Clinical Development

CLGX818X2109

The LOGIC 2 trial

A phase II, multi-center, open-label study of sequential encorafenib/binimetinib combination followed by a rational combination with targeted agents after progression, to overcome resistance in adult patients with locally advanced or metastatic BRAF V600 melanoma

SAP – Statistical Analysis Plan
Version 3.0

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List of abbreviations

ADI	Actual dose intensity
AE	Adverse Event
ALT/SGPT	Alanine transaminase/glutamic pyruvic transaminase
aPTT	Activated partial thromboplastin time
AST/SGOT	Aspartate transaminase/glutamic oxaloacetic transaminase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
AUCtau, ss	Area under the concentration-time curve from time zero to time tau at steady-state
BCRP	Breast Cancer Resistance Protein
BID	Bis In Diem/ twice daily
BOR	Best Overall Response
BRAF	V-raf murine sarcoma viral oncogene homolog B1
BRAFi	BRAF inhibitor
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
C_{max}	Maximum plasma concentration
Cmax, ss	The maximum (peak) observed plasma concentration after drug administration at steady state
CK/ CPK	Creatine kinase / Creatine phosphokinase
CL,ss/F	Apparent total plasma clearance of drug
Clast, ss	Last measurable plasma concentration at steady state
CR	Complete Response
CRC/ mCRC	Colorectal cancer/ metastatic CRC
CRF	Clinical Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
Ctrough, ss	Measured concentration at the end of a dosing interval at steady-state (taken directly before next administration)
CTT	Clinical Trial Team
CV	Coefficient of Variation
CYP	Cytochrome P450
DCR	Disease Control Rate
DDS	Dose-Determining Set
DLT	Dose Limiting Toxicity
DOR	Duration Of Response
DV	Protocol Deviation
ECG	Electrocardiogram
eCRF	Electronic case report/record form
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency

EOT	End Of Treatment
EPT	Early Program Team
ERK	Extracellular signal Regulated Kinase
EWOC	Escalation With Overdose Control
FAS	Full Analysis Set
FDA	Food and Drug Administration
FU	Follow Up
HDL	High-density lipoprotein
ICF	Informed Consent Form
IHC	Immunohistochemistry
KRAS	V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LVEF	Left ventricular ejection fraction
MA	Molecular alteration
mCRC	Metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated protein kinase
MR	Metabolite ratio
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NRAS	Neuroblastoma RAS viral oncogene homolog
OAT	Organic anion transporter
ORR	Overall Response Rate
OS	Overall Survival
PD	Pharmacodynamic / Progressive Disease
PDI	Planned dose intensity
PFS	Progression-Free Survival
P-gp	Permeability glycoprotein
PI3K	Phosphatidylinositol 3' Kinase
PIK3CA	Phosphatidylinositol 3' Kinase Catalytic Alphapolypeptide
PK	Pharmacokinetic
PPS	Per-Protocol Set
PR	Partial Response
PT	Prothrombin time
PTEN	Phosphatase and Tensin Homolog gene
QD	Quaque Die/ once daily
QOD	Every other day
QTcB	QT interval adjusted according to Bazett
QTcF	QT interval adjusted according to Fredericia
RA	Accumulation ratio
RAF	V-raf murine sarcoma viral oncogene
SAP	Statistical Analysis Plan

RBC	Red Blood Cell
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	Recommended Phase II Dose
RT-PCR	Reverse-transcriptase polymerase chain reaction
SAE	Serious Adverse Event
SD	Stable Disease
SOD	Sum of Diameters
T1/2, ss	Terminal elimination half-life at steady state.
Tmax, ss	Time to reach maximum plasma concentration at steady state
TSH	Thyroid-stimulating hormone
TTR	Time To (overall) Response
TA	Tumor Assessment
VAP	Validation and Analysis Planning
Vz,ss/F	The apparent volume of distribution at steady state
WBC	White Blood Cell
WHO	World Health Organization

1 Introduction

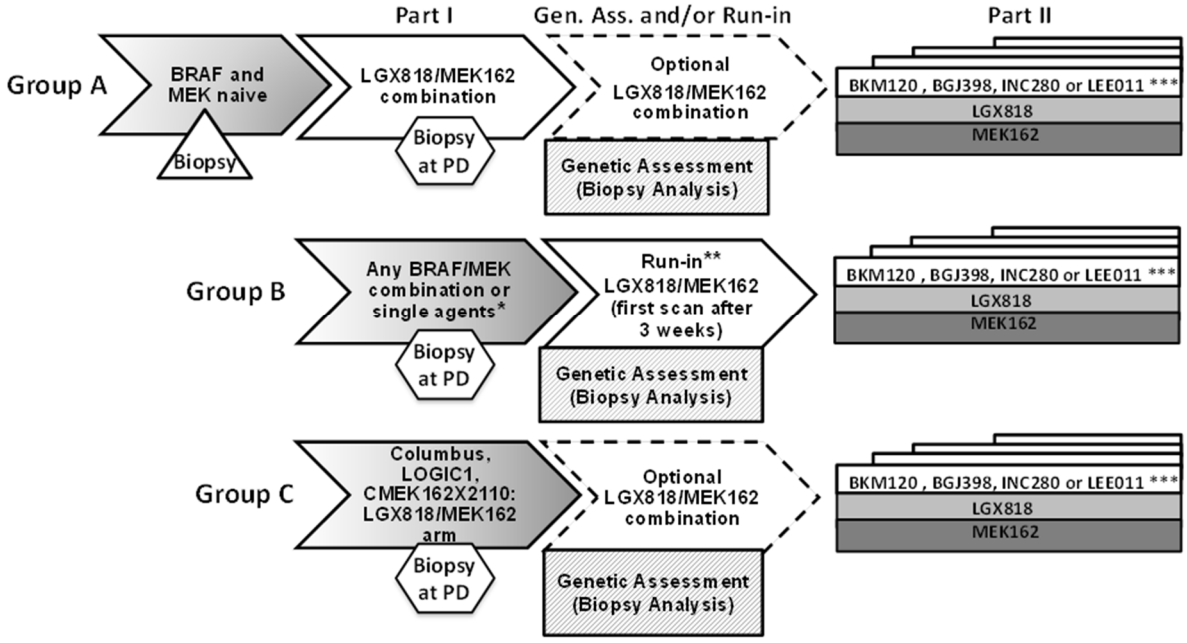
This document provides detailed statistical methodology for the analysis of Part I (patients naive to selective BRAF and MEK inhibitors), Run-in (non-naive patients for BRAF and/or MEK inhibitor treatment who are relapsing and who are receiving a brief run-in with encorafenib (LGX818)/binimetinib (MEK162) combination), and Part II (patients who are receiving a tailored triple combination treatment in one of the four arms: encorafenib/ binimetinib + infigratinib (BKM120), buparlisib (BGJ398), capmatinib (INC280) or ribociclib (LEE011) based on the genetic assessment of a tumor biopsy obtained at progression of disease (PD) on Part I/Run-in) data from study CLGX818X2109 that will be presented in the Clinical Study Report (CSR). The statistical analysis plan (SAP) specification provides the programming specifications for derived variables, datasets, and outputs.

All changes to the planned analysis described in SAP shell and specifications required before or after database lock will be made through an amendment or addendum, respectively. Note that obvious corrections will be made at the time of analysis to address minor formatting or spelling mistakes present in SAP shell without the need to amend these modules.

The SAP shell and specifications may also serve as a reference for the creation of any outputs required outside of the CSR, e.g., maximum tolerated dose (MTD)/recommended Phase 2 dose (RP2D) declaration, Investigator's Brochure (IB) updates, abstracts, posters, presentations, manuscripts, and management updates, unless otherwise specified.

1.1 This SAP was created based on final protocol amendment version 07 released on 16-Dec-2019.Study design

Figure 1-1 Study design



*Single agents: i.e., vemurafenib, dabrafenib, encorafenib , trametinib, binimetinib; Combos: i.e., dabrafenib/trametinib, encorafenib/binimetinib combination

**Patients who progressed on a previous BRAFi and/or MEKi regimen will continue on encorafenib/binimetinib if PR is observed, followed by new Biopsy at progression. Patients who did not progress on their prior BRAFi/MEKi regimen may continue encorafenib/binimetinib combination until evidence of disease progression at which point a tumor biopsy will be taken and analyzed to guide assignment to a triple combination arm in Part II.

*** ribociclib cohort might start directly at the RP2D established in CMEK162X2110, if available.

Note: As of 10 July 2015, the triple combination of encorafenib/binimetinib+ infigratinib is no longer being explored

1.2 Objectives and endpoints

Objectives and related endpoints are described in Table 1-1 below.

Table 1-1 Objectives and endpoints

Objective	Endpoints
Primary To assess the anti-tumor activity of encorafenib/binimetinib in combination with third targeted agents after progression on encorafenib/binimetinib combination therapy.	Overall response rate (ORR)
Secondary To estimate the MTD/RP2D of triple combinations after progression on encorafenib/binimetinib therapy To characterize the safety and tolerability of encorafenib/binimetinib in combination with targeted agents	Incidence of Dose Limiting Toxicities (DLTs) in Cycle 1 of Combination Part (Part II) Adverse Events (AEs), serious AEs (SAEs), changes in hematology and chemistry values, vital signs, electrocardiograms (ECGs), dose interruptions, reductions and dose intensity.
To further assess anti-tumor activity of encorafenib/binimetinib combination, and in combination with targeted agents after progression on encorafenib/binimetinib combination To characterize genomic alterations in tumor tissue at baseline and at tumor progression. To determine the PK profiles of encorafenib, binimetinib and the third agents when given in combination and to assess drug-drug interaction	PFS, DOR, TTR, DCR, and OS (Part II only) Genomic alteration status (e.g., mutation, amplification, deletion, overexpression, ligand activation and splice variants) of pre-defined markers Plasma concentration and derived parameters of encorafenib/binimetinib, and targeted agents
CCI [redacted]	

2 Data Analysis

The data will be analyzed by PPD using SAS version 9.2 or higher. For Bayesian modeling, SAS version 9.2 or higher will be used. PK parameters will be calculated using non-compartmental methods available in Phoenix WinNonlin version 8.3 or higher.

An interim analysis CSR was prepared based on all data collected from the Part I/Run-in patients enrolled up to the data cutoff date of 28Jun2022. A primary CSR will be prepared based on all data collected from Part I/Run-in and Part II once all Part II patients have either completed at least six cycles of treatment or have discontinued the study.

Data from participating centers in this study protocol will be combined, so that an adequate number of patients will be available for analysis.

Study data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and all relevant PK and biomarker measurements. Quantitative data will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) and categorical data will be summarized using contingency tables (frequencies and percentages).

The following rules will be followed for reporting results unless stated otherwise:

All data including efficacy, safety, and biomarker summaries will be provided by part and treatment group. Unless specified otherwise, Part I/Run-in and Part II will be presented separately and the outputs for Part II will be combined across all dose levels within each combination arm. The order of the arms for part II patients will be reported in the descending order based on the number of patients (N) receiving the combination treatment. All patients from a combination arm will be pooled together irrespective of their initial planned combination treatment dose level.

Patients will be grouped for Part I/Run-in as follows:

Group A: Patients naive to selective BRAF and binimetinib inhibitors

Group B: Patients who progressed after treatment with single-agent BRAF or MEK inhibitor or the combination of BRAF/ binimetinib inhibitors (excluding encorafenib/binimetinib combination)

Group C: Patients who progressed after treatment with encorafenib/binimetinib combination in other Sponsor studies

The treatment groups for reporting Part I/Run-in will be:

- encorafenib 450mg + binimetinib 45mg (naive)
- encorafenib 450mg + binimetinib 45mg (non-naive)
- All patients (naive and non-naive)

The non-naive treatment group will summarize the period of dual combination treatment during the run-in for Group B patients and the screening phase for Group C patients.

The treatment groups for reporting Part II will be:

- encorafenib+ binimetinib + ribociclib
- encorafenib+ binimetinib + infigratinib
- encorafenib+ binimetinib + buparlisib
- encorafenib+ binimetinib + capmatinib

2.1 Baseline

Baseline is the last available and valid assessment performed or value measured within 14 days before the first administration of study drug in each part (Part I/Run-in and Part II), unless otherwise stated (e.g., within 21[for Part I/Run-in]/28 [for Part II] days for baseline imaging assessment) under the related visit schedules and assessments section of the CSP (Section 7). For patients entering from Part I/Run-in to Part II or directly to Part II, the most recent of the end of study treatment assessments (Part I or Run-in or other studies e.g, Columbus, CMEK162X2110) or of the assessments done on Cycle 1 Day 1 before the start of study drug of any combination will be considered baseline for Part II. The summaries and listings for Part I/Run-in will be based on the assessments from the corresponding screening/baseline visits.

Baseline can be the day before first study drug administration or the same day as first treatment administration if a pre-dose assessment/value is available (e.g., ECG, PK samples, samples for biomarkers). For certain assessments including triplicate ECG's, multiple supine BP readings etc., an average of the multiple measurements will be considered as baseline.

If more than 1 baseline assessment is performed for any parameter, then the latest assessment prior to the first dose administration of the study treatment will be considered as the baseline.

If time is not recorded, a specific assessment performed the day of first dose administration will be considered as baseline if, according to protocol, it should be performed before the first dose.

For biomarkers, the baseline will be considered for the following samples:

- Tumor samples: when archival and fresh samples are available at baseline only the fresh sample will be used as baseline. Only fresh samples analyzed at baseline and on-treatment should be considered for any PD markers.
- Blood samples: only one sample is foreseen for the /screening baseline, however, if it is the case that more than one assessment/value is available; the last valid pre-treatment assessments will be used as baseline.

Patients with no data on a particular parameter before the first treatment administration will have a missing baseline for this parameter.

2.2 Scheduled study visits and window for the analysis

Unless otherwise specified, when more than one assessment is available for a visit, all assessments will be listed under the visit while only the assessment closest to the planned day for the visit will be used for summaries and analyses.

2.3 Handling of Incomplete Dates

As of the date of data-cutoff for the purposes of reporting in a CSR:

Continuing events (e.g., adverse events, concomitant therapies, etc.) will be listed as continuing.

For patients who discontinue the study with ongoing events, the discontinuation date will be used as the completion date of the event.

The reason for discontinuation from study will be summarized and listed, along with dates of first and last study treatment, duration of exposure to study treatment and date of discontinuation for each patient.

Other missing data will simply be noted as missing on appropriate tables/listings.

For patients not known to have died prior to the cut-off date other than primary CSR:

All events (e.g., AEs and concomitant medications) that started before or on the cut-off date, and with end date missing or after the cut-off date will be reported as continuing at the cut-off date.

For patients known to have died prior to or on the cut-off date:

If imputation of an end date is required for a specific analysis (e.g., a dose administration record with missing end date, or last date of study treatment is after the cut-off date), the end date will be imputed as the cut-off date or death date, whichever is earlier, to calculate e.g., the duration of exposure to study treatment. The imputed date will be displayed and flagged in the listings.

AE date imputation

The imputation of missing and partial dates for AE will be handled according to Section 10.1.

Concomitant medication date imputation

The imputation of the start date and end data of concomitant medication will follow the same conventions as for AE start date and end date.

Prior therapy date imputation

Start date:

The same rule which is applied to the imputation of AE/concomitant medication start date.

End date:

Imputed date = min (treatment start date -1, last day of the month), if day is missing.

Imputed date = min (treatment start date -1, 31DEC), if month and day are missing.

Date of progression:

Imputed date = min (treatment start date -1, last day of the month), if day is missing.

Imputed date = min (treatment start date -1, 31DEC), if month and day are missing.

If the end date or the date of progression is not missing and the imputed start date is after the end date or after the date of progression, use the min (end date, date of progression) as the imputed start date.

Subsequent therapy date imputation

Start date:

Imputed date = max (last date of study drug + 1, first day of the month), if day is missing.

Imputed date = max (last date of study drug + 1, 01JAN), if day and month are missing.

End date: No imputation.

3 Analysis Sets

For inclusion in any analysis set it is required that a patient has correctly consented and has received at least one dose of study treatment.

The following analysis sets will be used.

3.1 Full Analysis Set

For Part I, the Full Analysis Set (FAS) consists of all patients who received at least one dose (partial or full) of encorafenib or binimetinib

For Part II, the FAS consists of all patients who received at least one dose of encorafenib or binimetinib or the assigned third agent following the assignment of the triple combination treatment.

Note that patients who were screened and/or are eligible but never started treatment for a study part will not be included in the FAS for that study part. This is considered as an acceptable deviation from the ITT principle in the context of a non-randomized exploratory study.

The FAS will be used for all listings of raw data. Unless otherwise specified, the FAS will be the default analysis set used for all analyses. Patients will be analyzed according to the treatment they have been assigned to.

3.2 Safety Set

The Safety Set includes all patients who received at least one dose of encorafenib or binimetinib for Part I/Run-in or 3rd combination agent for Part II patients and have at least one valid post-baseline safety assessment.

For each part (Part I/Run-in and Part II), patients will be classified according to treatment received, where treatment received is defined as:

1. The treatment assigned as a combination if it was received at least once in the first cycle, or
2. The first treatment received as a combination when starting therapy with study treatment if the assigned treatment was never received.

The Safety Set will be the primary analysis set for all safety related endpoints except DLT related outputs.

3.3 Per-Protocol Set

The per-protocol set (PPS) consists of all Part II patients in the FAS who are compliant with the protocol in the following ways:

1. Diagnosis: histologically confirmed diagnosis of locally advanced or metastatic melanoma.
2. Stage of disease: stage IIIC to IV per American Joint Committee on Cancer [AJCC].
3. Prior treatment: Progressive disease following prior treatment with encorafenib/binimetinib combination.
4. The patient was evaluated at least once for the primary efficacy variable or discontinued due to adverse event, unacceptable toxicity, Investigator's decision, patient's refusal, disease progression, or died prior to the first evaluation of the primary efficacy variable.
5. Patients will be evaluable for efficacy if they have at least one response assessed differently from 'unknown' or 'not assessed' under RECIST v1.1.

The per-protocol set will be used in Part II to define the patients used in the sensitivity analysis of the primary endpoint.

3.4 Dose-Determining Set

The dose-determining analysis set (DDS) consists of all patients from the Safety Set for Part II who have met the minimum requirements for safety evaluation and minimum exposure or experienced DLT during the first cycle of the assigned triple combination treatment.

To complete the minimum safety evaluations a patient must be observed for at least 1 cycle (21 days following the first dose of the combination treatment with infigratinib, or capmatinib ; 28 days for the combination with ribociclib or buparlisib) and considered to have sufficient safety data by both the Sponsor and Investigators to conclude that a DLT did not occur during this 1st cycle.

Patients meet the minimum exposure requirements if they have received at least 16 out of the 21 planned daily doses of the defined triple combinations.

Note: Patients treated in the ribociclib or buparlisib will meet the minimum exposure requirements if they receive at least 16 planned doses of the triple combination out of the first 21 days of the cycle 1 (28 days). All DLT related outputs will be based on the DDS.

3.5 Pharmacokinetic Analysis Set

The pharmacokinetic analysis set (PAS) consists of all patients who have at least one blood sample providing evaluable pharmacokinetic (PK) data. The PAS will be used for summaries of PK data (tables and figures) as well as for listings of derived parameters.

4 Patient demographics and other baseline characteristics

Unless specified otherwise, summaries described in this section will be based on the FAS and presented by Part I/Run-in and Part II separately.

4.1 Basic demographic and background data

Demographic data including age, sex, race, ethnicity, height, weight, and ECOG performance status will be listed and summarized. In addition, age (<65, ≥65 years) and weight (<55, 55-75, ≥75 kg) categories will be summarized.

The summaries and listings for each part will be based on the assessments from the screening visit/baseline. Where screening/baseline variables are not collected for patients transitioning from Part I/Run-in to Part II, the corresponding screening/baseline variables collected at the time of entering Part I/Run-in will be utilized.

4.2 Medical History

Medical history and current (ongoing) medical conditions, including cancer-related conditions and symptoms will be summarized and listed. Separate summaries will be presented for current and historical medical conditions by primary system organ class and preferred term. Medical history and current medical conditions are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

4.3 Prior antineoplastic therapy

Prior anti-neoplastic therapy will be summarized for three distinct subtypes (medication, radiotherapy, and surgery) in a single output.

The number (%) of patients who received, separately, any prior anti-neoplastic medication, radiotherapy or surgery will be summarized.

The summary of prior anti-neoplastic medications will include the total number of regimens (note: there can be more than one medication per regimen), setting and best response at last medication, time (in days) between end of last medication to start of study treatment. The last medication is defined based on the last end date of all prior regimen components. Prior

antineoplastic medications will also be summarized by Anatomical Therapeutic Chemical (ATC) class, and preferred term.

The summary of prior anti-neoplastic radiotherapy will include the patients who had radiotherapy and the time (in months) between the last radiotherapy end date to start of study treatment.

The summary of prior anti-neoplastic surgery will include the patients who had surgery and the time (in months) between the last surgery date (non-biopsy procedure) to start of study treatment.

4.4 Disease History

The summary of diagnosis and extent of cancer will include primary site of cancer, details of tumor histology/cytology, histological grade, stage at initial diagnosis, stage at time of study entry, time from initial diagnosis of primary site to start of study treatment (months), time from initial diagnosis to first recurrence/relapse or progression (months), time since most recent recurrence/relapse or progression to start of study treatment (months), number of organs involved at baseline, current extent of disease (metastatic sites).

5 Patient disposition

The FAS will be used for the patient disposition summary tables and listings. The following will be tabulated:

- Number (%) of patients who are still on-treatment presented by Part I/Run-in and Part II (based on non-completion of the 'End of Treatment' page),
- Number (%) of patients who discontinued treatment presented by Part I/Run-in and Part II (based on completion of the 'End of Treatment' page with discontinuation date and reason entered),
- Primary reasons for study treatment discontinuation presented by Part I/Run-in and Part II (based on discontinuation reason entered in the 'End of Treatment' page),
- Number (%) of patients who discontinued from study presented by Part I/Run-in and Part II (based on completion of the 'End of post treatment phase disposition' page with discontinuation date and reason entered)
- Primary reasons for study evaluation completion presented by Part I/Run-in and Part II (based on discontinuation reason entered in the 'End of post treatment phase disposition' page).

6 Protocol deviations

The number and percentage of patients with any protocol or non-protocol deviation will be tabulated by the deviation category (entry criteria not satisfied; wrong treatment or incorrect dose; developed withdrawal criteria, but not withdrawn; took an excluded concomitant medication; others) and will be listed. Protocol deviations will be presented separately for Part I/Run-in and Part II.

7 COVID-19 and Related Events

Study disruption due to COVID-19 will be reported in a summary table and a listing.

8 Treatments (study treatment, rescue medication, other concomitant therapies, compliance)

Unless otherwise noted, the Safety Set will be used for all medication data summaries.

Study drug and study treatment

Study drugs refer to encorafenib, binimetinib, ribociclib, capmatinib, infigratinib, or buparlisib. Study treatment refers to any combination of doses of either encorafenib+ binimetinib or encorafenib + binimetinib + third combination (ribociclib, capmatinib, infigratinib, or buparlisib).

Combination arm

This refers to the dual combination (encorafenib+ binimetinib) or triple combination, where third agent (ribociclib, capmatinib, infigratinib, or buparlisib) is added to the encorafenib+ binimetinib combination in Part II.

Date of first/last administration of study drug and study treatment

The date of first/last administration of study treatment is derived as the first/last date when a non-zero dose of any of the study drugs of the study treatment was administered and recorded on the Dosage Administration (ZQ) of the eCRF. For the sake of simplicity, the date of first/last administration of study treatment will also be referred as start/last date of study treatment.

Last date of exposure to study drug and study treatment

Last date of exposure to study treatment is derived as the last date among the study drugs received in a study treatment.

Study day

The study day for all assessments/events will be calculated using the start date of study treatment as reference. Part I/Run-in study day is defined as the event date from the first dose of dual combination treatment. Part II study day is defined as the event date from the first dose of triple combination treatment. For assessments/events occurring on or after the start date of study treatment, study day will be calculated as:

Study day (days) = Event date – Start date of study treatment + 1.

Therefore, the first day of study treatment is study day 1.

For all assessment/events occurring prior to the start of the study treatment, study day will be negative and will be calculated as:

Study day (days) = Event date – Start date of study treatment.

Study day will be displayed in the data listings.

On-treatment assessments/events

An on-treatment assessment/event is defined as any assessment/event obtained in the time interval from the start date of study treatment until the last date of study treatment + 30 days inclusive.

Note: Assessment/events that occur to patients moving from Part I/Run-in to Part II before 30 days of last study drug will be counted in the relevant combination arm of Part II.

8.1 Treatment Exposure and Compliance

Definitions of duration of exposure, cumulative dose, actual dose intensity (DI), planned dose intensity (PDI), relative dose intensity (RDI), percentage of days dosed, percentage of days the planned/intended dose was received, as well as intermediate calculations for each study drug of treatment groups include:

- Duration of exposure (days): last date of exposure to study treatment − first date of study treatment + 1 (periods of interruption are not excluded)
- Duration of dose interruptions (days): Sum of all dose interruptions
- Cumulative dose (mg): sum of all doses of study drug taken by a patient
- Cumulative planned dose (mg): sum of all doses of study drug that was intended to have been taken during the treated period by a patient
- DI (mg/day): cumulative dose (mg)／duration of exposure (days)
- PDI (mg/day): cumulative planned dose (mg)／duration of exposure (days)
- RDI (%): DI (mg/day)／PDI (mg/day)

Planned dose in Part I is 450 mg QD for encorafenib and 45 mg BID for binimetinib. Planned dose in Run-in and Part II with non-naïve treatment is the first non-zero dose in the respective period, given it is not a dosing error. Planned dose in Part II with triple combination of ribociclib or capmatinib and actual treatment of encorafenib then considering the minimum of 200 mg QD or first dose per patient per actual dose, given it is not a dosing error. Planned dose in Part II with triple combination of ribociclib or capmatinib and actual treatment of binimetinib, capmatinib, or ribociclib is the first non-zero dose in the respective period, given it is not a dosing error. If actual dose is ribociclib and the subject only on the PER PROTOCOL OFF WEEKS (i.e., Reason for Dose Adjustment="AS PER PROTOCOL" and Total Daily Dose is zero) then the planned dose is zero for those subjects. If actual dose is infigratinib in Part II and Dose per Administration is greater than 60 mg QD then the Planned dose is equal to Dose per Administration, else planned dose is 60 mg QD. If actual dose is buparlisib in Part II and Dose per Administration is greater than 75 mg QD then the Planned dose is equal to Dose per Administration. Else if Dose per Administration is zero and Reason for Dose Adjustment="AS PER PROTOCOL", then the planned dose is zero, else Planned dose is 75 mg QD. Duration of exposure (in weeks) will be summarized for each combination, including the categories: <4, 4-8, 8-12, 12-24, and >= 24 weeks. Additional categories may be evaluated depending on the distribution of the data. The DI and RDI (including categories: <0.5, 0.5-<0.75, 0.75- <0.9, 0.9-<1.1, ≥1.1) will be summarized for each study drug. Number (n) and percentage (%) of patients who have dose reductions and interruptions, and the corresponding reasons, will be summarized.

All doses of the study treatment along with reasons for any dose change will be listed.

Dose interruption: An actual dose equal to zero (where the planned dose is not zero) between the first and last non-zero doses, following a non-zero actual dose and for which the reason is other than "as per protocol".

Dose reduction: A decrease in dose from the protocol planned dose or a decrease from the previous non-zero dose, even if this decrease has been directly preceded by an interruption. For example, in the sequence of total daily dose 90 mg – 0 mg – 45 mg, the 45 mg dose will be counted as a reduction.

8.2 Concomitant therapies

Concomitant therapies are defined as any medications (excluding study treatment, prior antineoplastic treatments) and significant non-drug therapies (including physical therapy and blood transfusions) administered in the study and are recorded in the Concomitant Medications/significant non-drug therapies eCRF. These therapies will be coded using the WHO Drug Reference Listing (WHO DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (WHO ATC) classification system.

Concomitant therapies will be summarized by ATC class and preferred term. These summaries will include 1) medications starting on or after the start of study treatment but starting no later than 30 days after last dose of study drug and 2) medications starting prior to the start of study drug and continuing after the start of study treatment.

All therapies will be listed. Any therapies starting and ending prior to the start of study drug or starting more than 30 days after the last date of study treatment will be flagged in the listing.

Note: Patients transitioning to Part II who receive concomitant therapies during their transition to Part II prior to 30 days after last Part I/Run-in study drug will be counted in the relevant combination arm of Part II.

Anti-neoplastic therapies since discontinuation of study treatment will be listed and tabulated by ATC class and preferred term.

9 Efficacy Evaluation

9.1 Analysis of the primary endpoint

Evaluation of anti-tumor activity will be based on investigator assessment of overall lesion response according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (see Protocol Appendix 14.8) by Part I/Run-in and Part II, separately. The FAS will be used to analyze the endpoints that evaluate anti-tumor activity.

Best Overall Response

Best Overall Response (BOR) is the best response recorded from the start of the treatment until disease/clinical progression or death or early study discontinuation, whichever happens earlier. However, any radiological assessments taken more than 30 days after the last dose of study therapy or after antineoplastic agents other than study treatments taken by the patients will be excluded from the best overall response derivation.

The follow-up periods required to classify overall response as SD should be at least 6 weeks after treatment start date. Confirmation of CR or PR should be at least 4 weeks apart from the previous radiological assessment. BOR will be considered missing if the patient does not have both baseline and at least one post-baseline RECIST assessment by the investigator.

Number and percentage of patients with CR and PR (confirmed), SD, PD and unknown categories will be summarized. Any unconfirmed CR or PR as the best response will be counted in the SD category. Both ORR and Disease control rate (DCR) and their corresponding 95% confidence intervals (CIs) based on the exact binomial distribution will also be presented in the BOR table. Note: DCR is the proportion of patients with a best overall response of CR or PR or SD. The ORR and DCR will be calculated separately for confirmed and unconfirmed responses. A waterfall plot for best percent change from baseline (for sum of the longest diameters) will also be presented.

BOR will be used to evaluate the tumor response in terms of Overall Response Rate (ORR) for combinations of encorafenib, binimetinib and the third agents. This will be based on investigator-assessed tumor evaluations per RECIST v1.1.

The ORR will be provided with a corresponding 95% confidence interval based on Clopper and Pearson's method for all patients.

In addition, since the encorafenib+ binimetinib+ ribociclib is expected to be the triple combination with the largest number of patients on study (approximately 40 patients), a Bayesian inference will be performed to estimate the true ORR of this combination to provide inferential summaries (e.g., mean, median, interval probabilities). The analysis will be performed when all patients in the respective group have completed at least 6 cycles of treatment or discontinued prior to that time for any reason.

A minimally informative unimodal Beta prior distribution of the true ORR is derived as follows. A priori it is assumed that the true mean of the ORR equals 20%. A true ORR of 20% is the midpoint between limited and clinically relevant efficacy and serves as a compromise between a skeptical view assuming the treatment has only limited efficacy and an optimistic view assuming the treatment has clinically relevant efficacy. The parameters of the minimally informative Beta prior distribution of the ORR are then derived as a = 1/4 and b = 1.

At completion of the study, this prior distribution will be updated with all of the data available in the encorafenib+ binimetinib+ ribociclib combination arm. Once updated, the probabilities that the true ORR lies in the following categories will be reported:

- [0, 10%) unacceptable efficacy
- [10%, 20%) limited efficacy
- [20%, 30%) clinically relevant efficacy
- [30%, 100%] highly clinically significant efficacy

If the observed ORR is equal to or greater than 20%, then this will be considered as preliminary evidence of clinically relevant efficacy of the combination. If the observed ORR is less than 20% (i.e. $\leq$ 7 CR or PR out of 40), then insufficient efficacy will be concluded.

Bayesian estimates (mean and 95% credible intervals) of the ORR will be provided.

If the number of patients recruited to any other triple-agent combination within Part II exceeds 30 patients, the ORR analysis will be performed for that combination in the same way as defined for the encorafenib+ binimetinib+ ribociclib combination.

The efficacy analysis for the encorafenib/ binimetinib+ ribociclib combination arm or other triple combination arms which exceed 30 patients will also be performed using the PPS.

9.2 Analysis of the secondary endpoint(s)

Progression-Free Survival (PFS)

Progression-free survival (PFS) is defined as the time from the start date of study drug (or study treatment for Part II) until documented disease progression or death due to any cause. All patients who have not progressed or died at the time of the data cut-off will be censored at the date of last tumor assessment (TA) other than those who are unknown or missing.

Disease progression per RECIST 1.1 and death (from any cause) will be considered as events. If a patient has not had a documented event by the date of analysis cut-off or before (s)he initiates treatment with further anticancer therapy, the PFS will be censored at the date of last adequate tumor assessment (i.e. at the date of last tumor assessment of CR, PR or SD) prior to cut-off date or start date of new anti-neoplastic therapy, whichever is earlier. In this case the last tumor evaluation date at that assessment is used. By default, if disease progression or death is documented after one single missing tumor evaluation, the actual event date of disease progression/death will be used for the PFS event date. If disease progression is documented after two or more missing tumor evaluations, the PFS time of these patients will be censored at the date of the last tumor evaluation with overall lesion response of CR, PR or SD.

Censoring rules to be applied to the PFS endpoint are described in Table 8-1.

Table 9-1 Options for PFS analysis

	Situation	Event Date	Outcome
A	No baseline assessment	(1) Date of start of treatment*	Censored
B	No post-baseline assessment	(1) Date of start of treatment*	Censored
C1	Progression or death at or before next scheduled assessment	(1) Date of progression (or death)	Progressed
C2	Progression or death after exactly one missing assessment	(1) Date of progression (or death)	Progressed
D	Progression or death after two or more missed assessments	(1) Date of last adequate tumor assessment**	Censored
E	No progression or death	(1) Date of last adequate tumor assessment**	Censored
F	New anti-neoplastic therapy given	(1) Date of last adequate tumor assessment**	Censored

* The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

** tumor assessment with non-missing and non-unknown overall lesion response

An exact rule to determine whether there is none, one, or two missing tumor assessments is needed. This rule will be based on the distance between the last adequate tumor assessment date and the event date. If the distance is larger than the threshold D_1 or D_2 then the analysis will assume one or two missing tumor assessments, respectively. The threshold D_1 will be defined as the protocol specified interval between the TAs plus the protocol allowed window around the assessments. Similarly, the threshold D_2 is defined as two times the protocol specified interval between the TAs plus the protocol allowed window around the assessments. As per protocol, tumor assessments are expected as follows:

- Part I (Group A)
    - Evaluated for all potential sites of tumor lesions at screening/baseline.
    - First post-baseline tumor assessment should be performed 6 weeks ±3 days after starting treatment.
    - Subsequent tumor assessments should be performed every 6 weeks ±7 days thereafter until disease progression.
    - Once patients have completed ≥ 24 months of study treatment, the frequency of tumor assessments can be reduced to every 6-12 weeks ±7 days based on Investigator discretion.
    - Patients who discontinue study treatment due to a reason other than disease progression should undergo tumor assessments every 9 weeks ± 7 days until disease progression or initiation of subsequent anti-neoplastic therapy, or death, whichever occurs first.
    - Patients who have completed ≥ 24 months of study treatment and then discontinue study treatment due to a reason other than disease progression should undergo tumor assessments every 9-12 weeks ± 7 days until disease progression or initiation of subsequent anti-neoplastic therapy, or death, whichever occurs first.
- Run-in (Group B)
    - Evaluated for all potential sites of tumor lesions after receiving ≥21 days of study treatment.
    - First post-baseline tumor assessment should be performed 3 weeks ±3 days after starting treatment.
    - Subsequent tumor assessments should be performed every 6 weeks ±7 days thereafter until disease progression.
    - Once patients have completed ≥ 24 months of study treatment, the frequency of tumor assessments can be reduced to every 6-12 weeks ±7 days based on Investigator discretion.
    - Patients who discontinue study treatment due to a reason other than disease progression should undergo tumor assessments every 9 weeks ± 7 days until disease progression or initiation of subsequent anti-neoplastic therapy, or death, whichever occurs first.

  - Patients who have completed ≥ 24 months of study treatment and then discontinue study treatment due to a reason other than disease progression should undergo tumor assessments every 9-12 weeks ± 7 days until disease progression or initiation of subsequent anti-neoplastic therapy, or death, whichever occurs first.
- Part II
  - Baseline assessments must be completed within 28 days of the previous assessment performed in Part I/Run-in. For patients in Group C assigned to ribociclib, the assessment must be completed within 28 days before triple combination first dose.
  - First post-baseline tumor assessment and subsequent tumor assessments should be performed 9 weeks ± 7 days after starting treatment until disease progression.
  - Patients who discontinue study treatment due to a reason other than disease progression should undergo tumor assessments every 9 weeks ± 7 days until disease progression or initiation of subsequent anti-neoplastic therapy, or death, whichever occurs first.

Therefore, for Group A:

- if the last adequate tumor assessment is performed between study day 1 and study day 21 (inclusive)
  1. and the patient has not discontinued treatment as of 45 days after the last assessment for D1 and 91 days after the last assessment for D2, then D1=6*7+3=45 days and D2=2*6*7+7=91 days.
  2. and the patient has discontinued treatment as of 45 days after the last assessment, then D1=9*7+3=66 days and D2=2*9*7+7=133 days.
  3. and the patient has discontinued treatment between 45 days and 91 days (exclusive) after the last assessment, then D2=6*7+9*7+7=112 days.
- if the last adequate tumor assessment is performed between study day 22 and study day 42 (inclusive)
  1. and the patient has not discontinued treatment as of 52 days after the last assessment for D1 and 94 days after the last assessment for D2, then D1=6*7+3+7=52 days and D2=2*6*7+3+7=94 days.
  2. and the patient has discontinued treatment as of 52 days after the last assessment, then D1=9*7+3+7=73 days and D2=2*9*7+3+7=136 days.
  3. and the patient has discontinued treatment between 52 days and 94 days (exclusive) after the last assessment, then D2=6*7+9*7+3+7=115 days.
- if the last adequate tumor assessment is performed between study day 43 and study day 652 (inclusive)
  1. and the patient has not discontinued treatment as of 56 days after the last assessment for D1 and 98 days after the last assessment for D2, then D1=6*7+2*7=56 days and D2=2*6*7+2*7=98 days.

2. and the patient has discontinued treatment as of 56 days after the last assessment then D1=9*7+7=77 days and D2=2*9*7+2*7=140 days.
3. and the patient has discontinued treatment between 56 days and 98 days (exclusive) after the last assessment, then D2=6*7+9*7+2*7=119 days.

- if the last adequate tumor assessment is performed between study day 653 and study day 694 (inclusive), then D1=6*7+2*7=56 days and D2 = (6+12)*7+2*7=140 days;
- otherwise, when the last adequate tumor assessment is performed after study day 694, then D1 = 12*7+2*7=98 days and D2 =2*12*7+2*7=182 days.

For Group B:

- if the last adequate tumor assessment is performed between study day 1 and study day 21 (inclusive)
  1. and the patient has not discontinued treatment as of 24 days after the last assessment for D1 and 91 days after the last assessment for D2, then D1=3*7+3=24 days and D2=3*7+6*7+7=73 days.
  2. and the patient has discontinued treatment as of 24 days after the last assessment, then D1=9*7+7=70 days and D2=2*9*7+7+ 7=140 days.
  3. and the patient has discontinued treatment between 24 days and 73 days (exclusive) after the last assessment, then D2=3*7+9*3+7=91 days.
- if the last adequate tumor assessment is performed between study day 22 and study day 652 (inclusive)
  1. and the patient has not discontinued treatment as of 56 days after the last assessment for D1 and 98 days after the last assessment for D2, then D1=6*7+7+7=56 days and D2=2*6*7+2*7=98 days.
  2. and the patient has discontinued treatment as of 56 days after the last assessment, then D1 =9*7+7=77 days and D2=2*9*7+2*7=140 days.
  3. and the patient has discontinued treatment between 56 days and 98 days (exclusive) after the last assessment, then D2=6*7+9*7+2*7=119 days.
- if the last adequate tumor assessment is performed between study day 653 and study day 694 (inclusive), then D1=6*7+2*7=56 days and D2 = (6+12)*7+2*7=140 days;
- otherwise, when the last adequate tumor assessment is performed after study day 694, then D1 = 12*7+2*7=98 days and D2 =2*12*7+2*7=182 days.

For Part II

- if the last adequate tumor assessment is performed between study day 1 and study day 21 (inclusive) for encorafenib/ binimetinib + infigratinib, capmatinib

patients, or between study day 1 and study 28 (inclusive) for encorafenib/ binimetinib + ribociclib, buparlisib patients then D1=9*7+7=70 days and D2=2*9*7+7=133 days.

- if the last adequate tumor assessment is performed after study day 21 for encorafenib/ binimetinib+ infigratinib, capmatinib patients, or after study day 28 for encorafenib/ binimetinib+ ribociclib, buparlisib patients then D1=9*7+7+7=77 days and D2=2*9*7+7+7=140 days.

Therefore, using the D_2 definition above, the censoring of an event occurring after ≥2 missing TAs (in primary PFS analysis) can be refined as follows: if the distance between the last adequate tumor assessment date and the PFS event date is larger than D_2 then the patient will be censored, and the censoring reason will be 'Event after >= 2 or more missing assessments'.

A Kaplan-Meier plot for PFS will be presented limited to the groups where at least 10 events occur in each of the combination arms. Median PFS (in months) with corresponding 95% CI, 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs (Brookmeyer and Crowley, 1982) at several time points (including at least 6, 12, 18, and 24 months) will be presented. Censored reasons will also be summarized.

Note: When the estimated survival function is close to zero or unity, symmetric intervals are inappropriate since they can lead to confidence limits that lie outside the interval [0, 1]. Any limit that is greater than unity will be replaced by 1.0. Any limit that is less than zero will be replaced by 0.0.

Overall Survival (OS) (Part II only)

Overall survival is defined as the time from the start date of study treatment (3rd agent combined with encorafenib and binimetinib) until the date of death due to any reason. A patient who is still alive at the time of last known contact will be censored at the time of last known contact.

OS will be presented graphically using Kaplan Meier plots by combination arm. In addition, the OS will be listed and will be summarized by presenting the median OS time with accompanying 95% CI along with the Kaplan-Meier estimates for the OS rate with corresponding 95% CI at 6, 12, 18 and 24 months.

Duration of response

Duration of response (DOR) will be calculated for “responders” (confirmed) only and is defined as the time between the date of first documented response (CR or PR) and the date of first documented progression or death due to underlying cancer. If progression or death due to underlying cancer has not occurred, then the patient is censored at the date of last tumor assessment other than unknown. A listing and a K-M plot with median and 95% CIs will be reported.

Time to response

Time to response (TTR) will be calculated for “responders” (confirmed) only and is defined as the time between the start date of study drug and first documented response (CR or PR). A listing and K-M plot with median and 95% CIs will be reported.

Construction of waterfall graphs

The waterfall graph will be used to depict anti-tumor activity. This graph displays the best percentage change from baseline in the sum of diameter of all target lesions for each patient.

Patient with unknown/missing best percentage change from baseline will be excluded from this graph.

The waterfall graph will use the response based on investigator assessment evaluated by RECIST 1.1.

The best overall response (BOR) will be shown above each of the displayed bars in the graph.

The following display will be used (from left to right) in the descending order:

1. Bars above the horizontal axis representing tumor growth

2. Bars below the horizontal axis representing tumor shrinkage

Patients from Part I, Run-in, and Part II will be presented in separate plots.

10 Safety and tolerability evaluation

The safety and tolerability of encorafenib/ binimetinib and their combination with a third targeted agent will be assessed for incidence and severity of adverse drug reactions and serious adverse drug reactions (as assessed by CTCAE Version 4.03), changes in hematology and chemistry values, physical examinations, vital signs, electrocardiogram, cardiac monitoring, ophthalmological and dermatological examinations. Tolerability assessments include exposure and dose reductions/interruptions.

The Safety Set will be used for summaries and listings of safety data.

The safety summary tables (except deaths) will only include assessments collected no later than 30 days after study treatment discontinuation. All safety assessments will be listed, and those collected later than 30 days after study treatment discontinuation will be flagged.

Note: AE's that occur in patients moving to Part II prior to 30 days after last Part I/Run-in study drug will be counted in the relevant combination arm of Part II.

10.1 Adverse event

AEs will be coded using the latest version of MedDRA available prior to clinical database lock and will be graded using CTCAE version 4.03. CTCAE grade 5 (death) will not be used in this study. Death information will be collected on the "End of Treatment" or "Survival Information" eCRF pages.

All treatment-emergent AEs (new or worsening from baseline) will be summarized (counts (n) and percentage (%)) by system organ class and preferred term and severity grades (split by 'All grades' and 'Grade 3/4'), or only by preferred term, except where otherwise noted. Patients with a Grade 5 AE will be included in the "All grades" category but will not be included in the "Grade 3/4" category. Listings of adverse events of special interest will be based on the case retrieval strategy.

The following AE summaries will be produced:

- Overall summary of AEs
- AEs regardless of study drug relationship
- AEs of special interest (encorafenib) only for Part I/Run-in
- AEs of special interest (binimetinib) only for Part I/Run-in
- AEs suspected to be study drug related
- AEs leading to discontinuation of study drug
- AEs requiring dose adjustment or study drug interruption
- SAEs regardless of study drug relationship
- Deaths by primary system organ class and preferred term

The following AE listings will be produced:

- AEs
- SAEs
- AEs leading to study drug discontinuation

- AEs of special interest (encorafenib) (separate listings for all AESI and grade 3/4)
- AEs of special interest (binimetinib) (separate listings for all AESI and grade 3/4)
- All deaths

A patient with multiple CTC grades for an AE will be summarized under the maximum CTC grade recorded for the event. A patient with multiple occurrences of an AE is counted only once in the AE category (system organ class, preferred term etc.).

Missing and partial date for AE will be handled according to rules specified below.

Completely missing AE start dates will not be imputed. Partial AE start dates missing the year will be imputed to the earlier of the non-imputed AE end date – 1 day or the treatment start date – 1 day. Treatment start date for Part I/Run-in is defined as the date of the first dose of dual combination treatment. Treatment start date for Part II is defined as the first dose of triple combination treatment.

For partial AE start date, the date imputation will be based on the temporal relation between the partial date and start of treatment date.

For partial AE end date or completely missing end date (AE is ongoing), the date imputation will be based on the temporal relation between the partial date, the last contact date and the 30-day follow-up date.

A missing AE start date will be imputed using the following logic matrix described in Table 10-1

Table 10-1 AE start date imputation example scenarios

Partial AE start date	Treatment start date*	Temporal relationship compared to treatment start	Imputed Date
Missing	20OCT2001	Uncertain	Missing start date will not be imputed. AE treatment emergent flag for both Parts I & II will be set to "Y"
ddmmm2000	20OCT2001	Before	01JUL2000
ddmmm2002	20OCT2001	After	01JAN2002
ddmmm2001	20OCT2001	Uncertain	21OCT2001
ddSEP2001	20OCT2001	Before	15SEP2001
ddOCT2001	20OCT2001	Uncertain	21OCT2001
ddNOV2001	20OCT2001	After	01NOV2001

*AE start date will be imputed based upon Part I/Run-in first dose date and Part II first dose date, respectively. The treatment emergent AE flag for Part I/Run-in and Part II will be defined correspondingly. AEs with Part II imputed start date that occur before 30 days of last study drug of Part I/Run-in and after treatment start date of Part II will be counted only in the relevant combination arm of Part II.

Table 10-2 provides examples of the different considered imputations for AE end date.

Table 10-2 AE end date imputation example scenarios

Partial AE end date	Minimum (Last contact date, 30-day FU date)	Ongoing	Imputed Date
Missing	20OCT2001	Yes	20OCT2001
ddmmm2000	20OCT2001	No	31DEC2000
ddmmm2002	20OCT2001	No	31DEC2002
ddmmm2001	20OCT2001	No	20OCT2001
ddmmm2001	20OCT2001	Yes	31DEC2001
ddSEP2001	20OCT2001	No	30SEP2001
ddOCT2001	20OCT2001	No	20OCT2001
ddOCT2001	20OCT2001	Yes	31OCT2001

10.2 Laboratory data

Laboratory data will be converted into SI units and classified into CTCAE grades according to CTCAE v4.03 as applicable. Grade 5 will not be used.

Values entered as "<x", with x a numerical value, will be considered as x for the analysis.

For cases when the CTCAE grade definition includes change from baseline criteria (e.g., creatinine, ejection fraction, fibrinogen, hemoglobin, international normalized ratio [INR]): When a lab value is of Grade X based on threshold/ranges, but Grade X+1 when considering change from baseline, the final grade is set to X+1. For other cases, a Grade 0 CTCAE grade will be set when laboratory value is:

- Within LLN and ULN and grading in both directions,
- Below ULN and grading in hyper direction,
- Above LLN and grading in hypo direction.

Laboratory data for which a CTCAE grading does not exist will be classified into low, normal, or high based on local laboratory normal ranges as applicable.

The following summaries will be produced by laboratory parameter:

- For lab parameters with CTCAE grades: Shifts from baseline to the worst post-baseline CTCAE grade
- For laboratory parameters with no CTCAE grades defined: Shifts from baseline to the worst post-baseline using low/normal/high classifications
- Hy's law (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] > 3 x ULN with total bilirubin > 2 x ULN and alkaline phosphatase [ALP] < 2 x ULN) to assess drug-induced liver injury

The following listings will be produced:

- Listing of patients with laboratory abnormalities of CTCAE Grade 3 and 4,
- Listing of laboratory normal ranges by laboratory identification number and laboratory group

- Listing of all laboratory data with values flagged to show corresponding CTCAE grades and the classifications relative to the laboratory reference ranges (i.e., High [H] or Low [L])

Table 10-3 and Table 10-4 list all laboratory parameters that will be summarized.

Table 10-3 Laboratory parameters (and directions) for which CTCAE grades are defined

Hematology and coagulation		**Biochemistry**		**Urinalysis**	
White blood cells (WBC)	↑↓	Creatinine	↑	Protein	↑
Hemoglobin	↑↓	Sodium	↑↓		
Platelets counts	↓	Potassium	↑↓		
Absolute neutrophils	↓	Glucose	↑↓		
Absolute lymphocytes	↑↓	Calcium	↑↓		
INR	↑	Magnesium	↑↓		
		Albumin	↓		
		AST (SGOT)	↑		
		ALT (SGPT)	↑		
		Total bilirubin	↑		
		Inorganic phosphorus	↓		
		Amylase	↑		
		Lipase	↑		
		GGT	↑		
		Creatine kinase/CPK	↑		
		Alkaline phosphatase	↑		
		Uric acid	↑↓		

↑ Indicates that CTCAE grade increases as the parameter increases.
↓ Indicates that CTCAE grade increases as the parameter decreases.

Table 10-4 Laboratory parameters (without CTCAE grades) for which lab reference ranges are defined

Hematology and coagulation	Biochemistry
Prothrombin time (PT)	Urea or BUN
Hematocrit	Total protein
Basophils	
Eosinophils	
Monocytes	
Fibrinogen	Bicarbonate

Fasting plasma glucose, and HbA1c

A shift table from worst post-baseline value will be produced based on CTC grade for FPG.

10.2.1 Urinalysis

Urinalysis including, pH, ketones, leukocytes, protein, glucose, and blood will be listed. A microscopic urinalysis of RBC and WBC will also be listed.

10.3 Vital signs

Vital sign parameters collected are systolic and diastolic blood pressure (mmHg), pulse rate (beats per minute), respiratory rate (breaths per minute), body temperature (°C), and weight (kg). Vital sign values considered notably abnormal are defined in Table 10-5.

Table 10-5 Criteria for notable vital sign values

Vital sign	Criteria for clinically notable vital sign values
Systolic blood pressure [mmHg]	≥160 mmHg/≤90 mmHg with increase/decrease from baseline of ≥20 mmHg
Diastolic blood pressure [mmHg]	≥100 mmHg/≤50 mmHg with increase/decrease from baseline of ≥15 mmHg
Pulse rate [bpm]	≥120 bpm/≤50 bpm with increase/decrease from baseline of ≥15 bpm
Body temperature [°C]	≥ 37.5; ≤ 36
Weight [kg]	≥20% decrease/increase from baseline

Vital signs shift table based on values classified as notable low, normal, notable high or notable (high and low) at baseline and worst post-baseline will be produced.

10.4 Electrocardiograms

10.4.1 ECG data descriptive statistics

Baseline for electrocardiogram (ECG) analysis is defined as the average of all available ECG measurements associated with the baseline assessment. Scheduled study Day 1 pre-dose ECGs will be considered to have been obtained prior to study drug administration if dosing time is

missing. If a scheduled pre-dose measurement occurred post-dose, then the corresponding measurement will be treated and analyzed similar to an unscheduled post-dose measurement.

The following summaries will be provided for each applicable ECG parameter:

- For each QT interval (QT, QTcF), shift tables based on notable QT interval categories (≤450, >450 - ≤480, >480 - ≤500, >500 ms) at baseline to the worst post-baseline value observed**,**

10.5 Other safety analyses

10.5.1 Left Ventricular Ejection Fraction (LVEF)

A table summarizing the worst change from baseline and worst absolute change from baseline LVEF will be provided. The worst value is defined as lowest post-baseline value and the worst absolute value is the difference between the worst value and the baseline value.

10.6 Pharmacokinetic data

All PK analyses will use the FAS. PK analyses will be performed for all subjects in the FAS, where possible; however, only subjects included in the PAS will be presented in PK data summaries (tables and mean/median plots).

10.6.1 Plasma Concentrations

For Part II of the protocol, blood samples will be collected for the assessment of encorafenib, binimetinib (including its primary active metabolite AR00426032), ribociclib (and its metabolite LEQ803), buparlisib (including its active metabolites BHS697 and CQM157), infigratinib, and capmatinib at the following times:

<u>28-day Cycles</u>

Cycle 1	Day 1 (1.5 and 4 hours), Day 8 (pre-dose), Day 15 (pre-dose, 0.5, 1.5, 2.5, 4, 6, 8, and 24 hours), and Day 21 (pre-dose).
Cycle 2	Days 1 and 15 (pre-dose).
Cycles 3-5	Day 1 (pre-dose).

<u>21-day Cycles</u>

Cycle 1	Day 1 (1.5 hours), Day 8 (pre-dose), and Day 15 (pre-dose, 0.5, 1.5, 2.5, 4, 6, 8, and 24 hours).
Cycle 2	Days 1 and 15 (pre-dose).
Cycles 3-5	Day 1 (pre-dose).

Additional end of treatment (EOT) samples will be collected for each regimen, and unscheduled samples may also be collected, where deemed necessary.

The plasma concentration/time data will be summarized by treatment group, dose and formulation (when applicable) and listed on a per patient basis; concentration summaries will include the number of observations (n), number of non-missing observations (n*), mean, standard deviation (SD), CV% mean, geometric mean, CV% geo-mean, median, minimum, and maximum. Arithmetic mean concentration-time profiles will be presented by treatment

group for Cycle 1 Day 15, and separate individual concentration-time course with median overlaid will also be presented by treatment group.

10.6.2 PK Parameter Analysis

Non-compartmental PK analysis will be performed using Phoenix WinNonlin®, Version 8.3 or higher (Certara USA, Inc., Princeton, NJ, USA). PK parameters for encorafenib, binimetinib (including its primary active metabolite AR00426032), ribociclib (including its metabolite LEQ803), buparlisib (including its active metabolites BHS697 and CQM157), infigratinib, and capmatinib will be determined for all PK-evaluable patients.

The PK parameters listed in Table 10-6, but not limited to, will be estimated and reported for all subjects in Cycle 1 (Day 15 only), as appropriate.

Table 10-6 Non compartmental pharmacokinetic parameters

Term	Definition
AUCtau, ss	Area under the concentration-time curve from time zero to time tau at steady-state
AUCtau, ss/D	Area under the concentration-time curve from time zero to time tau at steady-state normalized by actual dose administered
Cmax, ss	The maximum (peak) observed plasma concentration (Cmax) after drug administration at steady state
Cmax, ss/D	The maximum (peak) observed plasma concentration (Cmax) after drug administration at steady state normalized by actual dose given
Tmax, ss	The time to reach Cmax at steady state
Ctrough, ss	Measured concentration at the end of a dosing interval at steady-state (taken directly before next administration)
Clast, ss	Last measurable plasma concentration at steady state
T1/2, ss	The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve at steady state.
CL,ss/F	Apparent total plasma clearance of drug after oral administration at steady state (for parent drugs only)
Vz,ss/F	The apparent volume of distribution at the terminal elimination phase at steady state (for parent drugs only)
MR_Cmax	The metabolite ratio of Cmax, estimated as: Cmax,ss (Metabolite) / Cmax,ss (Parent), corrected for molecular weight [estimated for AR00426032, LEQ803, BHS697 and CQM157 only]
MR_AUC	The metabolite ratio of AUC, estimated as: AUCtau,ss (Metabolite) / AUCtau,ss (Parent), corrected for molecular weight [estimated for AR00426032, LEQ803, BHS697 and CQM157 only]
Note: it is assumed that C1D15 is at steady state. Cmax,ss/D and AUC,ss/D will be reported separately for treatments where a formulation switch had occurred.	

PK parameters will be summarized by treatment group, dose and formulation (when applicable) using the following descriptive statistics according to Table 10-7.

Table 10-7 PK parameters – descriptive statistics

Parameters	Descriptive statistics
AUCtau,ss, AUCtau,ss/D, Cmax,ss, Cmax,ss/D, Ctrough,ss, Clast,ss, Cl,ss, T1/2,ss, CL,ss/F, Vz,ss/F, , MR_Cmax, MR_AUC	Number of observations (n), mean, standard deviation (SD), CV% mean, geometric mean, CV% geo-mean, median, minimum, and maximum.
Tmax,ss	Median, minimum, and maximum.
ss – steady state (assumed on C1D15) CV% = coefficient of variation (%) = sd/mean*100 CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100	

10.6.3 Pharmacokinetic Data Handling

All concentrations of encorafenib, binimetinib, AR00426032, ribociclib, LEQ803, buparlisib, BHS697, CQM157, infigratinib and capmatinib below their respective lower limits of quantification (LLOQ) or missing data will be labeled as such where applicable. Concentrations below the LLOQ will be treated as zero in summary statistics and for the calculation of PK parameters.

Patients may be removed from the estimation of certain PK parameters on an individual basis when the PK parameters cannot be reliably estimated based on the available blood samples. These patients will be identified prior to the time of the data analysis. Only PK blood sample with date and time and for which the last prior dose dates and times are adequately recorded will be included in the PK analyses. For test articles administered in BID regimens, the 24 h time point on Day 15 will have the actual time since dose (in hours) on Day 15 subtracted by 12 to estimate AUCtau,ss over an appropriate dosing interval.

Plasma concentrations and PK parameters will be flagged in concentration and PK parameter data listings and excluded from all summary tables, mean figures, and statistical analyses of PK data if the following occur:

- Patient experienced vomiting or diarrhea within 4 hours of dosing.
- The planned dose was not administered (i.e., a change in dose occurred before the sampling occasion).
- Steady state was not deemed to have been achieved (i.e. dosing is required for a minimum 2 consecutive days prior to the collection of steady state samples).
- PK blood samples were collected outside the following time windows:

Scheduled time point		Window
Pre-dose	Before dosing	- 2 h
Post-dose	0.5 hours	± 10 min
	1.5 hours	± 15 min
	2.5 hours	± 15 min
	4 hours	± 30 min
	6 hours	± 30 min
	8 hours	± 1 h
	24 hours	± 2 h

10.7 Biomarkers

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There may be circumstances when a decision is made to stop sample collection, or not perform or discontinue the analysis of blood / archival tumor samples / fresh tumor biopsies / fine needle aspirates due to either practical or strategic reasons (e.g. issues related to the quality and/or quantity of the samples or issues related to the assay). Under such circumstances, the number of samples may be inadequate to perform a rigorous data analysis and the available data will be limited to listings.

The data analysis and reporting required to support the writing of the CSR will be included in this analysis plan. Additional or complementary analyses of biomarker and imaging data may be described in a stand-alone biomarker and imaging analysis plan document (BIAP).

The following table provides the details of the biomarker data collection and any planned statistical analyses:

Table 10-8 Biomarkers and assessments

Biomarker	Visit/Time point	Method	Datatype
Molecular status (mutation/ amplification/ expression) of markers related to RAF/MEK/ERK pathway, PI3K/AKT pathway or cancer (e.g. BRAF, RAF1[, KRAS, NRAS, PTEN, PIK3CA, MAP2K1, MAP2K2, MET, FGFR1, FGFR2, FGFR3, FGFR4, CCND1, CDK4, ERBB2, IGF-1R, EGFR) in archived/fresh tumor	Archived: Anytime during Part I, Run-in, Part II Fresh tumor sample: Screening/Baseline - Prior to first dose Part I and Run-in Part II 15 days after start of triple combination (part II) At the time of progression (Part I, Run-in, Part II)	Somatic mutation, Next generation sequencing	Categorical
PD markers (such as pERK, pAKT, p-pRB) from fresh biopsy tumors	Fresh tumor sample: Screening/Baseline - Prior to first dose Part II 15 days after start of triple combination (part II)	Immunohisto-chemistry	Continuous

1. Archival tumor sample is collected in Part II only from patients in Group C.

2. Newly obtained tumor biopsy is collected at molecular pre-screening or at the screening/baseline visit from patients in Group C, who cannot provide the progression biopsy from the previous study.

10.7.1 Biomarker data

Biomarker analysis data set

The Full Analysis Set will be used for all biomarker analysis. Unless otherwise specified, all statistical analyses of biomarker data will be performed on patients with biomarker data.

Baseline

The samples analysed before the start of study treatment (Cycle 1 Day 1) would be considered as the baseline value for any PD markers. Where replicate measurements are available at any other timepoint other than baseline, the average of the measurements will be used for statistical summary and analyses.

Molecular Alteration

Molecular Alteration is defined at the baseline for Part II (EOT for RUNIN/ EOT for Part I/ SCREENING for Part II) for each tumor biomarkers (BRAF, KRAS, NRAS, HRAS, CDKN2A, CDK4, MAP2K1). Molecular Alteration is used to identify the individual patient's tumor sample upon progression. The triple combination to be evaluated in an individual patient will be based on the molecular alteration(s) detected at progression after BRAF/MEK inhibitor combination treatment and, alterations identified by amino acid change(Y), amplification (A) and/or loss (L). For each tumor biomarkers (KRAS, NRAS, HRAS, CDKN2A, CDK4, MAP2K1), the Molecular Alteration is Y when subcategory for lab test is "SHORT VARIANT", and the examination name is "AMINO ACID CHANGE" with a non-missing value. Molecular Alteration is A when subcategory for lab test is "COPY NUMBER VARIANT" and the examination name is "COPY NUMBER RATIO" with value is greater than 1. Molecular Alteration is L when subcategory for lab test is "COPY NUMBER VARIANT" and the examination name is "COPY NUMBER RATIO" with value less than 1. For tumor biomarkers BRAF, the Molecular Alteration is Y when subcategory for lab test is "SHORT VARIANT", and the examination name is "AMINO ACID CHANGE" and the value is not missing or not in ("V600E" and "V600K"). Molecular Alteration is A when subcategory for lab test is "COPY NUMBER VARIANT" and the examination name "COPY NUMBER RATIO" with value greater than 1. Molecular Alteration is L when subcategory for lab test is "COPY NUMBER VARIANT" and PFTEST is "COPY NUMBER RATIO" with value less than 1. There is no molecular alteration if any of the criteria are met. Apply imputation if we have missing date for checking baseline, The imputation of the start date of Molecular Alteration will follow the same conventions as for AE start date.

10.7.2 Reporting (summary) and analyses of Biomarker data

Genomic biomarkers with tests such as Copy Number Ratio, Genomic Position and Amino Acid Change for each Tumor biomarkers (BRAF, RAF1CRAF, KRAS, NRAS, PTEN, PIK3CA, MAP2K1, MAP2K2, c-MET, FGFR1, FGFR2, FGFR3, FGFR4FGFRs, CCND1, CDK4, ERBB2HER2, IGF-1R, EGFR) will be summarized.

Overall summary for triple combination of Ribociclib using Kaplan Meier method by Molecular alteration for each tumor biomarker (BRAF, KRAS, NRAS, HRAS, CDKN2A, CDK4, MAP2K1) will be calculated.

Change from baseline at 15 days after start of triple combination (part II) and at the time of Cycle 1 Day 15 in the PD markers (such as pERK, pAKT, PTEN) will be summarized.

11 Sample size calculation

Part II encorafenib/binimetinib+ ribociclib arm

About 140 patients are expected to enroll in Part II of the study to address the primary objective of the study. From these 140 patients, it is anticipated that about 30% of patients progressing on encorafenib+ binimetinib would be eligible to the encorafenib+ binimetinib+ ribociclib arm. With 140 patients recruited it would give 89% probability that the number of patients assigned to the ribociclib arm will be at least 36.

Based on the ORR (per RECIST 1.1) intervals described in Section 8.1, it was assessed how likely it is to wrongly declare activity as defined by observing at least "clinical relevant efficacy" (i.e. seeing at least 8 responses out of 40 patients) given the true ORR = 10%, and how likely it is to correctly declare activity given the true ORR = 30% when 40 patients are evaluated.

- If the true ORR = 10%, the probability to wrongly declare activity is 4.2%.
- If the true ORR = 30%, the probability to correctly declare activity is 94.5%.

Given a sample size of 40, if 8 responses are seen, the observed ORR is 20% with a 90% credible interval of (10.8%, 30.9%). This will be considered as preliminary evidence of antitumor activity of the treatment at the MTD/RP2D within this arm.

Part II other arms

Dose escalation in Part II will proceed with groups of at least 3 evaluable patients receiving triple combination therapy at the current dose levels. At least six patients must be included at the MTD/RP2D level for each triple combination. Additional patients may be enrolled at any dose level below the current dose if this dose has not been tested before and if there are already 3 evaluable patients enrolled. Any dose level below the estimated MTD/RP2D may be expanded for further elaboration of safety and pharmacokinetic parameters as required.

12 References

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