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Study Title: Phase 1 Safety Study of Encorafenib in Chinese Patients With Advanced Metastatic BRAF V600E Mutant Solid Tumors

Protocol Reference Number: W00090GE102

NCT Number: NCT05003622

STATISTICAL ANALYSIS PLAN

Protocol Title:

Multicenter, open-label, phase 1 study investigating the safety and tolerability of encorafenib monotherapy in *BRAF* V600E-mutated Chinese patients with advanced metastatic solid tumors

Protocol Number: W00090GE102

Compound Number: Encorafenib

Short Title: Phase 1 safety study of encorafenib in Chinese patients with advanced metastatic *BRAF* V600E mutant solid tumors

Acronym: **OCEAN I**

Sponsor Name: Pierre Fabre Médicament

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Regulatory Agency Identifier Number(s)

Signature Page

I have read the statistical analysis plan for the OCEAN I study dated 06JUL2022 and confirm that to the best of my knowledge it accurately describes the planned analyses for the study.

	Title	Name (First & Last name)	Consistency between SAP and study protocol	Date	Signature
PII	Lead Statistician	PII	NA		
PII	Project Manager	PII	NA		
PII	Pharmacokineticist	PII	NA		
Pierre Fabre Médicament	Sponsor Lead Biostatistician	PII	☒Confirmed		
Pierre Fabre Médicament	Sponsor Medical Director	PII	☒Confirmed		
Pierre Fabre Médicament	Sponsor Phamacokinetics monitor	PII	☒Confirmed		
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Version History

This Statistical Analysis Plan (SAP) for the OCEAN I study is based on the protocol version 3.0 dated 30SEP2021.

SAP Version	Approval Date	Change	Rationale
1.0	29 June 2021	Not Applicable	Original version
2.0	06 July 2022	- PII [redacted] - Use of protocol version 3.0 dated 30SEP2021 (Version 1.0 was previously used) - Adjustments and clarification for statistical programming purpose	Use of non substantial protocol amendment #1 dated 04Aug2021: - Laboratory assessments: Removal of bicarbonate and PTT - Revisions in Schedule of Assessments Use of non substantial protocol amendment #2 dated 30Sep2021: - Creatine Kinase assessment : isoenzymes, serum creatinine and myoglobin in blood and urinalysis measures are deleted

1. Introduction

This document describes the statistical analyses and data presentations to be performed for the clinical protocol W00090GE102 entitled "Multicenter, open-label, phase 1 study investigating the safety and tolerability of encorafenib monotherapy in B-RAF Proto-oncogene, Serine/threonine Kinase V600E Mutant *(BRAF* V600E)-mutated Chinese patients with advanced metastatic solid tumors".

This Statistical Analysis Plan (SAP) provides a comprehensive and detailed description of the strategy, rationale and statistical techniques to be used to assess the safety and PharmacoKinetics (PK) analyses in population as outlined in the protocol. The summaries/analyses of baseline characteristics and demographics, important protocol deviations, derivations, will be described in appendix. The purpose of this SAP is to ensure the credibility of the study findings by specifying the statistical approaches for all analyses of study data.

This SAP will be prepared and finalized before the beginning of the study recruitment and signed prior to the clinical database lock for any analyses specified in this SAP.

This SAP should be read in conjunction with the study protocol and electronic Case Report Forms (eCRFs). This document has been developed using the protocol Version 3.0 dated 30Sep2021. Any further changes to the protocol or eCRFs may necessitate updates to the SAP (see section 6.2).

The Table Of Contents (TOC) of Tables Figures and Listings (TFLs) will be provided in a separate document, as well as the shell TFLs and specifications.

The study W00090GE102 also called OCEAN I study is a Phase I, multicenter, open-label single-arm study to investigate the safety and tolerability of encorafenib 300 mg once daily (QD) monotherapy in adult Chinese participants with *BRAF* V600E mutant advanced solid tumors (unresectable metastatic melanoma or metastatic Non-Small Cell Lung Cancer (NSCLC)), who are B-RAF Proto-oncogene, Serine/threonine Kinase (BRAF)-inhibitor treatment-naïve and have failed the previous therapy(ies) for advanced metastatic disease or are not eligible to standard therapy. Participants will be eligible for the study based on identification of a *BRAF* V600E mutation in tumor tissue by a local National Medical Products Administration (NMPA) approved assay obtained prior to screening.

1.1. Objectives and Endpoints

Objectives and associated endpoints are provided in Table 1 below.

Table 1: Objectives and Endpoints in W00090GE102

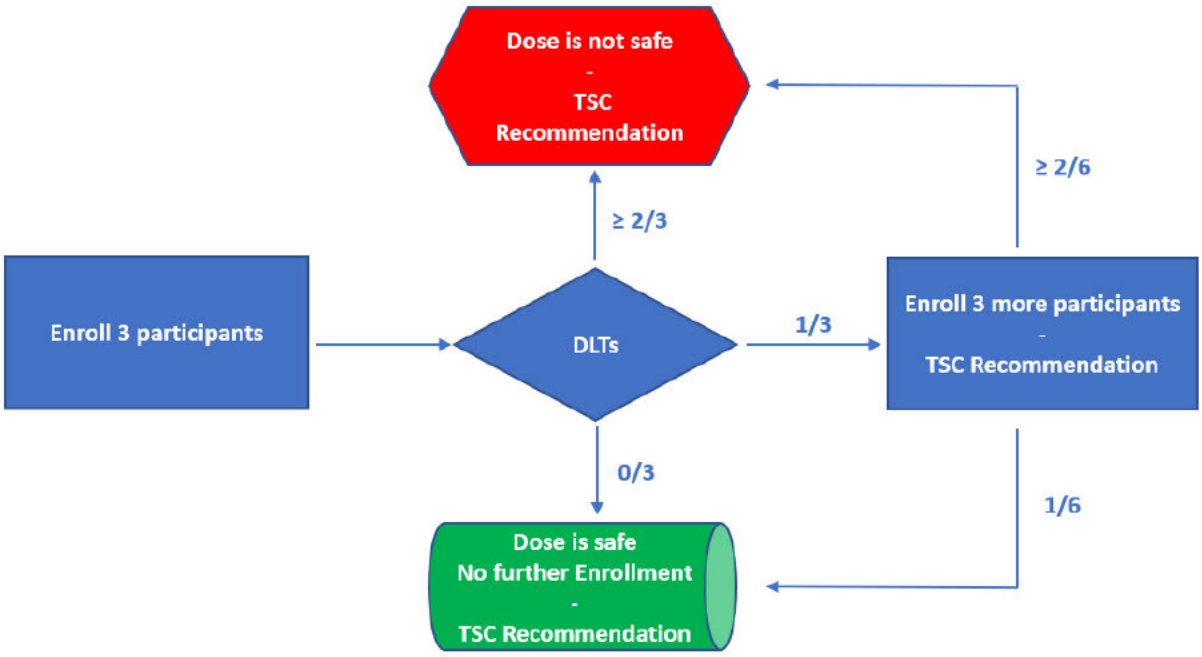
Objectives	Endpoints
Primary	
To assess the safety of encorafenib 300 mg QD in monotherapy during Cycle 1.	• Incidence of Dose-Limiting Toxicities (DLTs) experienced during Cycle 1 (Days 1 to 28) DLTs are defined in Section 1.2.2.
Secondary	
To characterize the safety and tolerability of encorafenib 300 mg QD in monotherapy in Chinese participants.	• Incidence, nature and severity of Treatment Emergent Adverse Events (TEAEs) graded as per National Cancer Institute Common Terminology Criteria for Adverse Event (NCI CTCAE) Version 4.03, TEAEs leading to dose interruption, reduction and discontinuation, treatment-emergent Serious Adverse Events (SAEs) and deaths • Changes in clinical laboratory parameters, vital signs, Electrocardiograms (ECGs) • Incidence of targeted TEAEs of special interest
To provide Pharmacokinetic (PK) data of encorafenib and its metabolite (LHY746) in monotherapy.	• PK parameters of encorafenib and its metabolite (LHY746) after single and repeated administration
Abbreviations: DLT = Dose Limiting Toxicity; ECG = Electrocardiogram; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PK = Pharmacokinetic; QD = Once Daily; SAE = Serious Adverse Event; TEAE = Treatment Emergent Adverse Event.	

1.2. Study Design

All participants will receive a fixed flat oral dose of 300 mg encorafenib QD.

It is planned to enrol up to six evaluable participants using an approach that is similar to a 3+3 design. The study schema is shown in the Figure 1 below:

Figure 1 Study Schema of 3+3 Design



Abbreviations: DLT = dose limiting toxicity; TSC = Trial Steering Committee

- Three participants will initially be enrolled and will be evaluated for DLTs during the first cycle of treatment (28 days) [the DLT evaluation period]:
  - If there are no DLTs in the first three participants in the DLT evaluation period, enrollment will be stopped.
  - If one of the first three participants experiences a DLT in the DLT evaluation period, a Trial Steering Committee (TSC) will make the recommendation whether three additional participants will be enrolled to expand the number of participants to a total of six.
  - If more than one of the first three treated participants experience a DLT, enrollment will be stopped.
- If the group is expanded and two or more of the six participants experience a DLT, enrollment will be stopped.
- The dose of the intervention will not be altered on the basis of the DLTs.

A DLT is defined as any adverse event or abnormal laboratory value assessed as unrelated to disease, disease progression, intercurrent illness or concomitant medications/therapies that satisfies at least one of the criteria listed in Table 2.

Table 2: Criteria for Defining Dose Limiting Toxicities

Toxicity		**Any of the following criteria**
Blood and lymphatic system disorders[a]		≥Grade 3 neutropenia (ANC <1.0 × 10^9/L) for >7 consecutive days
		≥Grade 3 thrombocytopenia (platelets <50 × 10^9/L) for >7 consecutive days
		Grade 4 thrombocytopenia
		Febrile neutropenia (ANC < 1.0 × 10^9/L with fever ≥38.5°C)
Investigations (renal)		≥Grade 3 serum creatinine
Investigations (hepatic)		≥Grade 3 blood bilirubin (> 3 × ULN)
		≥Grade 3 ALT or AST for > 7 consecutive days
		Grade 4 ALT or AST
		≥Grade 3 ALT or AST and ≥Grade 2 blood bilirubin
Investigations (metabolic)		Grade 3 lipase for >7 consecutive days
		Grade 4 lipase
Cardiac disorders		≥Grade 3
Gastrointestinal disorders		≥Grade 3 vomiting or nausea lasting more than 48 hours despite optimal antiemetic therapy[b]
		≥Grade 3 diarrhea lasting more than 48 hours despite optimal treatment
		≥Grade 3 pancreatitis
Skin and subcutaneous tissue disorders[c]**: rash, photosensitivity or HFSR**		Grade 3 rash/photosensitivity/HFSR for >7 consecutive days despite skin toxicity treatment (as per local practice)
		Grade 4 rash/photosensitivity/HFSR
General disorders and administration site conditions		Grade 3 fatigue/asthenia for >7 consecutive days
Ophthalmologic	**Uveitis**	Grade 3 for >21 consecutive days confirmed by ophthalmologic examination
		Grade 4 confirmed by ophthalmologic examination
	Any other eye disorders	Grade 3 for >21 consecutive days
		Grade 4

Toxicity	Any of the following criteria
Other adverse events[d]	≥Grade 3 adverse events (excluding SCC)

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; DLT = limiting dose toxicity; HFSR = hand-foot skin reaction (also known as palmar-plantar erythrodysesthesia [PPE] syndrome); NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events (Version 4.03); ULN = Upper limit of normal.

Grades according to NCI CTCAE grading system.

[a] ≥Grade 3 anemia will not be considered a DLT unless judged to be a hemolytic process secondary to study treatment. ≥Grade 3 lymphopenia will not to be considered a DLT unless clinically significant.

[b] Optimal therapy for vomiting or diarrhea will be based on study site guidelines with consideration of the prohibited medications listed in this protocol.

[c] Squamous cell carcinoma reported to be an on-target side-effect that was manageable will not be considered a DLT.

[d] An adverse event must be clinically significant to be defined as a DLT: alopecia, study treatment-related fever, electrolyte abnormalities (including K, NA, Cl, HCO3, Mg, Ca, PO4) that are ≤Grade 3 abnormalities will not be considered a DLT unless clinically significant.

To be evaluable for tolerability assessment by the TSC, participants must have *either* experienced an event meeting the DLT criteria during Cycle 1 *or* completed at least one cycle of study treatment and received at least 75% of the encorafenib dose intensity (administered dose in mg/planned dose in mg) in Cycle 1.

Participants who require a dose interruption or reduction during Cycle 1 will remain evaluable for tolerability decisions if the reason for the reduction and/or interruption represents a DLT.

Participants who terminate study participation for any reason other than an adverse event or abnormal laboratory value related to disease, disease progression, intercurrent illness or concomitant medications/therapies before having received at least the encorafenib dose intensity of 75% (administered dose in mg/planned dose in mg) in Cycle 1 will be considered ineligible for the safety assessment required for tolerability and will be replaced.

The TSC will analyze the available safety data and assess the toxicities as significant or not once the first three participants (and six participants if required) have fully completed the first cycle of treatment (28 days). The TSC will determine if encorafenib 300 mg QD is tolerable based on the DLT rate (DLTs observed in <33% of participants) and evaluation of the overall toxicity profile (based on deaths, treatment emergent SAEs, TEAEs leading to discontinuation and to dose interruption/reduction).

The TSC will make a recommendation if the dose of encorafenib 300 mg QD is not deemed tolerable.

Following analyses will be conducted during the study:

- First Trial Steering Committee after DLT period of the first participant. No statistical outputs will be provided.
- A Trial Steering Committee after DLT period of first 3 participants, based on subset of TFLs delivery (see Section 5.8.1) for recommendation purpose
- A Trial Steering Committee after 6 participants enrolled if TSC recommends enrolment of 3 further participants to expand number of participants to a total number of six, based on subset of TFLs delivery (see Section 5.8.1) for recommendation purpose
- Subsequent TSC meeting after all subjects have completed the safety 30 day follow-up visit. No statistical outputs will be provided.
- Final analysis at End of Study, with delivery of all planned TFLs including PK: The end of study is defined as the timepoint when the last participant enrolled has discontinued study treatment and completed the 30-day safety follow-up

1.2.1. Study Procedures and Assessments

For each participant, the study will include:

1. **Screening:** Participants with a locally determined *BRAF* V600E mutation will provide informed consent for screening and study procedures and assessments and will be screened for eligibility in the 28 days before the first dose of encorafenib.
2. **Treatment Period:** Participants fulfilling all the eligibility criteria (see Protocol Section 5) will receive encorafenib 300 mg QD in 28 day (± 7 days) cycles until death, disease progression (in special circumstances, continuation of treatment beyond disease progression may be allowed (see Protocol Section 6.1)) or one of the other predefined criteria for study treatment discontinuation is met (see Protocol Section 7.1). The participants will be evaluated for DLTs during the first cycle of treatment (28 days) [the DLT evaluation period]. An end of treatment visit will be completed at the time of study treatment discontinuation (as soon as possible and ≤14 days after the last dose of study treatment).
3. **A 30-day Safety Follow-up:** A safety follow-up visit will be performed approximately 30 days after the last dose of study treatment or before the initiation of subsequent anticancer therapy, whichever occurs first.

The schedule of activities for each participant is shown in Table 3.

Table 3: Schedule of Activities

Cycle / Visit	Screening	Cycle 1				Cycle 2		Subsequent Cycles[a]			EOT visit	Safety 30-day follow-up visit[b]
								Odd cycles	Even cycles			
	Day -28 to -1	D1[c] *Inclusion/ Baseline*	D8	D15	D22	D1 ± 3 days	D28 ± 7 days	D1 ± 3 days	D1 ± 3 days	D28 ± 7 days	± 3 days	+ 7 days after EOT visit/last dose if EOT not performed
EPOCH	SCREENING	SCREENING TREATMENT	TREATMENT									FOLLOW-UP
Main study informed consent	X											
Inclusion/exclusion criteria	X	X										
Demographic data	X											
Medical and disease history	X											
Prior medications/therapies/procedures	X											
Smoking habits	X											
ECOG performance status	X	X				X		X	X		X	X
Height	X											
Physical examination[d] and body weight	X	X[h]	X	X	X	X		X	X		X	X
Vital signs[e]	X	X	X	X	X	X		X	X		X	X
Dermatological examination[f]	X							X			X	X
Hematology[g]	X	X[h]		X		X		X	X		X	X

Cycle / Visit	Screening	Cycle 1				Cycle 2		Subsequent Cycles[a]			EOT visit	Safety 30-day follow-up visit[b]
								Odd cycles	Even cycles			
	Day -28 to -1	D1[c] *Inclusion/ Baseline*	D8	D15	D22	D1 ± 3 days	D28 ± 7 days	D1 ± 3 days	D1 ± 3 days	D28 ± 7 days	± 3 days	+ 7 days after EOT visit/last dose if EOT not performed
Clinical chemistry[i]	X	X[h]		X		X		X	X		X	X
Coagulation[j]	X	X[h]		X		X		X	X		X	X
Urinalysis tests[k]	X	X[h]	X	X	X	X		X	X		X	X
Hepatitis B, C markers and HIV[l]	X											
Pregnancy test[m]	X	X[h]				X		X	X		X	
Chest, abdomen and pelvis CT scan[n]	X						X			X	X	X
MRI or CT scan of brain with IV contrast (if clinically indicated)[n]	X						X			X	X	X
Bone scan or PET scan (if clinically indicated)	X						X			X	X	X
12-lead ECG[o]	X		X	X	X	X			X		X	
Encorafenib dispensation (plus dosing diary)		X				X		X	X			
Encorafenib compliance assessment						X		X	X		X	
Concomitant medications/therapies	Assess continuously											
AE assessment (NCI CTCAE Version 4.03)	Assess continuously											
PK blood samples[p]		X				X						

Cycle / Visit	Screening	Cycle 1				Cycle 2		Subsequent Cycles[a]			EOT visit	Safety 30-day follow-up visit[b]
								Odd cycles	Even cycles			
	Day -28 to -1	D1[c] *Inclusion/ Baseline*	D8	D15	D22	D1 ± 3 days	D28 ± 7 days	D1 ± 3 days	D1 ± 3 days	D28 ± 7 days	± 3 days	+ 7 days after EOT visit/last dose if EOT not performed

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; β-HCG = beta human chorionic gonadotropin; BUN = blood urea nitrogen; CK = creatine kinase; CT = computed tomography; eCRF = electronic case report form; D=Day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; GGT = gamma glutamyltransferase; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; INR = international normalised ratio; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PET = positron emission tomography; PT = prothrombin time; PK = pharmacokinetics; RBC = red blood cell; WBC = white blood cell; ULN = upper limit of normal.

[a] Except Cycle 1 Day 1, if visit is missed theoretical cycles dates (7 days ± 3) are kept constant irrespectively of whether the visit is done and/or the study treatment is administered or not. If a participant does not attend for CnD1 visit, the CnD1 assessments will still need to be performed (and shall be recorded on the unscheduled visit in the eCRF).

[b] Following the 30-day safety follow up, when clinically appropriate, it is also recommended the participant be monitored with dermatologic examinations and chest CT scans for cutaneous and non-cutaneous secondary malignancies for up to 6 months after the last study treatment dose or until initiation of another antineoplastic therapy

[c] Cycle 1 Day1 refers to the day the participant receives the first dose of study treatment. Day 1 of Cycle 2 and of each subsequent cycle corresponds to Day 29 of the previous cycle.

[d] Physical examination:

At baseline: physical examination includes general appearance, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, skin, breast and pelvic examinations should be performed. Ophthalmic examination, at baseline, should include visual acuity (Snellen chart or equivalent, see Appendix 5), tonometry (intraocular pressure), slit lamp examination, and fundoscopy Ophthalmic examination should be repeated at subsequent visits if clinically indicated.

During treatment phase, at EOT visit and at Safety 30 day follow-up visit physical examination should be targeted as clinically indicated.

[e] Vital signs include blood pressure, pulse rate, body temperature and respiratory rate

[f] Dermatological examinations are to be performed every 8 weeks from Cycle 1 Day 1 (i.e. on Day 1 of Cycles 3, 5, 7, etc…) until the end of treatment. Following the 30-day follow-up, when clinically appropriate, it is recommended participants be monitored with dermatologic for up to 6 months after the last study treatment dose to check for possible keratoacanthoma and/or squamous cell carcinoma

[g] Hematology: hemoglobin, hematocrit, RBC, WBC with differential (absolutes values), platelet counts, neutrophils, lymphocytes, monocytes, basophils, eosinophils

[h] Procedure does not have to be repeated if performed within 72 hours prior to Cycle 1 Day 1 (i.e. first day of dosing)

Cycle / Visit	Screening	Cycle 1				Cycle 2		Subsequent Cycles[a]			EOT visit	Safety 30-day follow-up visit[b]
								Odd cycles	Even cycles			
	Day -28 to -1	D1[c] *Inclusion/ Baseline*	D8	D15	D22	D1 ± 3 days	D28 ± 7 days	D1 ± 3 days	D1 ± 3 days	D28 ± 7 days	± 3 days	+ 7 days after EOT visit/last dose if EOT not performed

[i] Clinical chemistry: Albumin, alkaline phosphatase, ALT, AST, total bilirubin (and direct bilirubin), BUN/urea, calcium, chloride, CK, creatinine, GGT, glucose, LDH, lipase and amylase, magnesium, phosphate, potassium, sodium, total protein, troponin I or T, uric acid. These tests will be done under fasting conditions.

[j] Coagulation: PT, INR, aPTT

[k] Urinalysis tests: appearance, colour, specific gravity, pH, protein, glucose, ketones, blood, nitrites, leukocytes

[l] Hepatitis B (HBsAg, HBsAg antibody, hepatitis B core antibody and HBV DNA if HBsAg or HBcAb is positive), hepatitis C antibody, HIV

[m] Pregnancy test

At baseline and EOT visit serum ß-HCG for women of childbearing potential only

During treatment phase urine pregnancy test for women of childbearing potential only

[n] Tumor assessment (MRI or CT scan): Tumor overall assessment (response, stable disease, progressive disease) will be determined locally by the investigator and reported in the eCRF along with the date of the radiological assessment:

During treatment phase radiological assessments should be performed at least every two cycles (8 weeks) ± 7 days for the first 12 months, then at least every three cycles (12 weeks) ± 7 days until disease progression. More frequent radiological assessments may be performed if needed.

At EOT visit if the previous tumor assessment has been performed less than 30 days, there is no need to repeat the tumor assessment.

[o] ECG: three serial ECGs conducted within approximately 5 to 10 minutes total time after at least 5 minutes rest. When an ECG is to be performed at the same time point as a blood collection, the ECG should be performed first.

[p] Serial PK sampling will be collected at pre-dose, and 1, 2, 4, 6 hours post-dose on Cycle 1 Day 1 and Cycle 2 Day 1 only

Tumor assessments will be performed by radiological imaging (including Computed Tomography [CT], Magnetic Resonance Imaging [MRI], X-ray, different methods of whole-body bone scans). Tumor overall assessment (response, stable disease, progressive disease) will be determined locally by the investigator according to RECIST Version 1.1 (see Appendix 11). Tumor assessments will be performed at screening/baseline (within 28 days prior to the first dose of study treatment), then at least every 8 weeks (± 7 days) for the first 12 months, then at least every 12 weeks (± 7 days) until disease progression, withdrawal of consent for treatment, initiation of subsequent anticancer therapy, participant is lost to follow-up, or death (whichever occurs first). More frequently tumor assessments may be performed if needed.

Safety assessments include monitoring of adverse events, DLTs, physical examinations, dermatological examinations, clinical laboratory safety tests (hematology, clinical chemistry, coagulation, urinalysis), vital signs, electrocardiograms (ECGs), and Eastern Co-operative Oncology Group (ECOG) performance status.

Serial blood samples to characterize the PK profile of encorafenib and its metabolites (LHY746) will be collected from participants on the first day of treatment (Cycle 1 Day 1) and at steady state after 1 month treatment (Cycle 2 Day 1).

1.2.2. Scientific Rationale for Study Design

The study design involves a 3+3 approach (commonly used in conducting phase 1 oncology studies) that allows the assessment of DLTs but does not include a dose escalation or de-escalation component. It is a well-established design for selecting a dose suitable for further investigation whilst minimising unnecessary exposure. In this study the design is employed to confirm the safety and tolerability of encorafenib 300 mg QD monotherapy in Chinese participants with *BRAF* V600E mutant melanoma or NSCLC to support further clinical development in combination with binimetinib.

1.2.3. Justification for Dose

The dose of encorafenib is 300 mg per oral (PO) QD, corresponding to its single agent Recommended Phase 2 Dose (RP2D). This dose has also been shown in clinical studies to result in tumor regression and clinical responses as a single agent (see Protocol Section 2.1.4).

1.2.4. End Of Study Definition

The end of study is defined as the timepoint when the last participant enrolled has discontinued study treatment and completed the 30-day safety follow-up.

2. Statistical Hypotheses

Because of the exploratory nature of the study, all data will be analyzed descriptively and not with an inferential approach. No formal statistical testing will therefore be performed.

2.1. Adjustment for multiplicity

Not Applicable.

3. Sample Size Determination

The planned sample size is up to six evaluable participants based on an approach that is similar to a 3+3 design (see Section 1.2). No formal sample size calculation has therefore been performed and sample size is based upon empirical considerations.

Participants will receive encorafenib 300 mg QD. This dose will be considered acceptable if the observed Cycle 1 DLT rate in evaluable participants is <33% (e.g. less than one participant with DLTs out of three participants or less than two participants with DLTs out of six participants). To be evaluable, participants must have *either* experienced an event meeting the DLT criteria in Cycle 1 *or* completed at least one cycle of study treatment and received at least 75% of the encorafenib dose intensity (administered dose in mg/planned dose in mg) in Cycle 1 (see Section 1.2).

4. Analysis Sets

The following populations will be analyzed:

4.1. Safety Set (SAF)

All participants who receive at least one dose of encorafenib (partial or full).

4.2. Dose-Determining Set (DDS)

All evaluable participants from the SAF who either achieve the minimum exposure requirement* and have sufficient safety evaluations** or experience a DLT.

*Encorafenib dose intensity of 75% (administered dose in mg/planned dose in mg) in Cycle 1

**Participants must have been observed for at least 1 cycle: (≥28 days) following the first dose on Cycle 1 Day 1.

4.3. PK Set

All participants who receive at least one dose of encorafenib and who have at least one postdose PK blood collection with associated bioanalytical results.

5. Statistical Analyses

5.1. General Considerations

All analyses will be performed using the SAF otherwise specified. Individual data will be listed on specific population as specified in the list of TFLs. In SAF and PK listings, participants excluded from DDS will be flagged (*).

Statistical analysis will be performed after database lock or data snapshot (see Protocol Section 10.1.8.3.5), using statistical analysis software (SAS®) Version 9.4 or higher.

In general, following descriptive methods will be used to present all relevant data:

- Continuous data will be presented using number of observations, number of missing (if any), mean, standard deviations, median, Q1, Q3, minimum and maximum. 95% Confidence Intervals (CI) will be presented if relevant.
- Categorical data will be summarized using number of observations, frequencies, percentages and number of missing (if any missing). Unless otherwise specified, the calculation of proportions will be based on the non-missing data. Counts of missing observations will be excluded from the denominator.

Baseline is defined as the last completed and available assessment prior to date of first dose of study treatment (including unscheduled or re-test). If an assessment that is planned to be performed prior to the first dose of study treatment in the protocol is performed on the same day as the first dose of treatment and the time is unknown, it will be assumed that it was performed prior to study treatment administration and will be considered as baseline assessment.

Unscheduled assessments will be used in the determination of baseline. Data reported at the end of treatment visit are not eligible for baseline selection.

ECG Baseline will be the mean of the last triplicate measurements performed before the first study treatment administration (i.e. screening assessment per Table 3 Schedule of Activities). If no triplicate available, then baseline will be the last single ECG measurement performed before the first study treatment administration. For the interpretation parameter (normal/abnormal and its related clinical significance), the baseline will be the last completed and available assessment performed before the first study treatment administration, regardless triplicate or single ECG.

For summary statistics by visit, only scheduled visits will be summarized. Re-test and unscheduled assessments will not be taken into account for summaries of post-baseline visit. For analyses of worst post-baseline assessment, all on-treatment values are considered regardless scheduled or unscheduled. For visits where triplicate ECG are collected, value of numeric parameters will be the average, and value of interpretation will be last non-missing record (ie both interpretation and clinical significance if abnormal should be non-missing).

For TFLs, visits will be identified as collected in CRF.

5.2. Participant Dispositions

Participant dispositions will be summarized with number and percentage of participants:

- screened;
- screened failure;
- included in each study population (analysis set);
- reason for treatment discontinuation.
- treatment discontinuation due to DLT during DLT evaluation period

Data will also be listed.

In addition, data collected in the CRF form "Covid-19 Impact" will be listed. Summary of Covid-19 (SARS-CoV-2) impact will be provided with number and percentages of participants impacted by: Visit, Case Report Form, Category.

A summary table will be provided for:

- Treatment discontinuations related to Covid-19 (SARS-CoV-2): This will be defined as an event reported in "Covid-19 impact form" having CRF form entered as "Disposition - End of Treatment" and visit name entered as "End of Treatment". It will be presented overall and by reason for treatment discontinuation
- Missed visit due to Covid-19 (SARS-CoV-2), overall and by visit label: This will be defined as a visit not performed with reason verbatim containing "COVID-19".

5.3. Primary Endpoint(s) Analysis

The primary endpoint is the incidence of DLTs experienced during Cycle 1 (Days 1 to 28) of encorafenib treatment.

5.3.1. Definition of Endpoint(s)

A DLT is defined as any adverse event or abnormal laboratory value assessed as unrelated to disease, disease progression, intercurrent illness or concomitant medications/therapies that satisfies at least one of the criteria listed in Table 2 (see Section 1.2).

DLTs will be identified using the DLT flag reported in the Adverse Event CRF form.

5.3.2. Main Analytical Approach

The occurrence of DLTs will be summarized descriptively for the DDS:

- The number and proportion of participants experiencing DLTs during the DLT evaluation period (defined as the first 28 days after the first dose of study intervention, i.e. from Day 1 to Day 28 inclusive)
- The number and proportion by Type of DLT, by Preferred Term, by Grade, by Action Taken.

All reported DLT will be listed for the DDS, including also any DLT occurring outside of DLT evaluation period (i.e. prior to encorafenib first intake or posterior to Day 28).

5.3.3. Sensitivity Analysis

Not Applicable

5.3.4. Supplementary Analyses

Not Applicable

5.4. Secondary Endpoint(s) Analysis

The secondary endpoints are:

- Incidence, nature and severity of TEAE graded as per NCI CTCAE Version 4.03, TEAEs leading to dose interruption, reduction and discontinuation, treatment-emergent Serious Adverse Events (SAEs) and deaths
- Changes clinical laboratory parameters, vital signs, ECGs
- Incidence of targeted TEAEs of special interest
- Dermatological examinations
- Performance status using the ECOG performance status scale
- PK parameters of encorafenib and its metabolite (LHY746) after single and repeated administration

5.4.1. Key Secondary Endpoint(s)

5.4.1.1. Definition of Endpoint(s)

- Grades of clinical safety laboratory assessments will be derived using NCI CTCAE Version 4.03.
- For vital signs, changes from baseline of continuous endpoints (SBP/ DBP/Temperature/ Pulse rate/ Respiratory rate) will be derived: Value at the visit – Value at baseline.
- For all other endpoints, raw values will be used.

5.4.1.2. Main Analytical Approach.

Secondary PK endpoints are described and will be analyzed as specified in Section 5.7.1.1.

Method for analysis of safety endpoints is detailed in Section 5.6.

5.4.1.3. Sensitivity Analysis

Not applicable

5.4.1.4. Supplementary Analyses

Not Applicable.

5.4.2. Supportive Secondary Endpoint(s)

Not Applicable.

5.5. Tertiary/Exploratory Endpoint(s) Analysis

5.5.1. Scan Assessment

Listing of all tumor assessments performed during the study will be provided with dates and responses determined according to RECIST version 1.1.

In addition, listings of target lesions, non-target lesions and new lesions will also be provided.

5.6. (Other) Safety Analyses

5.6.1. Study Intervention Exposure

The study intervention is the encorafenib, administrated daily.

Exposure to the encorafenib is defined as the time interval in days between the actual date of first encorafenib administration (included) and the actual date of last encorafenib administration (included), derived as:

[Date of last dose of encorafenib or date of cutoff*] – [date of first (non-zero) dose of encorafenib] + 1.

* If participant is off treatment, this is the last non-zero dose of the study drug. If the participant is on treatment at the cutoff date, this is the cutoff date.

The duration of exposure will also be computed in weeks (dividing by 7 the above computation) with one decimal place, and summarized in participants from the SAF for following variables:

- Duration as continuous (in weeks) using descriptive statistics
- Categorized by time intervals (< 4 weeks, 4-<8 weeks, …) for which frequency counts and percentages of participants will be provided

Total subject time, expressed in patient-months, will be provided in participants from the SAF. Total subject time will be a unique number, calculated as the sum of the duration of encorafenib exposure (in days) for each participant divided by 30.4375. The total subject time (aside the number of participants) will be provided according to:

- The duration of encorafenib exposure (i.e. for participants with at least 1, 3, 6 or 12 months of encorafenib exposure)
- The age group as per Risk Management Plan (18 - 64 years, 65 - 74 years, 75 - 84 years, 85+ years and, Total) cross tabulated with sex (Female vs Male).

The actual Dose Intensity (DI) and Relative Dose Intensity (RDI) will be defined for encorafenib as below.

The actual Dose intensity (DI) will be defined as DI (mg/day) = Cumulative actual dose/duration of planned exposure in days as computed above.

The RDI is defined as:

$$RDI\ (\%) = (DI/PDI)*100$$

where:

- DI is the dose intensity as defined above,
- PDI is the Planned Dose Intensity during the study for encorafenib, i.e. 300 mg/day.

Actual DI and RDI will be calculated with no more than one decimal.

Actual DI and RDI (%) will be summarized in participants from the SAF. Descriptive statistics will be provided. For RDI, number and percentage of participants will be provided for following categories: <50%, 50 - <80%, 80 - <100%, 100%, >100%.

In addition, the RDI specific to Cycle 1 will be defined as 100*administered dose (mg) through Cycle 1 divided by planned dose (mg), with planned dose being 8400 mg for encorafenib (28 daily doses of 300 mg).

Relative dose intensity in Cycle 1 will be listed in the listing of dose intensities.

Dose modifications will be defined as below:

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

  To avoid over-counting 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 permanent discontinuation analysis.

- A dose reduction is defined as a decrease in dose from the protocol-planned dose and a decrease from the previous non-zero dose, even if this decrease has been directly preceded by an interruption. For example, for encorafenib, in the sequence of total daily dose 300 mg – 0 mg – 200 mg, the 200 mg dose will be counted as a reduction.

  If a participant moves from a higher than protocol-planned dose down to the planned dose then this is not to be counted as a reduction, however if they move directly from a higher than planned dose down to a lower than protocol-planned dose or the planned dose on a less frequent regimen, then this is counted as a reduction.

  If the dose on the first dosing record is lower than protocol-planned dose this is also counted as a reduction.

Frequency counts and percentages of participants who have dose reductions or interruptions, and corresponding reasons, will be summarized for participants from the SAF. Dose reductions and interruptions will be tabulated both separately and in a combined fashion.

For participants with dose reduction as defined above, the percentages of days between the first and last non-zero dose with reduced dose i.e., below the protocol-planned dose will be summarized and specified in the related listing. Note, in this calculation a dose of 0 mg will also be considered a reduced dose.
For participants with dose interruption as defined above, the percentages of days with dose interruption will also be summarized and specified in the related listing.

Treatment interruptions due to Covid-19 (SARS-CoV-2) will be described as part of the data collected by the "Covid-19 impact" CRF form. Information about administration and exposure of encorafenib will be presented in data listings, with duration of exposure presented in days.

A listing of drug accountability will also be provided.

5.6.2. Adverse Events

The occurrence of an AE is defined by the appearance of a new single event, the reappearance of a previously recovered event or the worsening of a continuous event (relative to its previous status).

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) (latest version in use).

A TEAE is defined as any event that first occurred or worsens from the first study treatment administration date up to the last administration date + 30 days (inclusive). As conservative approach, if year of AE start is missing, and when end date is missing or >= first administration date, AE will be considered as a TEAE.

A participant with more than one occurrence of the same adverse event in a particular System Organ Class (SOC) will be counted only once in the total of those experiencing adverse events in that particular SOC.

If a participant experiences the same adverse event at more than one severity, or with more than one relationship to encorafenib, the most severe rating or the stronger causal relationship to encorafenib will be given precedence.

The denominator used to calculate incidence percentages consists of participants in the SAF.

AEs will be grouped by SOC and Preferred Term (PT) and sorted in descending frequency.

For tables by NCI CTCAE grade, if a participant has more than one AE, the worst grade will be summarized.

Following summaries with number and percentage of participants will be presented:

- Summary of AE (Overall, Related, Grade 3+, Related Grade 3+):
  - AEs,
  - TEAEs,
  - Serious TEAE,
  - TEAE by severity grade,
  - TEAE leading to discontinuation of encorafenib regardless of causality,
  - TEAEs leading to encorafenib dose modification (interruption or reduction),
  - TEAEs leading to encorafenib Drug interruption,
  - TEAEs leading to encorafenib dose reduction,
  - TEAEs requiring additional therapy,
  - TEAE last outcome,
  - TEAE last action taken with encorafenib.
- Summary of SAEs (Overall, Related, Grade 3+, Related Grade 3+):
  - SAEs,
  - Serious TEAEs,
  - Serious TEAE by severity grade,
  - Serious TEAE leading to discontinuation of encorafenib regardless of causality,
  - Serious TEAEs leading to encorafenib dose modification (interruption or reduction),
  - Serious TEAEs leading to encorafenib Drug interruption,
  - Serious TEAEs leading to encorafenib dose reduction,
  - Serious TEAEs requiring additional therapy,
  - Serious TEAE last outcome,
  - Serious TEAE last action taken with encorafenib.
  - Seriousness criteria for Serious TEAE

The following description of TEAE will also be provided (incidence of) with number and percentage of participants:

- TEAE by SOC and PT, also providing number of events
- Serious TEAEs by SOC and PT, also providing number of events
- Related Treatment Emergent Adverse Events by SOC and PT, also providing number of events

- TEAEs with a Grade 3 or 4 by SOC and PT
- TEAEs Leading to encorafenib Dose Reduction by SOC and PT
- TEAEs Leading to encorafenib Drug Interruption by SOC and PT
- TEAE Leading to encorafenib Dose Modification (Action Taken = "Dose reduced" or "Drug interrupted") by SOC and PT
- TEAEs by SOC and PT and Worst NCI CTCAE Grade
- Serious TEAEs by SOC and PT and Worst NCI CTCAE Grade
- Related TEAEs by SOC and PT and Worst NCI CTCAE Grade
- Related Serious TEAEs by SOC and PT and Worst NCI CTCAE Grade
- TEAE Requiring Additional Therapy by SOC and PT and Worst NCI CTCAE Grade

A participant with multiple occurrences of an adverse event will only be counted under the maximum NCI CTCAE grade or worse relationship for this event.

In case of a participant experiencing several episodes of a same continuous AE (ie, a first episode not recovered followed by another episode with a higher severity grade, or with a recovery date), in the table by SOC and PT, the event will be considered only once.
For the table by SOC, PT and Worst NCI CTCAE Grade, the worst episode (the one with the highest severity grade) will be considered.
See Example below for the same participant and the same PT:

PT	AE Number	Episode Number	Start Date	Stop Date	Description
Headache	1	1.01	20Jan2022		Grade 1
	1	1.02	01Feb2022	10Feb2022	Grade 3
Headache	2	2.01	15Mar2022	17Mar2022	Grade 2
Headache	3	3.01	11Apr2022		Grade 2
	3	3.02	16Apr2022	18Apr2022	Grade 3

With the example above, for the tables by SOC and PT, for this participant, we will consider that he experiences 3 Events of Headache (due to AE number), without considering the details of episodes.

For the table by SOC, PT and Worst NCI CTCAE grade, the participant will be counted only for worst grade equals to 3 with 2 Events due to episodes 1.02 and 3.02. Headache whose AE number equals to 2 will not be considered to this analysis by Worst NCI CTCAE grade as this is a grade 2 event.

Number and percentage of participants with at least one event of any AE of special interest (AESI) of encorafenib, and of each category of AESI will be reported in participants from the SAF. Corresponding summary table will be provided, for all grades as well as for Grade 3+. Such categories consist of grouping one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study intervention. The following AE of special interest of encorafenib will be analysed:

- Cutaneous non-squamous cell carcinoma, cutaneous squamous cell carcinoma, melanomas, facial paresis, uveitis-type events, QT prolongation, non-cutaneous malignancies with RAS mutation. Definition of those AESIs will be based on encorafenib case retrieval strategy as specified in Section 6.12.

For all deaths regardless occurrence period, details will be listed as reported in CRF form "Death Details".

The following listings will be provided with participant's code, sex and age, verbatim term, PT, action taken with encorafenib, use of a corrective treatment or procedure, outcome and relationship to encorafenib in the investigator's opinion:

- AE
- Grade 3 and 4 adverse events,
- Adverse events leading to encorafenib dose modifications (Action Taken = "Dose reduced" or "Drug interrupted"),
- Adverse events leading to encorafenib discontinuation,
- Grade 5 Adverse Events
- AE related to Covid-19 (SARS-CoV-2)

A listing will present all reported SAEs.

In those listings, vaccine-emergent AEs will be identified. Vaccine-emergent AE for vaccine dose i will be defined as any event that first occurred or worsens from the COVID-19 vaccine dose i date up to 30 days after (inclusive), for participants having received the i^{th} dose of a COVID-19 vaccine (SARS-CoV-2).

Notes:

- AE is defined as Related if "Causality related to Study Treatment: ENCORAFENIB" is entered as "Suspected"
- Missing severity, relationship or outcome will be classed as unknown.
- "AE requiring additional therapy" corresponds to the CRF item "Corrective treatment and/ or corrective procedure".
- Unless otherwise specified, "Deaths" and AE resulting in death are defined as any AE with grade=5.
- Grade 3+ is defined as maximum grade 3 or higher and is marked as "G3+" in the TFL shells
- AE related to Covid-19 (SARS-CoV-2) will be identified when AE verbatim includes "COVID-19" as prefix.

5.6.3. Clinical Safety Laboratory Evaluation

Viral serology and tests to confirm postmenopausal status for females will be performed before the start of study treatment to determine eligibility or baseline status only.

Blood samples for hematology, clinical chemistry, coagulation and urine samples for dipstick urinalysis will be taken at screening and repeated on Cycle 1 Day 1 (if not performed within 72 hours before the first dose of study intervention), Cycle 1 Day 15, on Day 1 of each subsequent cycle, the end of treatment visit and the 30-day safety follow-up visit. Additional urinalysis tests will be performed on Cycle 1 Days 8 and 22.

All assessments during the treatment phase should be made prior to study treatment administration. Blood samples for the chemistry panel will be taken under fasting conditions

The parameters to be assessed at each timepoint are listed in Table 4.

Unscheduled clinical laboratory tests may be obtained at any time during the study at the investigator's discretion. Laboratory test results required to make decisions regarding potential dose modifications (as specified in Protocol Section 6.6) should be reviewed before study intervention administration.

Table 4: Protocol-required Clinical Laboratory Safety Assessments

Hematology	Erythrocytes (RBC), hematocrit, hemoglobin, platelets Leukocytes (WBC) count with differential (absolute values): basophils, eosinophils, lymphocytes, monocytes, neutrophils/ANC
Clinical Chemistry[a]	Albumin; Alkaline phosphatase (ALP), ALT, AST, total bilirubin (and direct bilirubin), Blood Urea Nitrogen (BUN)/urea, calcium, chloride, creatine kinase (CK), creatinine, Gamma Glutamyl Transferase (GGT), glucose, Lactate Dehydrogenase (LDH) , lipase and amylase, magnesium, phosphate, potassium, sodium, total protein, troponin I or T, uric acid
Coagulation	activated Partial Thromboplastin Time (aPTT), International Normalized Ratio (INR) or Prothrombin Time
Urinalysis	Appearance, color Specific gravity Blood, glucose, leukocytes, ketones, pH, protein by dipstick Microscopic examination (if blood or protein abnormal)
Serology (screening only)	• Hepatitis B: Hepatitis B surface Antigen (HBsAg), HBsAg antibody (Ab), hepatitis B core antibody, and hepatitis B virus (HBV) Deoxyribonucleic acid (DNA) if HBsAg or HBcAb was positive • Hepatitis C Virus (HCV) Ab and HCV Ribonucleic Acid (RNA) if HCV Ab was positive • Human Immunodeficiency Virus (HIV)
Postmenopausal status (screening only, if required)	FSH
Abbreviations: Ab = antibody; = aPPT = activated partial thromboplastin time; ALT = alanine aminotransferase;	

AST = aspartate aminotransferase; BUN = blood urea nitrogen; CK = creatine kinase; DNA = deoxyribonucleic acid; FSH = follicle stimulating hormone; GGT = gamma glutamyl transferase; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; LDH = lactate dehydrogenase; pH = hydrogen ion concentration; PT = prothrombin time; RBC = red blood cell(s); RNA = ribonucleic acid; SAE = serious adverse event; ULN = upper limit of normal; WBC=white blood cell.

[a] Details of liver clinical chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Protocol Appendix 10.4. All events of ALT >3 × ULN and bilirubin >2 × ULN (>35% direct bilirubin) or ALT >3 × ULN and INR >1.5, if INR measured which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE.

Samples may be collected up to 48 hours prior to scheduled clinic visits. Results must be reviewed by the investigator prior to study treatment administration.

Blood samples will be collected, handled and analyzed at the local laboratory according to the study site's standard procedures and the latest updated references. Ranges from the laboratory will be used to identify abnormal values. Urinalysis will be performed in the clinic or at the local laboratory, according to study site standards.

Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

Listings of all laboratory evaluations (hematology, chemistry, urinalysis including microscopic evaluation, coagulation) will be provided.

Serology will also be listed.

5.6.3.1. Hematology and Clinical Chemistry

Descriptive statistics of all parameters over time will be performed. Values at each visit and changes from baseline will be calculated and tabulated. Unscheduled visits or retest will not be analyzed.

Shift tables of maximum post baseline NCI CTCAE grades according to baseline NCI CTCAE grade (version 4.03) will be provided for the following parameters:

- Hematology
    - Hemoglobin (Low)
    - Hemoglobin (High)
    - Leukocytes (Low)
    - Leukocytes (High)
    - Neutrophils (Low)
    - Platelets (Low)

  - Lymphocytes (Low)
  - Lymphocyte (High)
- Biochemistry
  - Phosphate (Low)
  - Alanine Aminotransferase (High)
  - Albumin (Low)
  - Alkaline Phosphatase (High)
  - Amylase (High)
  - Aspartate Aminotransferase (High)
  - Bilirubin (High)
  - Calcium Corrected (Low)
  - Calcium Corrected (High)
  - Creatine Kinase (High)
  - Creatinine (High)
  - Gamma Glutamyl Transferase (High)
  - Glucose (Low)
  - Glucose (High)
  - Lipase (High)
  - Magnesium (Low)
  - Magnesium (High)
  - Potassium (Low)
  - Potassium (High)
  - Sodium (Low)
  - Sodium (High)
  - Urate (High) corresponding to uric acid

Laboratory data will be graded using NCI CTCAE Version 4.03. Grade 0 will be assigned for all non-missing values not graded as ≥1. Grade 5 will not be used.

Scatter plots of maximum post-baseline NCI CTCAE grade according to baseline grade will also be produced.

For some parameters, grades are defined for low and high values.

In addition, incidence of clinically notable shifts in laboratory parameters based on NCI CTCAE grade for the same list of parameters (as above) will be summarized, i.e. number and percentage

of participants with at least one clinically notable shift during study. Clinically notable shift is defined as a worsening from baseline by at least 2 grades, or to grade 3 or above.

For parameters that cannot be graded with NCI CTCAE, shift tables of worst post baseline normal/abnormal level according to baseline normal/abnormal level will be displayed.

Hepatic toxicity

Possible Hy's Law cases will be summarized as part of the analysis below (last category of Table 5).

Hepatic toxicity will be assessed based on the following Liver Function Tests (LFTs): Albumin, ALT, AST, ALP and Total Bilirubin (TBL). For these parameters, NCI CTCAE grades are defined.

Frequency counts and percentages of participants having a newly occurring hepatic value in the categories presented in Table 5 will be provided, for each category.

Table 5: Hepatic Toxicity Criteria

Parameter	Criterion
Albumin	< LLN
ALT	>3×ULN; >5×ULN; >8×ULN;>10×ULN;>20×ULN
AST	>3×ULN; >5×ULN; >8×ULN >10×ULN;>20×ULN
AT (ALT or AST)	>3×ULN; >5×ULN; >8×ULN >10×ULN;>20×ULN
TBL	>1.5×ULN, >2×ULN
ALP	>2×ULN, >3×ULN
AT & TBL	AT >3×ULN & TBL >2×ULN; AT >5×ULN & TBL >2×ULN; AT >10×ULN & TBL >2×ULN
ALP & TBL	ALP >3×ULN & TBL >2×ULN
AT & TBL & ALP (i.e., Hy's Law)	AT >3×ULN & TBL >2×ULN & ALP <2×ULN

LFTs will also be listed by visit.

5.6.3.2. Coagulation

Descriptive statistics of all parameters over time will be performed. Values at each visit and changes from baseline (for quantitative parameters) will be calculated and tabulated. Unscheduled visits or retest will not be analyzed.

Shift tables of maximum post baseline NCI CTCAE grades according to baseline NCI CTCAE grade will be provided for INR (high values): It will be graded using NCI CTCAE Version 4.03. Grade 0 will be assigned for all non-missing values not graded as ≥1. Grade 5 will not be used.

For parameters that cannot be graded with NCI CTCAE, shift tables of worst post baseline normal/abnormal level according to baseline normal/abnormal level will be displayed.

5.6.3.3. Urinalysis

For dipstick, descriptive statistics of all parameters over time will be performed. Values at each visit and changes from baseline (for quantitative parameters) will be calculated and tabulated. Unscheduled visits or retest will not be analyzed.

Microscopy findings (normal/abnormal and clinical significance) will be listed as part of the urinalysis listing.

5.6.4. Physical Examinations

A physical examination will be carried out on each body system at screening and repeated on Cycle 1 Day 1 (if not performed within 72 hours before the first dose of study intervention), Cycle 1 Days 8, 15 and 22, on Day 1 of each subsequent cycle, the end of treatment visit and the 30-day safety follow-up visit. Body weight will also be measured as part of the physical examination. Height will be measured at screening only.

The physical examination at baseline should include general appearance, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. Visual acuity should also be performed. If indicated based on medical history and/or symptoms, rectal, external genitalia, skin, breast and pelvic examinations should be included. The physical examination at other timepoints should be targeted as clinically indicated.

Descriptive statistics of weight (kg) and changes from baseline at each scheduled visit will be performed in participants from the SAF.

Physical examination results (normal/abnormal and clinical significance) and details of abnormalities will also be listed for each participant and visit (scheduled or not).

Weight will be listed as part of the Vital Signs (see Section 5.6.5).

Ophthalmic examination will also be listed: visual acuity, tonometry (Intraocular Pressure), slit lamp examination, and fundoscopy. All baseline assessments will be listed. For post-baseline assessments, only performed ones will be displayed.

5.6.5. Vital Signs

Tympanic temperature (°C), pulse rate (collected as heart rate in the vital signs eCRF, in beats/min), respiratory rate (breaths/min), Systolic Blood Pressure (SBP, in mmHg) and Diastolic Blood Pressure (DBP, in mmHg) will be measured using study site standard techniques at screening and repeated on Cycle 1 Days 1, 8, 15 and 22, Day 1 of each subsequent cycle, the end of treatment visit and the 30-day safety follow-up visit.

All parameters will be described at each scheduled visit with changes from baseline in participants from the SAF.

In addition, shift tables of worst post baseline grade according to the baseline grade will be provided for blood pressure hypertension criteria (systolic, diastolic, and both combined). It will be derived as follows:

- Systolic BP (SBP) only (mmHg):
  - Grade 0: < 120
  - Grade 1: 120-139
  - Grade 2: 140-159
  - Grade 3: ≥ 160
  - No Grade 4 or 5
- Diastolic BP (DBP) only (mmHg):
  - Grade 0: < 80
  - Grade 1: 80-89
  - Grade 2: 90-99
  - Grade 3: ≥ 100
- Systolic and diastolic BP combined (mmHg). Maximum grade based on SBP and DBP values at the same assessment will be considered:
  - Grade 0: SBP < 120 and DBP < 80
  - Grade 1: SBP in 120-139 or DBP in 80-89
  - Grade 2: SBP in 140-159 or DBP in 90-99
  - Grade 3: SBP ≥ 160 or DBP ≥ 100
  - No Grade 4 or 5

The following criteria define clinically notable 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 (collected as heart rate in the vital signs eCRF): ≥ 120 bpm with increase from baseline of ≥15 bpm;
  - Weight: increase from baseline of ≥ 10%;
  - Body temperature [C]: ≥ 37.5 C.

- Clinically notable low values
  - Systolic BP: ≤ 90 mmHg with decrease from baseline of ≥ 20 mmHg;
  - Diastolic BP: ≤ 50 mmHg with decrease from baseline of ≥ 15 mmHg;
  - Pulse rate (collected as heart rate in the vital signs eCRF): ≤ 50 bpm with decrease from baseline of ≥ 15 bpm;
  - Weight: ≥ 20% decrease from baseline;
  - Body temperature [C]: ≤ 36 C.

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

All vital signs parameters (including weight) and clinically notable values flag will be also presented in a data listing.

5.6.6. ECG

12-lead ECGs will be performed at screening, Cycle 1 Day 8, 15 and 22, Day 1 of each subsequent even cycle (Cycle 2, 4, 6, …) and the end of treatment visit.

12-lead ECGs will be performed before blood collection, where applicable.

For a given parameter at a given post-baseline visit, mean of the results at the available timepoints will be used for summary statistics.

ECG parameters will be described at each scheduled visit and listed in participants from the SAF, with a flag for clinically notable values.

Frequency counts and percentages of participants having at least one post-baseline clinically notable ECG values during study (Table 6) will also be described.

Table 6: Clinical Notable ECG Criteria

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

5.6.7. Dermatological Examinations

Dermatological examinations will be performed to monitor for the possible development of keratoacanthoma and/or squamous cell carcinoma, as these have been reported to occur with selective BRAF inhibitor treatment. This assessment will be performed at screening, Day 1 of each odd cycle (Cycle 3 onwards), the end of treatment visit and the 30-day safety follow-up visit. All assessments during the treatment phase should be made prior to study treatment administration.

Following the 30-day safety follow-up (when clinically appropriate) it is recommended further dermatological examinations be performed every 8 weeks for up to 6 months after the last encorafenib dose or until initiation of another antineoplastic therapy.

All dermatological parameters will be described at each scheduled visit in participants from the SAF and will be presented in a data listing.

5.6.8. ECOG Performance Status

An assessment of ECOG performance status will be made at screening. All participants must have a score of 0 or 1 for inclusion. Assessments will be repeated on Cycle 1 Day 1, on Day 1 of each subsequent cycle, the end of treatment visit and the 30-day safety follow-up visit to assess progression of disease and how the daily living abilities of the participant are affected. ECOG performance status should be obtained on the scheduled day, even if study treatment is being held (see Table 7).

Table 7: Eastern Cooperative Oncology Group Performance Status Scale

0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

ECOG performance status will be described at each visit in participants from the SAF and presented in a data listing.

In addition, shift tables in ECOG performance status will be also provided for worst on-study value versus baseline value on the SAF.

5.6.9. Pregnancy Testing

Pregnancy tests will be performed on females determined to be Women of Childbearing Potential only. All tests must be sensitive to 25 IU/L β-HCG.

A serum test will be performed by the study site's local laboratory at screening. Local urine pregnancy tests will be repeated on Cycle 2 Day 1, on Day 1 of each subsequent cycle, and at the end of treatment visit. Further tests may be performed at any time if pregnancy is suspected. All assessments during the treatment phase should be made prior to study treatment administration.

All pregnancy tests will be presented in a data listing. Reproductive status will also be listed.

5.7. Other Analyses

5.7.1. Other Variables and/or Parameters

5.7.1.1. PK

5.7.1.1.1. PK samples

Blood samples will be collected to characterize the PK profile of encorafenib and its metabolite (LHY746) on the first day of treatment (Cycle 1 Day 1) and at steady state after 1 month treatment (Cycle 2 Day 1). Serial blood samples will be taken predose and 1 (±10 minutes), 2 (±10 minutes), 4 (±30 minutes) and 6 (±30 minutes) hours postdose on both days.

5.7.1.1.2. Non-compartmental PK Analysis

Encorafenib and LHY746 concentrations will be transmitted by the bioanalytical laboratory to PII

PK analyses will be performed on the PK Set.

The following PK parameters for encorafenib and its metabolite LHY746 will be determined where possible using non-compartmental methods in the validated software program Phoenix WinNonlin (Certara, Version 8.1 or higher):

Parameter	Definition
AUC_{0-6}	area under the concentration-time curve from time 0 to 6 hours post dose
$AUC_{0-tlast}$	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (t_{last})
C_{max}	maximum observed concentration
t_{max}	time of the maximum observed concentration
C_{min}	minimum observed concentration following multiple dosing (taken as the predose concentration on Cycle 2 Day 1) – determine for Cycle 2 Day 1 only
C_{last}	last quantifiable concentration
t_{last}	time of last quantifiable concentration
AR_{AUC}	observed accumulation ratio based on AUC_{0-6}
MR_{AUC}	metabolite: parent ratio based on AUC_{0-6}

Additional PK parameters may be determined where appropriate.

During the study, a preliminary PK analysis will be carried out after 3 first participants, using the theoretical blood sampling times (planned time or scheduled time) and the validated concentration data. After the data base lock, the final PK analysis will be carried out using the validated concentrations data and the actual blood sampling times postdose where possible. If an actual time is missing, nominal time (i.e. theoretical time) will be assigned to the sample concentration.

The parameters C_{max}, C_{min}, C_{last}, t_{last} and t_{max} will be obtained directly from the concentration-time profiles. If C_{max} occurs at more than 1 timepoint, t_{max} will be assigned to the first occurrence of C_{max}.

All AUC values will be calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations (linear up/log down rule).

AR_{AUC} will be derived by dividing AUC_{0-6} from Cycle 2 Day 1 by AUC_{0-6} from Cycle 1 Day 1.

MR_{AUC} will account for differences in molecular weights (MW) between LHY746 and encorafenib using the formula: MR_{AUC} = (LHY746 AUC / LHY746 MW) / (encorafenib AUC / encorafenib MW)

Encorafenib MW = 540

LHY746 MW = 424.88

5.7.1.1.2.1.Criteria for Handling Concentrations Below the Limit of Quantification

Handling of PK concentrations below limit of quantification (BLQ) will be applied as follows:

	Substitution value if BLQ occurs:		
Type of analysis	Before t_{max}	After t_{max} & between 2 quantifiable concentrations	After t_{max} & NOT between 2 quantifiable concentrations
PK Non-compartmental analysis	0	Missing	Missing
Descriptive statistics	0	0	0
Plotting of individual data	0	Missing	Missing
Listing of individual data	BLQ	BLQ	BLQ

If an entire concentration-time profile is BLQ, it will be excluded from PK analysis.

If a predose concentration on Cycle 1 Day 1 is missing, it will be set to zero by default for PK analysis.

5.7.1.1.2.2. Treatment of Outliers in PK Analysis

If a value is considered to be anomalous due to being inconsistent with the expected PK profile, it may be appropriate to exclude the value from the PK analysis. However, the exclusion of any data must have strong justification and will be documented in the CSR.

Any quantifiable predose concentration value on Cycle 1 Day 1 will be considered anomalous and set to missing for the PK analysis.

5.7.1.1.2.3. Criteria for Calculation of AUC

The minimum requirement for the calculation of AUC values will be the inclusion of at least three consecutive plasma concentrations above Lower Limit Of Quantification (LLOQ). If there are only 3 consecutive concentrations, at least one should follow C_{max}.

5.7.1.1.3. Presentation of PK Data

- Preliminary analysis

Preliminary individual PK encorafenib and LHY746 parameters will be listed.

Individual concentration-time profiles will be presented graphically for encorafenib and LHY746 on both linear and semi-logarithmic scales.

Only Phoenix WinNonlin outputs could be used at this stage. No statistical analysis on concentrations and PK parameters will be done.

- Final analysis

All encorafenib and LHY746 plasma concentrations will be listed by cycle and summarised by cycle for each analyte.

Listing of samples collection and concentrations will be provided on SAF, where participants excluded from PK Set will be flagged (**).

Listing of PK parameters will be provided on PK Set.

Figures and tables will be provided on PK Set.

In all listings, participants excluded from DDS will be flagged (*).

If the actual time of sample collection deviates from the nominal time by more than ±10%, the concentration will be flagged and excluded from the descriptive statistics. Individual concentrations deemed to be anomalous will be flagged in the listings, with the reason for exclusion footnoted, and excluded from the descriptive statistics.

PK concentrations will be summarised by cycle for each analyte using the description statistics: geometric mean, geometric coefficient of variation (CV%), arithmetic mean, arithmetic standard deviation (SD), median, minimum, maximum, number of observations (n), and number of participants (N). The following rules will apply for summarising of PK concentrations:

- At least 3 evaluable data (N≥3), otherwise only the minimum and the maximum are displayed and other statistics are indicated as "Not Applicable" (NA)
- Values that are BLQ will be set to 0 for the calculation of descriptive statistics.
- Arithmetic mean or median values that are BLQ will be presented as 0.
- If any BLQ results (treated as 0) are in a series of summarized data, geometric mean and CV% of geometric mean will be reported as not calculated (NC).

PK parameters will be listed by cycle and summarised by cycle for each analyte using the description statistics: geometric mean, geometric coefficient of variation (CV%), arithmetic mean, arithmetic standard deviation (SD), median, minimum, maximum, number of observations (n), and number of participants (N), with the exception of t_{max} and t_{last} where only N, n, median, minimum and maximum will be presented.

For derived PK parameters, descriptive statistics are calculated according to the following rules:

- at least 3 evaluable data (N≥3) are available, otherwise only the N, n, minimum and the maximum are presented and other statistics are shown as NA

Participant's encorafenib and LHY746 PK concentrations and parameters will be flagged and excluded from descriptive statistics if:

- vomiting occurs within the first 4 hours postdose on Cycle 1 Day 1 and Cycle 2 Day 1
- vomiting episode occurs within the first 4 hours postdose on the day of the last encorafenib dose prior to collection of PK samples (i.e. relating to the day before Cycle 2 Day 1)
- a participant missed any encorafenib dose or dose reduced within the 3 days immediately prior or the day of Cycle 2 Day 1 PK sample collection (i.e for PK parameters and concentrations)

Individual and summary concentration-time profiles will be presented graphically for encorafenib and LHY746 on both linear and semi-logarithmic scales, using the following 3 types of plots:

- Graphical display of the concentration-time profiles *(spaghetti plot)* by overlaying individual profiles (using actual sampling times) and the median profile (using nominal sampling times) on linear and semi-logarithmic scales. Figure will be repeated by analyte (encorafenib and LHY746) and by cycle (Cycle 1 Day 1 and Cycle 2 Day 1). Participants excluded from statistical analysis will be flagged.

- Individual profiles are by-participants plots and will use the actual sampling times. Cycle 1 Day 1 and Cycle 2 Day 1 concentration-time profiles will be overlaid on the same plot. Figure will be repeated by analyte (encorafenib and LHY746). Participants excluded from statistical analysis will be flagged.

- Arithmetic mean concentration-time profiles with error (+/-SD) bars using the nominal sampling times. Cycle 1 Day 1 and Cycle 2 Day 1 concentration-time profiles will be overlaid on the same plot. Figure will be repeated by analyte (encorafenib and LHY746).

Linear and semi logarithmic plots will be displayed on the same page side by side as appropriate.

5.7.2. Subgroup Analyses

Not Applicable due to the low number of participants to be included in the study

5.8. Interim Analyses

There are no interim analyses planned.

5.8.1. Trial Steering Committee (TSC)

The TSC will analyze the available safety data in order to evaluate the tolerability of encorafenib 300 mg QD.

The TSC will assess any toxicities as significant or not once the first three participants (and six participants if required) have fully completed the first cycle of treatment (28 days). The tolerability assessment will be based on the DLT rate (DLTs observed in <33% of participants) and evaluation of the overall toxicity profile (based on deaths, treatment emergent SAEs, TEAEs leading to discontinuation and to dose interruption/reduction). The TSC will make a recommendation if the dose of encorafenib is not deemed tolerable.

The TSC membership, data to be reviewed, timing of the planned reviews as well as the operating procedures will be described in the TSC Charter.

6. Supporting Documentation

6.1. Appendix 1: List of Abbreviations

Abbreviation	Definition
Ab	*Antibody*
AE	*Adverse Event*
AESI	*Adverse Event of Special Interest*
ALP	*Alkaline Phosphatase*
ALT	*Alanine Aminotransferase*
aPTT	*activated Partial Thromboplastin Time*
AST	*Aspartate Aminotransferase*
ANC	*Absolute Neutrophil Count*
ATC	*Anatomical Therapeutic Classification*
AUC	*Area Under the Curve*
BLQ	*Below the Level of Quantification*
BRAF	*B-RAF Proto-oncogene, Serine/threonine Kinase*
BRAF V600E	*B-RAF Proto-oncogene, Serine/threonine Kinase V600E Mutant*
BRAF wt	*B-RAF Proto-oncogene, Serine/threonine Kinase Wild Type*
BMI	*Body Mass Index*
CI	*Confidence Interval*
C_{last}	*Last quantifiable concentration*
C_{max}	*Maximum Concentration*
C_{min}	*Minimum Concentration*
CrCl	*Creatinine Clearance*

CT	*Computed Tomography*
CTCAE	*Common Terminology Criteria for Adverse Event*
DBP	*Diastolic Blood Pressure*
DDS	*Dose-Determining Set*
DI	*Dose Intensity*
DILI	*Drug-Induced Liver Injury*
DLT	*Dose-Limiting Toxicity*
DNA	*Deoxyribonucleic Acid*
ECG	*Electrocardiogram*
ECOG	*Eastern Co-operative Oncology Group*
eCRF	*Electronic Case Report Form*
EGFR	*Epidermal Growth Factor Receptor*
EMA	*European Medicines Agency*
FDA	*US Food and Drug Administration*
FSH	*Follicle Stimulating Hormone*
GGT	*Gamma Glutamyl Transferase*
HBsAg	*Hepatitis B Surface Antigen*
HBV	*Hepatitis B Virus*
HCV	*Hepatitis C Virus*
HIV	*Human Immunodeficiency Virus*
INR	*International Normalized Ratio*
LDH	*Lactate Dehydrogenase*
LFT	*Liver Function Test*
LLN	*Lower Limit of Normal*

LLoQ	*Lower Limit of Quantification*
MedDRA	*Medical Dictionary for Regulatory Activities*
MEK	*Mitogen-activated Protein Kinase Kinase*
MRI	*Magnetic Resonance Imaging*
NCI	*National Cancer Institute*
NCI CTCAE	*National Cancer Institute Common Terminology Criteria for Adverse Event*
NMPA	*National Medical Products Administration*
NSCLC	*Non-small Cell Lung Cancer*
PDI	*Planned Dose Intensity*
PK	*Pharmacokinetic*
PO	*Per Oral*
PT	*Preferred Term*
QD	*Once Daily*
RBC	*Red Blood Cells*
RDI	*Relative Dose Intensity*
RP2D	*Recommended Phase 2 Dose*
RNA	*Ribonucleic Acid*
SAE	*Serious Adverse Event*
SAF	*Safety Set*
SAP	*Statistical Analysis Plan*
SAS®	*Statistical Analysis Software*
SBP	*Systolic Blood Pressure*
SI	*System International*
SOC	*System Organ Class*

SMQs	*Standardized MedDRA Queries*
TBL	*Total Bilirubin*
TEAE	*Treatment Emergent Adverse Event*
TFL	*Tables Figures and Listings*
t_{last}	*Time of last quantifiable concentration*
t_{max}	*Time of the maximum observed concentration*
TOC	*Table Of Contents*
TSC	*Trial Steering Committee*
ULN	*Upper Limit of Normal*
WBC	*White Blood Cells*
WHO	*World Health Organization*

6.2. Appendix 2: Changes to Protocol-planned Analyses

Following changes to protocol-planned analyses are reported in current SAP:

- Due to limited sample size in this study, some summaries planned by protocol will be replaced by listings of individual data.

- As stated in Section 5.7.1.1.2, a preliminary PK analysis will be carried out after 3 first participants, using the theoretical blood sampling times (planned time or scheduled time) and the validated concentration data.

6.3. Appendix 3: List of TFLs

The Table Of Contents (TOC) of Tables Figures and Listings (TFLs) will be provided in a separate document, as well as the shell TFLs and specifications.

In the TOC of TFLs, the outputs selected for TSC will be flagged.

6.4. Appendix 4: Disease Characteristics and demographics

All demographic data and baseline characteristics will be summarized in output tables in all participants from the SAF and the DDS (if different from the SAF), and presented in data listings for the SAF.

The Baseline Characteristics and demographics data are described in the Table 8 below:

Table 8: Baseline Characteristics and demographic data

Variable	Quantitative parameters	Qualitative parameters	Derived variable	SAF	DDS*
Country		X		X	X
Sex (M/F)		X		X	X
Race		X		X	X
Age (years)	X			X	X
Weight (kg)	X			X	X
Height (cm)	X			X	X
Body Mass Index (BMI) (kg/m^2)	X		X	X	X
ECOG performance status		X		X	X
Smoking history		X		X	X
BRAF V600E Mutation Result (Local)		X		X	X

*: If different from the SAF

Notes:

- The Age described in the table is the age reported in the eCRF.
- BMI will be calculated as weight(kg)/height^2(m^2)

6.5. Appendix 5: Cancer History

Cancer History will be summarized in participants from the SAF and the DDS (if different from the SAF). Cancer History will also be listed for the SAF.

Note:

- In case of missing initial diagnosis date or missing date of first metastasis, substituting rules defined in appendix 9 (Section 6.9.3) will be applied.

The Cancer History data are described in the Table 9 below:

Table 9: Cancer History data

Variable	Quantitative parameters	Qualitative parameters	Derived variable	SAF	DDS*
Diagnosis at study entry		X	X	X	X
Time since initial diagnosis (months) computed as [date of treatment assignment minus the date of initial diagnosis + 1]/30.4375	X		X	X	X
Primary tumor location		X		X	X
Delay between diagnosis of the primary tumor and metastasis (months)	X		X	X	X
Diagnosis method		X		X	X
Metastatic disease sites ("List of metastatic organs ")		X		X	X
Number of metastatic organs (1, 2, >2)		X		X	X
Number of Prior Systemic Regimens in the metastatic setting	X			X	X

*: If different from the SAF

6.6. Appendix 6: Medical History, Baseline Signs and Symptoms

Medical history data will be coded using MedDRA dictionary (latest version in use) and summarized by SOC and PT with the number and percentage for the SAF. A by-participant listing of medical history information will be provided for the SAF. Medical history related to Covid-19 (SARS-CoV-2) will be identified during coding process using verbatim (by default when MH verbatim includes "COVID-19" as prefix), and will be flagged in the listing.

Incomplete dates will be handled as described in Appendix 9.

6.7. Appendix 7: Prior/concomitant/follow-up therapies

Medications will be coded using the latest version of the World Health Organization (WHO) Drug Dictionary (March 2021 Enhanced Dictionary Version Global B3 at set-up, and latest version in use for final analysis) and recorded on the "Prior Anti-Neoplastic Therapy – Medication " and "Prior/Concomitant Medications" eCRF pages.

Medications used to treat Covid-19 (SARS-CoV-2) will be identified using WHODrug Standardised Drug Groupings (SDG) "Drugs for COVID-19".

Therapeutic / Diagnostic Procedures (both prior and concomitant) will be coded using MedDRA dictionary (latest version in use) and recorded on the "Medical and Surgical Procedures" eCRF pages.

Prior anti-neoplastic surgeries will be coded similarly.

Procedures used to treat Covid-19 (SARS-CoV-2) will be flagged when the "Adverse Event ID linked to the procedure" or "Medical History ID linked to the procedure" is coded as related to Covid-19 (SARS-CoV-2), or when "COVID-19" words are located at any location inside the "Reason (Indication)" provided in CRF.

The SAF will be used to describe all Prior/concomitant/follow-up therapies summaries and listing, unless otherwise specified.

Where a medication start date is partially or fully missing, and it is unclear as to whether the medication is prior or concomitant, it will be assumed that it is concomitant.

6.7.1. Prior Therapies

Prior therapies are defined as any therapies starting and ending before the start of study treatment.

Prior therapies include:

- prior antineoplastic treatments
- prior medications (excluding prior anticancer treatments).
- prior diagnostic/therapeutic procedures (excluding prior anticancer treatments).

6.7.1.1. Prior Anticancer Therapy

Prior antineoplastic therapies will be classified in three separate categories: medications, radiotherapy, and surgery.

Listings will be provided for each category separately (medication, radiotherapy, surgery) and presented in SAF, showing at least data detailed below:

- Prior antineoplastic therapy– medications:
    - Participant reported with medications (Yes/No)
    - Start Date/End Date
    - Drug Name
    - Anatomical Therapeutic Classification (ATC) code level 4 and Preferred Drug Name
    - Setting
    - Reason for discontinuation
    - Best overall response
    - Type of Treatment
    - Time from medication start to progression (months), using the "Date of Relapse/Progression" as collected in the medication form
    - Time from medication end to first intake (<1 month, 1-<6 months, 6-<12 months, >=12 months)
- Prior antineoplastic therapy - radiotherapy :
    - Participant reported with radiotherapy (Yes/No)
    - Start Date/End Date
    - Dose, Unit
    - Location/Site
    - Intent
    - Setting
    - Best Overall Response
    - Time from radiotherapy end to first intake (<1 month, 1-<6 months, 6-<12 months, >=12 months)
- Prior antineoplastic therapy – surgery (excluding biopsies):
    - Participant reported with prior surgeries (Yes/No)
    - Date
    - Site/Location
    - Result of Surgery
    - Treatment intent
    - SOC and PT
    - Time from surgery to first intake (<1 month, 1-<6 months, 6-<12 months, >=12 months)

Incomplete dates will be handled as described in Appendix 9 (Section 6.9.4).

Note:

- Time from last medication to progression will be derived if first intake date of last medication and PD dates are not completely missing. In that case, participant will be counted in the missing category. It will be computed in months as [date of PD - start date of last medication + 1] / 30.4375.

- Time from last medication to first intake (respectively time from last radiotherapy to first intake, time from last surgery to first intake) will be derived if last intake date of the last medication (respectively last radiotherapy date, last surgery date) is not completely missing. In that case, participant will be counted in the missing category. It will be computed in months as [date of first encorafenib administration - end date of last medication (resp. last radiotherapy, last surgery) + 1] / 30.4375.

6.7.1.2. Prior medications (excluding antineoplastic therapy)

Prior medications (excluding antineoplastic therapy) will be listed by ATC code level 4, Preferred Drug Name using the SAF, in the same listing as concomitant medications (see Section 6.7.2.2) and flagged as prior medications.

Incomplete dates will be handled as described in Appendix 9 (Section 6.9.2).

6.7.1.3. Prior Therapeutic / Diagnostic Procedures

Prior Therapeutic / Diagnostic Procedures (excluding prior anticancer treatments) will be listed by SOC and PT for the SAF, in the same listing as concomitant procedures (see Section 6.7.2.3) and flagged as prior procedures.

Incomplete dates will be handled as described in Appendix 9 (Section 6.9.2).

6.7.2. Concomitant therapies

Concomitant therapies are defined as any therapies starting on or after the start of study treatment but no later than 30 days (<30 days) after the last dose of study treatment or medications starting prior to the start of study treatment and continuing after the start of study treatment.

Concomitant therapies include:

- Concomitant antineoplastic therapies: radiotherapies
- Concomitant medications.
- Concomitant diagnostic/therapeutic procedures.

6.7.2.1. Concomitant Anticancer radiotherapies

Listing will be provided using the SAF. There will be no imputation for missing end dates.

6.7.2.2. Concomitant medications

Concomitant Medications will be summarized and listed by ATC code level 4 and Preferred Drug Name, using the SAF.

Of note, the listing will include all medications reported in the CRF form "Prior and Concomitant Medication", regardless start date. Drugs started prior to first intake or during the follow up period will be identified. A flag to identify the medications used to treat Covid-19 (SARS-CoV-2) will also be included in the listing.

A summary table of Covid-19 (SARS-CoV-2) vaccines will be provided on SAF, with:

- Number and proportion of participants vaccinated. Participant analyzed as Vaccinated are participants having received at least one dose of a COVID-19 vaccine within 28 days before the 1st study drug administration, up to study discontinuation.
- Number and proportion of participants vaccinated with 1, 2, 3 doses. Participant analyzed as Vaccinated with X dose(s) means that he received X dose(s) within 28 days before the 1st study drug administration, up to study discontinuation.
- Summary of Covid-19 vaccines by ATC code level 4 and Preferred Drug Name. The selection of COVID (SARS-CoV-2) vaccines will be identified using WHODrug SDG "Vaccines for COVID-19" (narrow scope, ATC4 J07BX).

Incomplete dates will be handled as described in Appendix 9 (Section 6.9.2).

6.7.2.3. Concomitant Therapeutic / Diagnostic Procedures

A by-participant listing will be provided on the SAF including a flag to identify procedures used to treat Covid-19. Procedures started prior to first intake or during the follow up period will be identified.

6.7.3. Follow-up Medications

Any therapy started more than 30 days (>=30) after encorafenib last intake, will be included in the listing specified in section 6.7.2.2 (for medication) or 6.7.2.3 (for procedure).

6.8. Appendix 8: Protocol Deviations

All protocol deviations will be evaluated at least prior to database lock or any snapshot.

Protocol deviations and additional reasons of exclusion from analysis sets (such as missing primary criterion or insufficient exposure to the treatment due to premature withdrawal), will be described in the dedicated protocol deviations list based on TransCelerate PDAP template, separately from the statistical analysis plan and classified as important/non-important deviation before the first participant inclusion or prior to any snapshot.

A listing of all deviations and a listing of additional reasons of exclusion for statistical analysis will be provided for all assigned to treatment participants, including the type of impact (Important/Non important) as validated during the data review/ Validation Committee meeting.

Summary of protocol deviations will be provided on the SAF with:

- Number and percentage of participants with at least one deviation
- Number and percentage of participants with at least one important deviation, overall, then by category of deviations, then by description inside each category,
- Number and percentage of participants with at least one non-important deviation, overall, then by category of deviations

This table will be repeated for protocol deviations related to Covid-19 (SARS-CoV-2).

Protocol deviations related to Covid-19 (SARS-CoV-2) will be flagged in the data listing. Otherwise specified, protocol deviations related to Covid-19 (SARS-CoV-2) will be identified when prefix “COVID-19” is used in the deviation description.

6.9. Appendix 9: Missing Values – Missing Visits

For partially missing dates for efficacy endpoints, the following imputation rules will be used: if the day of the month is missing, but month and year are known (UN-MMM-YYYY), it will be imputed by the 1st of the month (01-MMM-YYYY). If this implementation rule produces a date before start of treatment, then the date of start of treatment is used.

6.9.1. Adverse Events

In case of missing information for AEs, this will be treated as described in Section 5.6.2.

For partial AE start dates or completely missing AE start dates, the date imputation will be based on the temporal relation between the partial date and the treatment start date as detailed in the Table 10 below. No imputation will be performed when the year is missing for the start date.

Table 10: AE Start Date Imputation Example Scenarios

Partial AE start date	Treatment start date	Temporal relationship compared to treatment start	Imputed Date
12mmyyyy	20OCT2001	Uncertain	<blank>
ddmmm2000	20OCT2001	Before	01JUL2000
ddmmm2001	20OCT2001	Uncertain	20OCT2001
ddmmm2002	20OCT2001	After	01JAN2002
ddSEP2001	20OCT2001	Before	15SEP2001
ddOCT2001	20OCT2001	Uncertain	20OCT2001
ddNOV2001	20OCT2001	After	01NOV2001

For missing or partially missing stop dates of AE, the imputation date will be based on the temporal relation between the partial date, the last contact date and the 30-day safety follow-up date as detailed in the Table 11 below:

Table 11: End Date Imputation Example Scenarios

Partial end date (assumes that "ongoing" is not ticked)	Minimum (Last contact date, 30-day FU date)	Ongoing	Imputed Date
Missing	20OCT2001	No	20OCT2001
ddmmm2000	20OCT2001	No	31DEC2000
ddmmm2002	20OCT2001	No	31DEC2002
ddmmm2001	20OCT2001	No	20OCT2001
ddSEP2001	20OCT2001	No	30SEP2001
ddOCT2001	20OCT2001	No	20OCT2001

6.9.2. Prior and Concomitant Medication

In case of missing or partially missing start dates (resp. stop date) for prior/concomitant medication, same rules as those described in Table 10 (resp. Table 11) for AE will be applied.

6.9.3. Initial Diagnosis Date

In case of missing or partially missing dates for initial diagnosis, the following rules will be applied:

- If initial diagnosis date=../mmm/yyyy (= missing day), then it will be substituted by **01/mmm/yyyy**
- If initial diagnosis date=.../.../yyyy (= missing day and month), then it will be substituted by **01/JAN/yyyy**
- If initial diagnosis date=.../.../…. (= completely missing), then it won't be substituted.

Same applies for missing or partially missing dates for first metastasis.

6.9.4. Antineoplastic therapies

Prior Antineoplastic therapies

Incomplete start dates will be handled by applying the same imputation rules as described for AE/concomitant medications start date (Sections 6.9.1 and 6.9.2) except:

- If only day is missing, and month and year match that of the treatment start date, impute as first dose of study -1;
- If both day and month are missing, and the year matches that of the treatment start date, then impute as date of first dose of study drug - 1.

Completely missing start date is imputed as date of first dose of study drug - 1;

Incomplete end dates and dates of progression on the prior antineoplastic therapies will be handled using the following rule:

- If only day is missing, imputed date = min (date of first dose of study drug -1, last day of the month);
- If both month and day are missing, imputed date = min (date of first dose of study drug -1, 31DEC).
- 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.

Post-treatment therapies:

If any, it will be reported as part of the concomitant medications, and handled as specified in Section 6.9.2.

6.10. Appendix 10: Reporting conventions

6.10.1. P-values presentation

Not Applicable

6.11. Appendix 11: Response Evaluation Criteria in Solid Tumors Version 1.1

Taken from Eisenhaur 2009.

6.11.1. Methods of Measurement

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the start of study intervention and never more than 28 days before the first dose.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the treatment phase and follow-up phase (if applicable). Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies

are obtained or to determine relapse in studies where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers *alone* cannot be used to assess *objective* tumor response. If markers are initially above the ULN, however, they must normalize for a participant to be considered in CR. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds of angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

6.11.2. Measurability of Tumour at Baseline

6.11.2.1. Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

- Measurable

  Tumor lesions: Must be accurately measured in at least one dimension (*longest* diameter in the plane of measurement is to be recorded) with a *minimum* size of:

  – 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).

  – 10 mm caliper measurement by clinical examination (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).

  – 20 mm by chest X-ray.

  Malignant lymph nodes: To be considered pathologically enlarged *and* measurable, a lymph node must be ≥15 mm in *short* axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the *short* axis will be measured and followed.

- Non-measurable

  All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion and inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

6.11.2.2. Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered measurable lesions if the *soft tissue component* meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

6.11.3. Tumor Response Evaluation

To assess objective response or future progression, it is necessary to estimate the *overall tumor burden at baseline* and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion (see Section 6.11.2.1).

6.11.3.1. Baseline Documentation of 'Target' and 'Non-target' Lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as *target lesions* and will be recorded and measured at baseline (this means in

instances where participants have only one or two organ sites involved, a *maximum* of two and four lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As previously noted, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the *short* axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis.

For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A *sum of the diameters* (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the *baseline sum diameters*. If lymph nodes are to be included in the sum, then as previously noted, only the *short* axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as *non-target lesions* and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent' or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

6.11.3.2. Response Criteria

Tumour Response for Target and Non-target Lesions

- Evaluation of Target Lesions

  This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum on study* (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Special notes on the assessment of target lesions:

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesion.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs, it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. If the radiologist is able to provide an actual measurement, that should be recorded, even if below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

- Evaluation of Non-target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only *qualitatively* at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Progressive Disease (PD): *Unequivocal progression* of existing non-target lesions. The appearance of one or more new lesions is also considered progression.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Special Notes on Assessment of Progression of Non-target Disease

The concept of progression of non-target disease requires additional explanations as follows:

When the participant also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression *solely* on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the participant has only non-measurable disease. This circumstance arises in some Phase III studies when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as previously noted, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified, a useful test that can be applied when assessing participants for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease i.e. an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread or may be described in

protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the participant should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

- New Lesions

The appearance of new malignant lesions denotes disease progression. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor. This is particularly important when the participant's baseline lesions show PR or CR.

A lesion identified on a follow-up study in an anatomical location that was *not* scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the participant who has visceral disease at baseline and while on study has a CT or MRI brain scan ordered which reveals metastases. The participant's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imagine can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion. A 'positive' FDG-PET scan lesion is one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up:

   – If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

   – If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that time (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

   – If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Timepoint Response

It is assumed that at each protocol specified timepoint, a response assessment occurs. A summary of the overall response status calculation at each timepoint for participant who have measurable disease at baseline is shown in Table 12.

Table 12: Timepoint Response: Participants with Target (± Non-target) Disease

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	**CR**
CR	Non-CR/non-PD	No	**PR**
CR	Not evaluated	No	**PR**
PR	Non-PD or not all evaluated	No	**PR**
SD	Non-PD or not all evaluated	No	**SD**
Not all evaluated	Non-PD	No	**NE**
PD	Any	Yes or No	**PD**
Any	PD	Yes or No	**PD**
Any	Any	Yes	**PD**

Abbreviations: CR = complete response; NE=not evaluable; PD=progressive disease; PR=partial response; SD=stable disease.

When no imaging/measurement is done at all at a particular timepoint, the participant is not evaluable at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that timepoint, unless convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint response. This would be most likely to happen in the case of PD.

Evaluation of Best Overall Response

The BOR is the best response across all timepoints recorded from the start of the study intervention until the end of intervention (taking into account any requirement for confirmation). On occasion a response may not be documented until after the end of therapy so protocols should be clear if postintervention assessments are to be considered in determination of BOR. Protocols must specify how any new therapy introduced before progression will affect best response designation. The participant's BOR assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'.

The BOR is determined once all the data for the participant are known.

Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on the increase in size of the nodes. As noted earlier, this means that participants with CR may not have total sum of 'zero' on the eCRF.

Participants with a global deterioration of health status requiring discontinuation of study intervention without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of study intervention. Symptomatic deterioration is *not* a descriptor of an objective response: it is a reason for stopping study intervention. The objective response status of such participants is to be determined by evaluation of target and non-target disease.

Conditions that define 'early progression, early death and inevaluability' are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of CR. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesion), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

6.12. Appendix 12: Encorafenib Case Retrieval Strategy

The list of Adverse Events of Special Interest using MedDRA version 25.0 will be included in an external Excel file and provided by Pierre Fabre pharmacovigilance team prior DB Lock. That file will be used to flag Adverse Events of Special Interest in ADAE datasets; and external file will be included in define.xml package.

7. References

Eisenhauer EA, Therasse P, Bogaerts J.

New response evaluation criteria in solid tumours: revised RECIST guideline (Version 1.1).

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