rules used for derivation of tumor response and progression based on derived investigator assessment of tumor data for secondary efficacy analyses.

Uses "start date" to denote the date of first dose of study drug.

SPECIFICATIONS FOR PROGRAMMATIC DERIVATION OF TUMOR RESPONSE USING RECIST 1.1

The primary efficacy analysis will be based on IRR interpretation of tumor assessment scans from study sites, performed by Bioclinica. The details of this process are described in the study specific Bioclinica charter. Analyses based on IRR will use data as transferred from IRR:

- BOR (but not the target response, non-target response and time point response at each time point) will be derived using the rules presented in this appendix.

- Date of progressive disease (PD) and determination of event or censoring for progression-free survival will be derived, from the PD date reported by IRR, the dates of time point tumor assessments reported by IRR and accounting for anticancer therapy and other censoring rules.

A secondary efficacy analysis will be based on a programmatic approach to derive tumor response/progression, using RECIST 1.1 and the investigator tumor assessment data recorded on the target, non-target, and new lesion eCRFs, as described below.

The tumor response criteria are based on RECIST 1.1 (Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline [Version 1.1]. Eur J Cancer. 2009;45(2):228-47).

10.1. Study Specific Information

10.1.1. Interchangeable Methods of Tumor Assessment

If an inconsistency in imaging technique has occurred (e.g., a switch from CT to MRI or a switch from contrast to non-contrast), the independent radiologist will determine whether this change in technique affects tumor evaluation. Issues affecting response will be documented.

For the derivation of investigator's assessment data CT/MRI/Spiral CT are considered interchangeable methods.

10.2. Lesion Evaluation at Assessment Times

10.2.1. Response Evaluation of Target Lesions

- Complete Response (CR) is defined by the disappearance of all non-lymph node target lesions (where all target lesions are recorded with a length of 0 mm on the "Target Lesions" eCRF). Any pathological lymph nodes (recorded as target lesion) must have reduction in short axis to <10 mm.
    - Note: the SOD may not be zero if lymph nodes are included as target lesions.
- Partial Response (PR) is defined by a 30% or more decrease in SOD of target lesions, taking as reference the baseline SOD.
- PD is defined by a 20% or more increase in the SOD of target lesions relative to nadir (smallest SOD considering baseline and all assessments prior to the time point under evaluation), with a minimum absolute increase of 5 mm relative to nadir.
    - Note: if only a subset of target lesions are assessed and the sum of the non-missing lesion diameters results in an increase above of at least 5 mm and at least 20% above the nadir, then the SOD will still be calculated and the progression criteria will have been otherwise met. If the sum of non-missing lesions does not indicate PD, then the SOD will be left as missing.
- Stable Disease (SD) is assigned when neither sufficient shrinkage to qualify for CR or PR, nor sufficient increase to qualify for PD is observed, taking as reference the nadir.
- No Target Lesion at Baseline (NB) is assigned if "No Target Lesion" is checked, on the "Lesion Assessment Y/N" eCRF at baseline.
    - Note: a protocol deviation should be reported.
- Not All Evaluated (NAE) is assigned if, in the absence of PD based on evaluated target lesions:
    - Any individual target lesion is evaluated as "Indeterminate" on the "Target Lesions" eCRF.
    - Inconsistent methods (unless considered "interchangeable") are used for any target lesions after start date.
    - One or more target lesions are not assessed.
    - One or more target lesions were excised or irradiated and have not reappeared or increased.

Determination of target lesion response in case of reappearance of one or more target lesion(s) that have previously disappeared:

- If the previous target lesion response was CR, and a non-lymph node target lesion reappears, then the response is always PD.
- If the previous target lesion response was CR, and a lymph node target lesion reappears, then the response (whether CR or PD) is assessed based on PD criteria noted above. The response will be PD only if SOD criterion for PD is met and if the lymph node returns to pathologic size (≥10 mm) and meets the absolute requirement of 5 mm increase over nadir for the reappearing lesion. Otherwise, the response is CR.
- If the previous target lesion response was PR, then the response should be evaluated based on the SOD.

Notes:

The SOD is only considered if the methods of assessment are consistent with baseline. The "interchangeable" methods noted in Section 10.1.1 above are all considered consistent methods.

In the SOD, the longest diameter will be used for non-nodal lesions and the short axis dimension will be used for each lymph node included in the sum.

10.2.2. Response Evaluation of Non-Target Lesions

- CR is defined by the complete disappearance of all non-target lesions (where all non-target lesions are marked "Absent" on the "Non-Target Lesion" eCRF). All lymph nodes must be non-pathological in size (<10 mm in short axis).
- Non-CR/Non-PD is defined by persistence of one or more non-target lesions (ie, if any non-target lesions are marked "Present" on the "Non-Target Lesion" eCRF).
- NB is assigned if "No Non-Target Lesions" is marked on the "Lesion Assessment Y/N" eCRF at baseline.
- NAE is assigned if, in the absence of PD based on evaluated non-target lesions:
  - Any individual non-target lesion is evaluated as "Not Evaluable" (marked as "Not Evaluable" on the "Non-Target Lesions" eCRF).
  - Inconsistent methods (unless considered "interchangeable" as noted in Section 1.2) are used for any non-target lesions after start date.
  - One or more non-target lesions are not assessed.

- PD is assigned if any non-target lesion is marked “unequivocal progression” on the “Non-Target Lesion” eCRF.

    - Note: the lesions assessed are only considered for CR, Non-CR/Non-PD and PD if the methods of assessments are consistent with baseline. The “interchangeable” methods noted in Section 10.1.1 above are all considered consistent methods.

10.2.3. New Lesion Evaluation Criteria

A new lesion is defined by the appearance of 1 or more new lesions on the “New Lesions” eCRF.

Any lesion that is recorded for the first time after the start date without being marked on the “New Lesions” eCRF must be queried. In case the inconsistency is not resolved at time of database snapshot/lock, the lesion will be considered as new and the participant in progression at that time point.

The requirement for consistent methods of assessment with baseline does not apply for new lesions.

10.3. Objective Response Status at Each Assessment

Objective response status is determined from the derived target and derived non-target lesion data using the conventions in

Table 11. Derivation of Objective Status Based on Target and Non-Target Lesion Response Assuming No New Lesions*

under the assumption that there are no new lesions identified at the visit.

Objective status after a change in modality that is not considered interchangeable is classified as Not Evaluable (NE).

If there are any new lesions at a time point, then the response is PD at that time point regardless of target or non-target lesion response.

Table 11. Derivation of Objective Status Based on Target and Non-Target Lesion Response Assuming No New Lesions*

Target lesion response	Non-Target lesion response	Objective response status
CR	CR	CR
CR	Non-CR/Non-PD	PR
CR	PD	PD
CR	NAE	PR
PR	CR	PR
PR	Non-CR/Non-PD	PR
PR	PD	PD
PR	NAE	PR
SD	CR	SD
SD	Non-CR/Non-PD	SD
SD	PD	PD
SD	NAE	SD
PD	Any	PD
NAE	PD	PD
NAE	CR Non-CR/Non-PD NAE	NE
NB	CR	CR
	Non-CR/Non-PD	Non-CR/Non-PD
	PD	PD
	NAE	NE
CR	NB	CR
PR		PR
SD		SD
PD		PD
NAE		NE

*If there are any new lesions at a time point, then the response is PD at that time point regardless of target or non-target lesion response.
Abbreviations: CR = Complete Response; PR = Partial Response; SD = Stable Disease; PD = Progressive Disease; NAE = Not All Evaluated; NB = No Baseline; NE = Not Evaluable.
Note: If non-target (or target) lesions are not collected at baseline, then the overall response is equivalent to the target (or non-target) lesions response, respectively.

10.4. Date of Response at Each Assessment/Overall:

The date of CR, PR, PD, non-CR/non-PD, SD, NE is derived as the date of the first radiographic evaluation included in the cluster.

The date of first response for purposes of calculating duration of response and time to response is defined as the first date a CR or PR was documented.

10.4.1. Best Overall Response Evaluation for Each Participant

BOR is derived from the sequence of objective responses reported during the “Period for Derivation of Best Overall Response” according to the rules specified in the Oncology Rulebook.

Table 12 presents derivation of BOR for specific cases assuming that confirmation of response is required and is adapted from Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

Table 12. Best Overall Response When Confirmation of Response is Required

Overall response first time point	Overall response subsequent time point	Best overall response
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

Note that best overall response of CR or PR requires confirmation ≥4 weeks after response is first observed. Minimum duration criteria for SD must be met for a best overall response of SD.
Abbreviations: CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable.
a. If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes "CR" may be claimed when subsequent scans suggest small lesions were likely still present and in fact the participant had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Table 13. Best Overall Response When Confirmation of Response is Required: Further Examples

presents derivation of BOR for specific examples of overall response at sequential time points.

Table 13. Best Overall Response When Confirmation of Response is Required: Further Examples

Overall response sequential time points	Best overall response
SD - CR - CR - PR	CR if the two CRs were ≥4 weeks apart; else, SD if at any time on or before the 3rd time point evaluation the minimum criteria for SD duration was met; else PD
SD - PR - CR - PR	PR if the 2nd and 3rd evaluations (PR, CR) were ≥4 weeks apart; else SD if at any time on or before the 3rd time point evaluation the minimum criteria for SD duration was met; else PD
SD - CR - SD - CR	SD if at any time on or before the 2nd time point evaluation the minimum criteria for SD duration was met; else PD
PR - CR - NA - CR - PR	CR if the 2nd and 4th evaluations (CR, CR) were ≥4 weeks apart; else PR if the 1st and 2nd evaluations (PR, CR) or the 1st and 4th evaluations (PR, CR) were ≥4 weeks apart; else SD if at any time on or before the 4th time point evaluation the minimum criteria for SD duration was met; else PD
PR - CR - CR - PR	CR if the 2nd and 3rd evaluations (CR, CR) were ≥4 weeks apart; else PR if the 1st and 2nd evaluations (PR, CR) or the 1st and 3rd evaluations (PR, CR) were ≥4 weeks apart; else SD if at any time on or before the 3rd time point evaluation the minimum criteria for SD duration was met; else PD
PR - CR - CR - SD	CR if the 2nd and 3rd evaluations (CR, CR) were ≥4 weeks apart; else PR if the 1st and 2nd evaluations (PR, CR) or the 1st and 3rd evaluations (PR, CR) were ≥4 weeks apart; else SD if at any time on or before the 3rd time point evaluation the minimum criteria for SD duration was met; else PD
CR - NE - CR - SD	CR if the 1st and 3rd evaluations (CR, CR) were ≥4 weeks apart; else SD if at any time on or before the 3rd time point evaluation the minimum criteria for SD duration was met; else PD
PR - PR - CR - PR	PR if 2 of the first 3 evaluations (1st to 2nd, or 1st to 3rd, or, 2nd to 3rd) were ≥4 weeks apart; else SD if at any time on or before the 3rd time point evaluation the minimum criteria for SD duration was met; else PD
PR - PR - CR - SD	PR if 2 of the first 3 evaluations were ≥4 weeks apart (1st to 2nd, or 1st to 3rd, or, 2nd to 3rd); else SD if at any time on or before the 3rd time point evaluation the minimum criteria for SD duration was met; else PD
CR - SD - SD - CR	SD if at the 1st time point evaluation the minimum criteria for SD duration was met; else PD
PR - CR - PR - CR	PR if the 1st and 2nd time point evaluations (PR, CR) were ≥4 weeks apart; else SD if at any time on or before the 2nd time point evaluation the minimum criteria for SD duration was met; else PD

If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met.
Abbreviations: CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable; NA = not assessed.