Document Type: Final Protocol

Document Date: 30 September 2021

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

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Represented by: Institut de Recherche Pierre Fabre

Clinical Study Protocol

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 Study Code: **W00090GE102**

Protocol Version: **Version 3.0 – 30 September 2021**

Amendment Number: **#2 (Non substantial)**

Compound: **Encorafenib**

Study Phase: **I**

Short Title:

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

Acronym: **OCEAN I**

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Regulatory Agency Identifier Number(s)

W00090GE102

AGREEMENT PAGE

Sponsor Medically Qualified Representative Signatory:

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08-Oct-2021 | 17:52:32 CEST

PII

Date

PII

Study Coordinating Investigator Signatory:

PII

09-10-2021 | 04:52:59 CEST

PII

Date

Clinical study manager, medical monitor and all sponsor personnel names with contact information will be provided in Appendix 10.11.

W00090GE102

INVESTIGATOR SIGNATURE FORM

Protocol Version 3.0 dated 30 September 2021.

By my signature below, I, ……. hereby confirm that I agree:

- To conduct the study described in the protocol referenced above, in compliance with GCP, with applicable regulatory requirements and with the protocol agreed upon by the Sponsor and given approval / favorable opinion by the IRB/IEC.
- To document the delegation of significant study-related tasks and to notify the sponsor of changes in site personnel involved in the study.
- To comply with the procedure for data recording and reporting.
- To allow monitoring, auditing and inspection.
- To retain the study-related essential documents until the sponsor informs that these documents are no longer needed.

Furthermore, I hereby confirm that I will have and will use the available adequate resources, personnel and facilities for conduct this study.

I have been informed that certain regulatory authorities require the sponsor to obtain and supply details about the investigator's ownership interest in the sponsor or the study treatment and more generally about his/her financial relationships with the sponsor. The sponsor will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I agree:

- To supply the sponsor with any information regarding ownership interest and financial relationships with the sponsor (including those of my spouse and dependent children).
- To promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
- That the Sponsor may disclose this information about such ownership interests and financial relationships to regulatory authorities.

Investigator	**Date**

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1. Protocol Summary

1.1. Synopsis

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 (OCEAN I study)
Short Title:	Phase 1 safety study of encorafenib in Chinese patients with advanced metastatic *BRAF* V600E mutant solid tumors
Rationale:	B-RAF proto-oncogene, serine/threonine kinase (BRAF) mutations, which lead to constitutive activation of BRAF kinase and sustained rat sarcoma viral oncogene homologue (RAS)/proto-oncogene serine/threonine-protein kinase (RAF)/mitogen-activated protein kinase kinase (MEK)/extracellular signal-related kinase (ERK) pathway signaling resulting in increased cell proliferation and survival occur in approximately 25% of melanomas and 0.5 to 2.8% of non-small cell lung cancer (NSCLC)s in China. These data also showed that the V600E mutation was the most frequent BRAF mutation in both melanoma and NSCLC (89% and 32 to 86%, respectively). In real-world setting and clinical studies, melanoma and NSCLC patients with a B-RAF proto-oncogene, serine/threonine kinase V600E *(BRAF* V600E) mutation have unfavorable clinical outcome when treated with chemotherapy and immunotherapy compared to non-*BRAF* V600E and/or *BRAF* wild-type patients. Poor clinical outcome with chemotherapy has also been reported in Chinese populations. Encorafenib inhibits BRAF kinase, thereby inhibiting B-RAF proto-oncogene, serine/threonine kinase V600 (*BRAF* V600) positive cell growth. Encorafenib is registered in combination with the MEK inhibitor binimetinib in several jurisdictions for the treatment of patients with unresectable or metastatic melanoma with a *BRAF* V600E or *BRAF* V600K mutation, based on results from the phase 3 COLUMBUS study [Dummer 2018a, Dummer 2018b]. It could therefore be anticipated that the efficacy of encorafenib in combination with binimetinib in other *BRAF* V600 driven cancer types such as *BRAF* V600E mutant NSCLC may be similar than that observed with the combination of dabrafenib and trametinib. Tumor regression has been shown with encorafenib and binimetinib monotherapy in a BRAF-mutant human NSCLC xenograft model, and enhanced tumor regression was observed with the combination of encorafenib plus binimetinib. In a human xenograft melanoma mice model, encorafenib plus binimetinib combination treatment has delayed the emergence of resistance due to RAS/RAF/MEK/ERK pathway reactivation. The safety and tolerability of encorafenib as single agent or in combination with binimetinib is well-established in studies outside China. The overall safety profile of encorafenib is consistent with the respective mechanism of action and the known profile

	of BRAF inhibitors. The differentiated efficacy and safety profile of encorafenib is attributable to its substantially longer dissociation half-life ($T_{1/2diss}$). No targeted therapy for the treatment of *BRAF* V600E mutant NSCLC has been approved in China and and vemurafenib is the only molecular-targeted drug approved for the treatment of patients with *BRAF* V600E mutant melanoma. Chemotherapy and immunotherapy (the same as that for melanoma and NSCLC without oncogenic driver mutations) remain the standard treatment in China, depending on the accessibility and affordability of these drugs. There is therefore an urgent medical need for targeted therapy for Chinese melanoma and NSCLC patients with *BRAF* V600E mutation in the era of personalized healthcare. Limited clinical data of encorafenib monotherapy (or in combination with binimetinib) are available specifically in Chinese *BRAF* V600E mutant patients. This study therefore aims to provide additional clinical safety and tolerability data with encorafenib monotherapy in Chinese patients with *BRAF* V600E mutant melanoma or NSCLC to support further clinical development in combination with binimetinib.

Objectives and EndpointsObjectives	**Endpoints**
Primary	
• To assess the safety of encorafenib 300 mg QD in monotherapy during Cycle 1.	• Incidence of DLTs experienced during Cycle 1 (Days 1 to 28)
Secondary	
• To characterize the safety and tolerability of encorafenib 300 mg QD in monotherapy in Chinese participants.	• Incidence, nature and severity of TEAEs graded as per NCI CTCAE Version 4.03, TEAEs leading to dose interruption, reduction and discontinuation, treatment-emergent SAEs and deaths • Changes in clinical laboratory parameters, vital signs, ECGs • Incidence of targeted TEAEs of special interest
• To provide 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 = pharmacokinetics; QD = once daily; SAE = serious adverse event; TEAE = treatment emergent adverse event.

Overall Design:	This is a phase 1, 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 NSCLC), who are 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. A dose limiting toxicity (DLT) is defined as any adverse event or abnormal laboratory value assessed as unrelated to disease, disease progression, intercurrent illness or concomitant medications/therapies resulting in the inability to tolerate at least 75% dose

	intensity [(administered dose in mg/planned dose in mg) × 100] occurring within the first 28 days of study treatment (Cycle 1) that satisfies at least one of the predefined DLT criteria. It is planned to enrol up to six evaluable participants using a 3+3 design. To be evaluable for tolerability assessment, 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 in Cycle 1. Non-evaluable participants, including withdrawals during Cycle 1 for reasons other than a DLT, will be replaced. • Three participants will initially be enrolled and receive encorafenib 300 mg QD, 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.
Study Principal Investigator:	PII [redacted]
Number of participants	Up to 6 evaluable participants will be enrolled in the study which will be conducted at two or three sites in mainland China.
Treatment group and duration	Encorafenib will be administered as a fixed, flat oral dose of 300 mg QD. Study treatment will be administered in 28-day cycles until death, disease progression or one of the other predefined criteria for study treatment discontinuation is met. • If the study treatment is discontinued, the participant will have an end of treatment visit followed by a 30-day safety follow-up assessment Recruitment duration: 6 months. Estimated duration of the follow-up period after last participant in: approximately 6 months.
Trial Steering Committee:	The trial steering committee (TSC) will analyse 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, treatment emergent adverse events (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.

1.2. Schedule of Activities

The schedule of activities for all participants is shown in Table 1.

Table 1: 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
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	

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
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						

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)

[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

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
[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												

2. Introduction

Encorafenib (Braftovi®; also known as PF-07263896, W0090, LGX818 or ONO-7702) is currently being developed in combination with binimetinib (Mektovi®), for the treatment of adult patients with metastatic melanoma and metastatic non-small cell lung cancer (NSCLC), who are B-RAF proto-oncogene, serine/threonine kinase (BRAF)- and mitogen-activated protein kinase (MEK)-inhibitor treatment-naïve and are either previously untreated or treated with one line of prior therapy in the metastatic setting.

2.1. Background

2.1.1. Disease Background

2.1.1.1. Melanoma

Melanoma is a cancer that arises from melanocytes, the cells that produce the pigment melanin; however, in rare instances, it can originate in the eye or other non-skin organs. There is a clear association between ultraviolet light exposure and melanoma. Melanoma occurs predominantly in adults, and more than 50% of the cases arise in apparently normal areas of the skin. Despite being a rare form of skin cancer, melanoma accounts for nearly 75% of skin cancer deaths.

About 80% of melanomas are detected in a localized stage and can be treated with surgical resection. When detected early, the 5-year survival rate of melanoma is above 90%; however, when melanoma is diagnosed after distant metastasis, the prognosis is, by contrast, very poor. The 5-year survival rate decreases to 15% with a median survival between 8 and 9 months [**Jemal 2011**]. Advanced melanoma is one of the most aggressive human malignancies.

Both incidence of melanoma and mortality rate are rapidly increasing throughout the world, constituting a significant and growing health burden [**Ferlay 2010].** The worldwide incidence of new cases of melanoma was 287,723 (1.6% of all new cancer cases) and number of deaths 60,712 (0.6% of all cancers) in 2018. In China, there were 7,379 newly diagnosed cases accounting for 0.17% of new cancer cases and 3,766 (0.13%) deaths [**Bray 2018, Globocan 2018**].

2.1.1.2. Non-small Cell Lung Cancer

Lung cancer is the most frequently diagnosed cancers and is also the leading cause of cancer-related death worldwide. It accounts for more than 2.1 million newly diagnosed cancer cases (11.6% of the total diagnosed cancer cases) and 1.76 million cancer-related deaths (18.4% of the total) worldwide every year [**Bray 2018, Globocan 2018**]. Lung cancer is a heterogenous disease clinically, biologically, histologically and molecularly. Non-small cell lung cancer, the predominant

histological subtype of lung cancer, accounts for approximately 85% of all cases, of which lung adenocarcinoma and lung squamous cell carcinoma are the most common subtypes [**Herbst 2018**].

Lung cancer accounts for approximately 18% of total diagnosed cancer in China. It is also the leading cause of cancer death in both males (26.4%) and females (20.3%) [**Bray 2018**, **Globocan 2018**]. It was estimated that there would be 774,323 new cases of lung cancer (~37% of global total) and 690,567 lung cancer deaths (~39% of global total) in 2018 [**Feng 2019**]. It is also estimated that mortality from lung cancer may increase by approximately 40% between 2015 and 2030 [**Cao and Chen 2019**].

Although the incidence of lung cancer (~35/100,000) is similar between China and the United States (US), the mortality rate of lung cancer in China (130.1/100,000) is 1.4 times greater than that in the US (91.0/100,000). This finding might be attributable to the lower early cancer detection rate and sub-standard treatment strategies provided by different regions in China [**Feng 2019**].

The overall 5-year survival rate for advanced disease treated with chemotherapy remains poor, <2% [**Cetin 2011**]. In China, the age-standardized 5-year relative survival in men was 16.8% (62.5% worse than in thyroid cancer which has the highest survival rate) and 25.1% in women between 2012 and 2015 [**Cao and Chen 2019, Zeng 2018]**.

Non-small cell lung cancer, approximately 86% of total, is also the most predominant histological subtype of lung cancer with adenocarcinoma and squamous cell carcinoma as the most common subtypes [**Gou 2014**].

2.1.2. BRAF Mutations

BRAF mutations, which lead to constitutive activation of BRAF kinase and sustained rat sarcoma viral oncogene homologue (RAS)/proto-oncogene serine/threonine-protein kinase (RAF)/MEK/extracellular signal-related kinase (ERK) pathway signaling resulting in increased cell proliferation and survival [**Corcoran 2012**] occur in approximately 25% of melanomas [**Si 2012**] and 0.5 to 2.8% of NSCLCs [**Li 2014, Ding 2017, Lin 2019**] in China. These data also showed that the V600E mutation was the most frequent BRAF mutation in both melanoma and NSCLC (89% and 32 to 86%, respectively).

2.1.3. Treatment Options for *BRAF* V600E Metastatic Melanoma and Non-small Cell Lung Cancer

In real-world setting and clinical studies, although some reports have correlated BRAF mutation in NSCLC with a poor outcome and reduced efficacy of platinum doublets [**Barlesi 2016, Cardarella 2013, Marchetti 2011]**, the prognosis implication of B-RAF proto-oncogene, serine/threonine kinase V600E *(BRAF* V600E) mutation in NSCLC remains unclear. In a recent French matched study, *BRAF* mutation in exon 15 was not found to be a prognostic factor for progression-free survival (PFS) and overall survival (OS) in either first or second line

[**Couraud 2019**]. When treated with immunotherapy, NSCLC patients with a *BRAF* V600E mutation have unfavourable clinical outcome as compared to *BRAF* wild-type patients [**Dudnik 2018, Mazieres, 2018, Rihawi, 2019, Tan 2019**]. Poor clinical outcome with standard chemotherapy for NSCLC has also been reported in Chinese *BRAF* V600 NSCLC population [**Ding 2017, Li 2015**]. The heterogeneity of the disease, the rarity of the mutation, small patient numbers, and limited number of studies contribute to this lack of understanding [**Baik 2017**].

In Chinese NSCLC population, retrospective studies have shown a trend in a shorter progression-free survival (PFS) to first-line chemotherapy in patients with *BRAF* V600E mutant tumors compared to patients with non-*BRAF* V600E mutations (5.2 versus 6.4 months; hazard ratio [HR]: 0.74 (0.29-1.94) p=0.561), an overall response rate (ORR) of 28.6% and disease control rate of 78.6% was also observed in the *BRAF* mutant patients [**Ding 2017**]. In another retrospective study of lung adenocarcinoma patients [**Li 2015**], a trend in shorter median overall survival (OS) was also observed in *BRAF* V600E mutant patients (24.0 months; 95% confidence interval (CI): 20.6-27.5) compared to non-*BRAF* V600E patients (28.0 months; 95% CI: 22.7-33.3).

Traditional options, such as chemotherapy, also lack substantial efficacy in melanoma. A novel immunotherapy, ipilimumab (Yervoy®, Bristol-Myers Squibb), an antibody against the cytotoxic T-lymphocyte antigen (anti-CTLA-4) was approved in the US in 2011, although melanoma that had spread to distant sites remained rarely curable.

The discovery of the genetic underpinnings of melanoma and NSCLC and their characterization has uncovered potential targets for therapy, including BRAF mutations. BRAF inhibitors as monotherapy has demonstrated an acceptable safety profile along with a clinical activity in different indications.

The BRAF inhibitor vemurafenib (Zelboraf®, Roche), has been approved in the US and Europe as a monotherapy for the treatment of adult patients with BRAF V600 unresectable or metastatic melanoma and is under investigation for treatment of NSCLC. In a phase 1 study with vemurafenib in 46 Chinese *BRAF* V600 mutant metastatic melanoma patients, the confirmed overall response rate (cORR) was 52.2% (95% CI: 37.0-67.1) with a median PFS of 8.3 months (95% CI: 5.7-10.9) and a median OS of 13.5 months (95% CI: 12.2-not estimable). The most common adverse events were dermatitis acneiform, arthralgia, diarrhea, blood cholesterol level increase, blood bilirubin level increase, melanocytic nevus and alopecia [Si, 2018]. Two patients (4%) had serious adverse events (SAEs): Grade 3 chest discomfort and Grade 3 uveitis, both were considered related to vemurafenib. The efficacy of vemurafenib in this Chinese phase 1 study was similar to that observed in the pivotal non-Chinese study [**Chapman 2011, Chapman 2017**] and has been approved for the treatment of patients with *BRAF* V600E mutant melanoma in China [Chinese guidelines for diagnosis and treatment of melanoma 2018].

Dabrafenib (Tafinlar®, Novartis) was approved for patients with *BRAF* V600E mutant advanced melanoma in the US in May 2013; it was further approved for use in Europe in August 2013. In a phase 2 study with dabrafenib in *BRAF* V600E mutant metastatic NSCLC, the cORR was 33% (95% CI: 23-45) with a median PFS of 5.5 months (95% CI: 3.4-7.3) and a median OS of 12.7

months (95% CI: 7.3-16.9). The most common adverse events were pyrexia, hyperkeratosis, asthenia, decreased appetite, cough, fatigue, skin papilloma, alopecia, dry skin, rash, vomiting and palmar-plantar erythrodysesthesia (PPE) syndrome[1] [**Planchard 2016a]**. Similar efficacy results were observed with vemurafenib in *BRAF* V600 mutant NSCLC [**Subbiah 2019**] and in the retrospective European EURAF cohort [**Gautschi**, 2015].

Although studies have shown that BRAF-targeted therapy is effective in *BRAF* V600E mutant melanoma, data also indicate that the duration of response is often short lived, with resistance developing quickly, within approximately 6 months [**Chapman 2011, Flaherty 2010, Flaherty 2012**, **Sosman 2012].** Re-activation RAS/RAF/MEK/ERK signaling occurs in the majority of cases of acquired resistance to BRAF inhibitors. In an attempt to delay resistance to BRAF inhibition, led to the development of combination treatments, including with MEK1/2-inhibitors.

Preclinical data has demonstrated the enhanced activity in combining BRAF and MEK inhibition in B-RAF proto-oncogene, serine/threonine kinase V600 *(BRAF* V600) driven tumors [**Flaherty 2012, Joshi 2015, Stuart 2012**]. This combination has been established as the standard of care in *BRAF* V600 mutant melanoma [**Ascierto 2016, Dummer 2018a, Dummer 2018b**, **Long 2014, Robert 2016**] and, has also been clinically validated in *BRAF* V600E mutant NSCLC [**Planchard 2016b, Planchard 2017a, Planchard 2017b**]. The combination of dabrafenib and the MEK inhihitor trametinib (Mekinist®, Novartis) was approved in the US in January 2014 for B-RAF proto-oncogene, serine/threonine kinase V600E/K (*BRAF* V600E/K) mutant metastatic melanoma and as an adjuvant treatment for *BRAF*V600E mutant Stage III melanoma after surgical resection in May 2018, based on the results of the COMBI-AD phase 3 study [Long 2017], making it the first oral regimen that prevents cancer relapse for node positive, BRAF mutant melanoma. The combination of dabrafenib with trametinib for *BRAF* V600 mutant advanced or metastatic NSCLC was approved in Europe in April 2017.

To date, no targeted therapy for the treatment of *BRAF* V600E mutant NSCLC has been approved in China and vemurafenib is the only molecular-targeted drug approved for the treatment of patients with *BRAF* V600E mutant melanoma. Chemotherapy and immunotherapy remain standard therapy, i.e. same as that for NSCLC or melanoma without oncogenic driver mutations – depending on the accessibility and affordability of these drugs.

As the *BRAF* V600E mutation implication in NSCLC and melanoma prognosis remains unclear with some data reporting unfavorable clinical outcome with chemotherapy and immunotherapy in Chinese *BRAF* V600 mutant melanoma and NSCLC population, there is an urgent medical need to provide effective and tolerable targeted therapy for these patients in China.

[1] Also known as hand-foot skin reaction (HFSR)

2.1.4. Encorafenib Therapy

Encorafenib is a potent and highly selective adenosine triphosphate (ATP)-competitive small molecule inhibitor of *BRAF* V600 mutant kinase. Encorafenib suppresses the RAS/RAF/MEK/ERK pathway in tumor cell expressing *BRAF* V600 mutation.

In a first-in-human phase 1 dose escalation and dose expansion study (CLGX818X2101), 54 participants with locally advanced or metastatic *BRAF* V600 mutant melanoma initially received doses of encorafenib from 50 to 700 mg once daily (QD) or 75 to 150 mg twice daily. Dose limiting toxicities (DLTs) were reported in seven participants across the dose groups and were hand-foot skin reaction (HFSR), foot pain, fatigue, insomnia/asthenia, diarrhea/rash, facial paresis/confusion, and pain/neuralgia. All DLTs were reversible. The most common adverse events suspected to be related to encorafenib were cutaneous (rash, dry skin, HFSR, pruritus, keratosis pilaris, alopecia), pain in extremity, arthralgia, and fatigue. On the basis of the Bayesian model, the maximum tolerated dose (MTD) of encorafenib monotherapy was declared as 450 mg QD [**Dummer 2013**]. A further 33 participants were treated in the dose expansion phase; nine (33.3%) participants with melanoma and three (17.6%) participants with mCRC experienced at least one DLT during the first 28 days of treatment. The most common DLTs (≥5%) observed in participants with melanoma treated at the MTD in the dose expansion phase were myalgia (33.3%), arthralgia (26.7%), fatigue (20.0%), asthenia (13.3%), and VIIth nerve paralysis and insomnia (6.7% each). Seven of the nine participants with a DLT required a dose reduction to 300 mg QD. Based on the early occurrence of these toxicities leading to dose reduction, the 300 mg QD dose was declared the recommended phase 2 dose (RP2D) for encorafenib monotherapy. The ORR for BRAF inhibitor-naïve and BRAF inhibitor-pretreated participants was 60.0% and 10.3% in the dose escalation phase and 60.0% and 22.2% in the dose expansion phase. Progression-free survival and OS were assessed for participants in the dose expansion phase only. Median PFS was 12.4 months (95% CI: 7.4–not reached) and 1.9 months (95% CI: 0.9–3.7) for BRAF inhibitor-naïve patients and BRAF inhibitor-pretreated participants. Median OS was not reached for BRAF inhibitor-naïve patients and was 9.7 months (95% CI: 3.68–10.84) for BRAF inhibitor-pretreated participants [**Delord 2017**].

In a large randomized phase 3 study in participants with advanced *BRAF*V600E/K mutant melanoma (CMEK162B2301, the COLUMBUS study) comparing encorafenib 300 mg QD with vemurafenib 960 mg twice daily, the PFS of 9.6 months (95% CI: 7.4-14.8) in the encorafenib group was longer than in vemurafenib group (7.3 months, 95% CI: 5.6-7.69). Encorafenib monotherapy provided a significant risk reduction to death (HR 0.76, 95% CI: 0.58-0.98, p=0.0033) and to progression (HR 0.68, 95% CI: 0.52-0.88, p=0.0038) compared to vemurafenib. The cORR was 52% in the encorafenib group and 41% in the vemurafenib group [**Dummer 2018b**]. The efficacy results of vemurafenib in this study were consistent on all endpoints compared to the results in other pivotal studies of *BRAF* V600 mutant melanoma where vemurafenib was used as a control [Ascierto 2016, Larkin 2014, Robert 2015].

The safety profile of encorafenib 300 mg QD monotherapy seen in the COLUMBUS study was comparable to those observed in the phase 1 dose escalation and dose expansion study

(CLGX818X2101) with the most common adverse events being alopecia (56%), PPE syndrome[2] (52%), arthralgia (44%), hyperkeratosis (39%), nausea (38%) and dry skin (30%) [**Delord 2017**, Dummer 2018b]. The safety and tolerability profile of encorafenib monotherapy was different to vemurafenib. Diarrhea, pyrexia and photosensitivity reaction were less frequently reported with encorafenib than with vemurafenib, and alopecia and PPE syndrome were more frequently reported with encorafenib than with vemurafenib (≥15% difference between the two treatment groups). These adverse events were generally low grade [**Dummer 2018a, Dummer 2018b**].

The differentiated efficacy and safety profile of encorafenib is attributable to its unique pharmacological properties, i.e. its substantially longer dissociation half--life ($T_{1/2diss}$) - more than 30 hours as compared with 0.5 hour reported for vemurafenib [**Koelblinger 2018, Stuart 2012**]. The long $T_{1/2diss}$ translates into prolonged target suppression leading to an increased efficacy (on-target effect) while reducing toxicity (off-target effect) as compared with other established BRAF inhibitors, such as cutaneous adverse reactions.

The co-administration of encorafenib with the MEK1/2 inhibitor binimetinib has demonstrated additive or synergistic anti-proliferative activity in *BRAF* V600E mutant cell lines (including melanoma, colorectal, pancreatic and lung-derived). This additive or synergistic anti-tumor activity (growth inhibition and induction of tumor regression) was also demonstrated in *BRAF* V600E mutant human melanoma and NSCLC xenograft studies in mice (internal data). The results confirmed that encorafenib and binimetinib combination prevented the emergence of resistant melanoma tumors over the 4-month treatment duration of the study, resulting in enhanced antitumor activity and survival.

To date, the antitumor effects of encorafenib monotherapy and the combination of encorafenib and binimetinib have been and is currently being clinically investigated in the following cancer types with *BRAF* V600 mutations:

- Advanced unresectable and metastatic BRAF V600E/K mutant melanoma (Study CMEK162B2301, COLUMBUS): encorafenib monotherapy, encorafenib plus binimetinib combination.
- Metastatic colorectal cancer with BRAF V600E mutation (Study ARRAY-818-301, BEACON): encorafenib plus cetuximab (doublet) and encorafenib plus cetuximab in combination with binimetinib (triplet) [**Kopetz 2019**].
- Metastatic non-small cell lung cancer (NSCLC) with BRAFV600E mutation (Study ARRAY-818-202, PHAROS): encorafenib given in combination with binimetinib.

Limited clinical data of encorafenib monotherapy or in combination with binimetinib is available specifically in Chinese *BRAF* V600E patients. Ethnic sensitivity analyses performed to date have shown showed no significant effect of ethnicity or race on the pharmacokinetics (PK) of encorafenib or binimetinib, administered as monotherapy or in combination. The evaluation on the impact of

[2] Also known as hand-foot skin reaction (HFSR)

ethnicity on safety and efficacy did not show meaningful clinical difference between Asian and non-Asian. However, no definitive conclusions could be made due to the limited number of Asian participants treated.

The purpose of this study is therefore to provide additional clinical safety and tolerability data with encorafenib 300 mg QD monotherapy in Chinese patients with *BRAF* V600E mutant melanoma or NSCLC to support further clinical development in combination with binimetinib.

2.2. Study Rationale

2.2.1. Rationale for Assessment of Encorafenib in the Study Population

Tumor regression has been shown with encorafenib and binimetinib monotherapy in a *BRAF*-mutant human NSCLC xenograft model, and enhanced tumor regression was observed with encorafenib plus binimetinib combination. In human xenograft melanoma mice model, encorafenib plus binimetinib combination treatment has delayed the emergence of resistance due to RAS/RAF/MEK/ERK pathway reactivation.

The safety and tolerability of encorafenib as single agent or in combination with binimetinib is well-established in studies outside China. The overall safety profile of encorafenib is consistent with the respective mechanism of action and the known profile of BRAF inhibitors. The differentiated efficacy and safety profile of encorafenib is attributable to its substantially longer $T_{1/2diss}$ (see Section 2.1.4).

No targeted therapy for the treatment of *BRAF* V600E mutant NSCLC has been approved in China and vemurafenib is the only molecular-targeted drug approved for the treatment of patients with *BRAF* V600E mutant melanoma. Chemotherapy and immunotherapy (same as that for melanoma and NSCLC without oncogenic driver mutations) remain the standard treatment in China, depending on the accessibility and affordability of these drugs. There is therefore an urgent medical need for targeted therapy for Chinese melanoma and NSCLC patients with *BRAF* V600E mutation in the era of personalized healthcare.

Limited clinical data of encorafenib monotherapy (or in combination with binimetinib) is available specifically in Chinese *BRAF* V600E mutant patients. This study therefore aims to provide additional clinical safety and tolerability data with encorafenib 300 mg QD monotherapy in Chinese patients with *BRAF* V600E mutant melanoma or NSCLC to support further clinical development in combination with binimetinib.

2.2.2. Rationale for Dose

The QD dosing regimen of encorafenib is based on the available PK data and its $T_{1/2diss}$. Encorafenib 300 mg QD has been determined to be the single agent RP2D in the clinical program.

In population PK analysis, ethnicity and/or race did not appear to have any major impact on the PK of encorafenib in Asian patients compared to non-Asian patients, with no resulting major differences in the safety and efficacy profiles between the two populations. Due to the limited number of patients, these findings should be interpreted with caution.

2.3. Benefit/Risk Assessment

The observed toxicities of encorafenib are generally of low grade, monitorable and manageable by treatment modification, interruption and discontinuation in conjunction with appropriate medical management. Detailed information regarding clinical safety and the known and expected benefits and risks, including reasonably expected adverse events, is provided in the Investigator's Brochure for encorafenib. Guidance on monitoring and dose modifications is provided in Section 6.6.

2.3.1. Benefit Assessment

In real-world setting and clinical studies, the implication of *BRAF* V600E mutation remains unclear, with some data reporting unfavorable clinical outcome with chemotherapy and immunotherapy in Chinese *BRAF* V600 mutant melanoma and NSCLC population compared to *BRAF* wild-type patients (see Section 2.1.3).

Targeted therapy has not been approved for the treatment of *BRAF* V600E mutant NSCLC patients in China and vemurafenib is the only molecular-targeted drug approved for the treatment of *BRAF* V600E mutant melanoma. Given the implication of *BRAF* V600E mutation in melanoma and NSCLC, the prognosis remains unclear with some data reporting unfavorable clinical outcome with chemotherapy and immunotherapy; there is therefore an urgent medical need for efficacious and well-tolerated targeted therapies for *BRAF* V600 mutant melanoma and NSCLC patients in the era of personalized healthcare.

BRAF inhibitor monotherapy has demonstrated an acceptable safety profile along with a clinical activity in different indications. The differentiated efficacy and safety profile of encorafenib compared to other BRAF inhibitors (see **Section 2.1.4**) is due to the longer $T_{1/2\text{-diss}}$. The observed toxicities are generally of low grade, monitorable and manageable through appropriate medical intervention.

Ethnic sensitivity analyses have shown that there are no significant effect of ethnicity or race on the PK of encorafenib administered as single agent or in combination with binimetinib.

Outcomes from Study CMEK162B2301, COLUMBUS, demonstrated an overall survival benefit with both the combination therapy of encorafenib and binimetinib as well as with encorafenib monotherapy alone. However, it should be noted that in this study, while this was not the primary endpoint, the benefit was numerically (but not statistically) superior with the combination therapy compared to encorafenib monotherapy, suggesting that encorafenib is contributing significantly to the overall efficacy of the combination therapy of encorafenib and binimetinib [**Dummer 2018b**].

There is therefore the potential for the encorafenib treatment to be efficacious in Chinese patients with *BRAF* V600E mutant melanoma and NSCLC.

2.3.2. Risk Assessment

The safety and tolerability of encorafenib monotherapy is consistent with the respective mechanism of action and known safety profiles of BRAF inhibitors. The majority of the reported adverse drug reactions reflect the common adverse events observed in the clinical program and are well-characterized. Important risks associated with the administration of encorafenib are summarized in Table 2.

Table 2: Important Risks of Encorafenib and the Respective Mitigation Strategy

Important Risks	Summary of Data/Rationale for Risk	Mitigation measures
Secondary skin neoplasms: cutaneous squamous cell carcinoma and new primary melanoma	Associations have been reported with older age (≥65 years) for vemurafenib and dabrafenib-treated patients, and with prior skin cancer, and chronic sun exposure for vemurafenib-treated patients.	Skin neoplasms are described in the Investigator's Brochure for encorafenib. Dermatological evaluations will be performed by the investigator to monitor for the possible development of keratoacanthoma and/or squamous cell carcinoma and new primary melanoma, as these have been reported to occur with selective BRAF inhibitor treatment. Dermatological screening for skin malignancies will be performed on a regular basis. Early reporting of skin symptoms through careful and ongoing dermatologic monitoring will be performed throughout treatment.
QT prolongation	Risk factors for Torsade de Pointes other than QTc interval >500 ms or >60 ms increase from baseline value include uncorrected hypokalemia, hypomagnesemia and hypocalcemia, long QT syndrome, concomitant therapy with multiple QTc interval–prolonging drugs. Other risk factors for Torsade de Pointes include acute myocardial infarction, heart failure with reduced ejection fraction, diuretic therapy, age ≥65 years, female sex, family history of sudden cardiac death at <50 years, cardiac disease and history of arrhythmia or bradycardia.	Risk for QT prolongation is described in the Investigator's Brochure for encorafenib. Administration with medicinal products with a known potential to prolong QT/QTc should be avoided, where possible. Participants at high risk of QT prolongation are excluded from the study. Monitoring and dose adjustments for QT prolongation are outlined in Appendix 10.4.
Non-cutaneous malignancies with RAS mutation	As for other BRAF inhibitors and based on its mechanism of action, encorafenib may promote malignancies associated with RAS mutation associated with activation of RAS	Routine cancer detection and treatment as well as preventive measures for different known risk

Important Risks	Summary of Data/Rationale for Risk	Mitigation measures
	through mutation or other mechanisms. No cases of non-cutaneous malignancy with RAS mutation possibly related to encorafenib were identified from the pooled safety data of the clinical development program, however due to the seriousness of this class-effect risk, non-cutaneous carcinoma is considered an important potential risk.	factors of different cancers will be performed. Dose modifications are outlined in Appendix 10.4.
Over-exposure due to concomitant use with strong and moderate CYP450 3A4 inhibitors	Encorafenib is primarily metabolised by CYP3A4. Based on the PK data, the use of strong CYP3A4 inhibitors was not allowed during clinical studies. Concomitant administration of encorafenib and strong or moderate CYP3A4 inhibitors may lead to increased encorafenib exposure and potential increase in toxicity.	Drug-drug interactions properties of encorafenib are described in the Investigator's Brochure for encorafenib. The use of strong inhibitors of CYP3A4 is prohibited. Concomitant use of moderate CYP3A4 inhibitors should be avoided. If use of moderate CYP3A4 inhibitors is unavoidable and no alternatives are available, short-term use (≤30 days) following discussion with the sponsor may be permitted with accompanying dose reduction to one-half of the encorafenib dose before use of moderate CYP3A4 inhibitors (or as close as can be achieved without exceeding the target dose).
Over-exposure in patients with moderate to severe hepatic impairment	Results from a dedicated clinical study indicate a 25% higher total encorafenib exposures in participants with mild hepatic impairment (Child-Pugh Class A) compared with participants with normal liver function. This translates into a 55% increase of the unbound encorafenib exposure. The PK of encorafenib has not been evaluated clinically in participants with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment. As encorafenib is primarily metabolised and eliminated via the liver and based on PBPK modelling, participants with moderate to severe hepatic impairment may have greater increases in exposure than participants with mild hepatic impairment. No dosing recommendation can be made in moderate or severe hepatic impairment.	Over-exposure in participants with moderate to severe hepatic impairment is described in the Investigator's Brochure for encorafenib. Participants with impaired hepatic function, defined as Child-Pugh Class B or C should not be included the study.
Abbreviations: BRAF = B-raf murine sarcoma viral oncogene homolog B1; CYP450 = cytochrome P450; PBPK = physiologically based pharmacokinetic; PK = pharmacokinetics; RAS = rat sarcoma viral oncogene homologue.		

Due to the substantially longer $T_{1/2diss}$ of encorafenib and consequently attenuated off-target effects, encorafenib has the potential to decrease BRAF inhibitor-related toxicities. Encorafenib has a differentiated safety profile compared to other BRAF inhibitors, which is mainly reflected in the lower incidence of pyrexia (dabrafenib-associated toxicity) and phototoxicity (vemurafenib-related toxicity). The majority of the observed toxicities with encorafenib are generally reversible and manageable by appropriate supportive medical care and/or dose modifications or discontinuation, and the risks will be mitigated through the implementation of the measures in Table 2 for clinical monitoring of participants during treatment.

Ethnic factors do not appear to influence the safety profile of encorafenib. These findings will be confirmed in Chinese melanoma and NSCLC participants with a *BRAF* V600E mutation in this study prior to conducting further, larger studies of encorafenib in combination with binimetinib in the Chinese population.

Review of the available safety data from post-marketing experience and clinical studies have not changed the benefit-risk profile of encorafenib which remains favorable when used in its approved indications and in accordance with the prescribing information. A review of individual case safety reports originating from Asian participants has shown that the pattern of adverse events related to study intervention grouped by Medical Dictionary for Regulatory Activities (MedDRA) is generally consistent with the global population.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the anticipated benefit and mitigating measures for the risks associated with encorafenib, the benefit of encorafenib treatment outweighs the potential risks for participants with *BRAF* V600E mutant melanoma and NSCLC in this study. The overall benefit/risk ratio is therefore deemed favorable.

3. Objectives and Endpoints

Objectives and endpoints are correlated in Table 3.

Table 3: Objectives and Endpoints in W00090GE102

Objectives	Endpoints
Primary	
• To assess the safety of encorafenib 300 mg QD in monotherapy during Cycle 1.	• Incidence of DLTs experienced during Cycle 1 (Days 1 to 28)
Secondary	
• To characterize the safety and tolerability of encorafenib 300 mg QD in monotherapy in Chinese participants.	• Incidence, nature and severity of TEAEs graded as per NCI CTCAE Version 4.03, TEAEs leading to dose interruption, reduction and discontinuation, treatment-emergent SAEs and deaths • Changes in clinical laboratory parameters, vital signs, ECGs • Incidence of targeted TEAEs of special interest
• To provide 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.	

4. Study Design

4.1. Overall Design

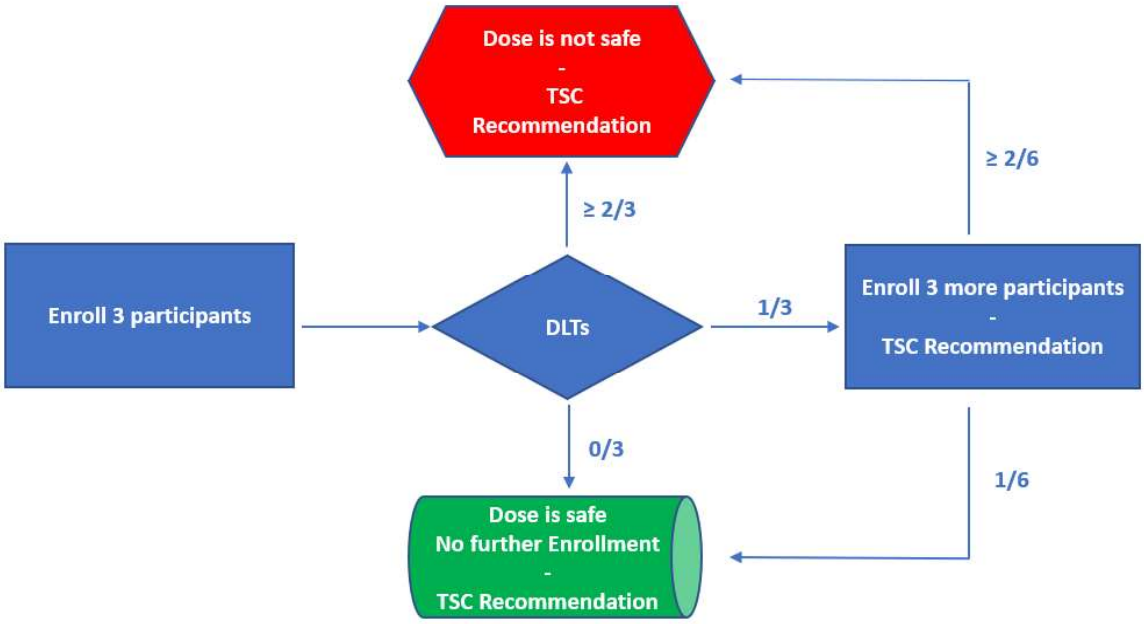
4.1.1. Study Design Overview

This is a phase 1, multicenter, open-label, single-arm study to investigate the safety and tolerability of encorafenib monotherapy in adult Chinese participants with *BRAF* V600E mutant advanced solid tumors (unresectable metastatic melanoma or metastatic NSCLC) who are BRAF- and MEK-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.

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 a 3+3 design, shown in Figure 1.

Figure 1: 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.

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 4** .

Table 4: 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

Toxicity		**Any of the following criteria**
		Grade 4 confirmed by ophthalmologic examination
	Any other eye disorders	Grade 3 for >21 consecutive days
		Grade 4
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; 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[3].

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 analyse 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, treatment emergent adverse events (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.

[3] 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.

4.1.2. 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 Section 5) will receive encorafenib 300 mg QD in 28 day (± 7 days) cycles until death, disease progression[4] or one of the other predefined criteria for study treatment discontinuation is met (see Section 7.1). 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 1.

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 10.7). 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).

4.2. 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

[4] In special circumstances, continuation of treatment beyond disease progression may be allowed (see Section 6.1).

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.

4.3. Justification for Dose

The dose of encorafenib is 300 mg per oral (PO) QD, corresponding to its single agent RP2D. This dose has also been shown in clinical studies to result in tumor regression and clinical responses as a single agent [Dummer 2013, Gomez-Roca 2014] (see Section 2.1.4).

Permitted dose modifications are detailed in Section 6.6.

4.4. 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.

5. Study Population

It is planned to treat up to six participants with metastatic *BRAF* V600E mutant melanoma or NSCLC who are BRAF inhibitor treatment-naïve and have failed the previous therapy(ies) for metastatic disease or are not eligible to standard therapy. The sample size rationale is provided in Section 9.2.

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Each participant fulfilling all inclusion criteria and none of the exclusion criteria will be eligible.

5.1. Inclusion Criteria

All the following inclusion criteria must be met for a participant to be eligible for this study:

1. Provide a signed and dated informed consent form (ICF).
2. Chinese male or female with age ≥18 years old at the time of the informed consent.
3. Documented histology- and/or cytology-confirmed metastatic melanoma or NSCLC (i.e. adenocarcinoma, large cell carcinoma, squamous cell carcinoma).
4. Presence of *BRAF* V600E mutation as determined by a local laboratory with a NMPA approved BRAF test.
5. BRAF inhibitor treatment-naïve participants and having failed the previous therapy(ies) for metastatic disease or are not eligible to standard therapy.

   Note:

   Alternative chemotherapy regimen is permitted if participants were platinum intolerant or ineligible.
6. At least one tumor lesion as per investigator assessment according to RECIST Version 1.1, which has neither been irradiated nor biopsied during the screening period. The irradiated lesion is acceptable only if it is proven as disease progression deemed measurable prior to study.
7. Life expectancy ≥3 months.
8. ECOG performance status of 0 or 1.
9. Adequate hematologic function at screening and baseline characterized by the following:
   a. *Absolute neutrophil count ≥1.5 × 10^9/L.*
   b. *Hemoglobin ≥90 g/L.*
   c. *Platelets ≥100 × 10^9/L.*

d. *International normalized ratio, prothrombin time or (activated) partial thromboplastin time ≤1.5 × upper limit of normal (ULN).*

10. Adequate hepatic function at screening and baseline characterized by the following:

    a. *Total bilirubin ≤ 1.5 × ULN.*

       Note: Total bilirubin > 1.5 × ULN is allowed if indirect bilirubin is ≤ 1.5 × ULN.

    b. *Alanine aminotransferase and aspartate aminotransferase ≤ 2.5 × ULN or ≤ 5 × ULN in case of documented liver metastases.*

11. Adequate renal function at screening and baseline characterized by the following:

    a. *Serum creatinine ≤ 1.5× ULN.*

    b. *Creatinine clearance ≥ 50 mL/min as calculated by the Cockcroft-Gault formula; or estimated glomerular filtration rate > 50 mL/min/1.72m^2.*

12. Able to comply with the study protocol as per investigator assessment including oral drug intake, complying scheduled visits, treatment plan, laboratory tests and other study procedures.

13. Women are either postmenopausal for at least 1 year, or are surgically sterile for at least 6 weeks, or women of childbearing potential (WOCBP) must agree to take appropriate precautions to avoid pregnancy.

    Appropriate precautions to avoid pregnancy for WOCBP:

    - Must have negative serum ß-human chorionic gonadotropin (HCG) test at screening.
    - Must agree to use highly effective methods of contraception from screening until 30 days after the last dose of the study treatment.
    - Must not donate ova from screening until 30 days after the last dose of study treatment.

14. Men must agree not to father child until 90 days after the last dose of study treatment.

    Note:

    - Must agree to use highly effective method of contraception to avoid fathering a child from screening until 90 days after the last dose of study treatment.
    - Must not donate sperm from screening until 90 days after the last dose of study treatment.

5.2. Exclusion Criteria

Participants meeting any of the following criteria are not eligible to be included in this study:

1. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to encorafenib, or its excipients.

2. For metastatic NSCLC: documented anaplastic lymphoma kinase (ALK) fusion oncogene, ROS1 (c-ros oncogene 1) rearrangement or epidermal growth factor receptor (EGFR) sensitizing or driver mutation.
3. Receipt of anticancer medications or investigational drugs within intervals before the first administration of study treatment.
    a. *Prior anticancer therapy:*
        i. *Chemotherapy and targeted small molecules (e.g. erlotinib, crizotinib): ≤28 days or 5 half-lives, with a minimum of 14 days.*
        ii. *Biologics (e.g. immunotherapy, bevacizumab): ≤28 days or 5 half-lives.*
    b. *Investigational agents: ≤4 weeks or 5 half-lives, with a minimum of 14 days. For investigational agents with long half-lives, enrolment before the 5th half-life requires medical monitor approval.*
    c. *Palliative radiation therapy must be complete 7 days prior to the first dose of study treatment.*
4. Symptomatic brain metastasis.

    Note: participants with previously treated or untreated asymptomatic brain metastases confirmed by CT or MRI may participate provided:

    - *Participants are stable (e.g. no evidence of progression by radiographic imaging for at least 28 days before the first dose of study treatment and neurologic symptoms must have returned to baseline) and do not need any treatment within 14 days prior to study treatment.*
    - *Participants must have no evidence of new or enlarging brain metastases or edema.*
    - *Lesions are <1 cm in the longest diameter.*
    - *Participants must have discontinued the use of steroids at least 14 days before the first dose of study treatment.*
5. Leptomeningeal disease.
6. Participant has not recovered to ≤Grade 1 from toxic effects of prior therapy and/or complications from prior surgical treatment before starting study treatment.

    Note: Stable chronic conditions (≤Grade 2) that are not expected to resolve (e.g. neuropathy, myalgia, alopecia and prior therapy-related endocrinopathies) are exceptions.
7. Current use of prohibited medication ≤1 week prior to start of the study treatment and/or concomitantly.

    Note:

i. *Of which herbal medications/supplements including use of St John's Wort (hypericum perforatum) and traditional Chinese medicines or any medications or food susceptible to be moderate or strong inhibitors cytochrome P450 (CYP) 3A4/5.*

ii. *However, participants who either discontinue moderate or strong inhibitors or inducers of CYP3A4/5 or switch to another medication at least 7 days prior to starting study treatment are eligible.*

8. Impairment of gastrointestinal function or disease which may significantly alter the absorption of oral study treatment.

   e.g. uncontrolled nausea, vomiting or diarrhea, malabsorption syndrome, small bowel resection.

9. Impaired cardiovascular function or clinically significant cardiovascular diseases.

   Including any of the following:

   a. *History of acute myocardial infarction, acute coronary syndromes (including unstable angina, coronary artery bypass graft, coronary angioplasty or stenting) within 6 months prior to start of study treatment.*

   b. *Congestive heart failure requiring treatment (New York Heart Association ≥Grade 2).*

   c. *Persistent systolic blood pressure >150 mmHg or diastolic blood pressure >100 mmHg despite optimal antihypertensive therapy.*

   d. *History or presence of clinically significant cardiac arrhythmias (including uncontrolled atrial fibrillation or uncontrolled paroxysmal supraventricular tachycardia).*

   e. *History of congenital prolonged QT syndrome or mean triplicate baseline QT interval corrected for pulse rate using Fridericia's formula (QTcF interval) ≥480 ms.*

10. Participants with active Hepatitis B virus (HBV) or Hepatitis C virus (HCV) or any other severe viral active infection (e.g. severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] infection).

    Active hepatitis is defined as:

    - Combination of HBV deoxyribonucleic acid (DNA) >1000 IU/mL or >2500 copies/mL plus positive Hepatitis B surface antigen (HBsAg) plus positive Hepatitis B core antibody.

    - Combination of HBV deoxyribonucleic acid (DNA) >1000 IU/mL or >2500 copies/mL plus positive Hepatitis B surface antigen (HBsAg)

    - Combination of HBV deoxyribonucleic acid (DNA) >1000 IU/mL or >2500 copies/mL plus positive Hepatitis B core antibody.

    - Positive serum HCV ribonucleic acid (RNA) and antibody to HCV (HCV Ab).

11. Evidence of active, non-infectious pneumonitis, history of interstitial lung disease that required oral or intravenous glucocorticoid steroids for management.

12. Known history of a positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). Testing for HIV must be performed at sites where mandated locally.
13. Participants who have had major surgery (e.g. inpatient procedure with regional or general anesthesia) within 6 weeks prior to start of study treatment.
14. Previous or concurrent malignancy within 2 years of study entry.

    Except:

    a. Bowen's disease.

    b. Cured basal cell or squamous cell skin cancer.

    c. Gleason 6 prostate cancer.

    d. Treated in-situ carcinoma of cervix.
15. Participant's conditions that contraindicates the use of study treatment and may affect interpretation of results or that may render the participant at high risk from treatment complications.

    Note:

    Conditions are, in the opinion of the investigator, any medical or psychiatric conditions, metabolic dysfunction, physical examination finding or clinical laboratory finding suggesting disease/condition.
16. Pregnant (confirmed by positive serum ß-HCG test), lactating or breast-feeding women.
17. Is a family member of the Investigator or any associate, colleague, and employee assisting in the conduct of the study (secretary, nurse, technician).
18. Is in a position likely to represent a conflict of interest.

5.3. Lifestyle Considerations

5.3.1. Contraception

Women of childbearing potential must agree to take appropriate precautions to avoid pregnancy from screening through 30 days after the last dose of encorafenib.

Male participants must agree to take appropriate precautions to avoid fathering a child and prevent exposure of seminal fluid to the partner from screening through 90 days after the last dose of encorafenib.

The methods of contraception outlined in Appendix 10.2.2 are permitted under this protocol for use by the participant and his/her partner. These methods should be communicated to the participants and their understanding confirmed.

Note: Due to the potential of encorafenib to induce CYP3A4, hormonal agents (including but not limited to birth control patch, vaginal ring, oral, injectable or implanted contraceptives) are permissible only when combined with other highly effective methods of contraception.

5.3.2. Meals and Dietary Restrictions

Participants must refrain from the consumption of grapefruit, pomegranates, star fruits, Seville oranges, lime, sour orange, citrus depressa, other local fruits or products containing the juice of any of these items from 7 days before the start of study treatment until after the final dose due to potential CYP3A4 interaction with encorafenib (**see Section 6.5.1**). Orange juice is allowed.

There are no restrictions on dosing or PK sampling in relation to the timing of meals.

5.4. Screen Failures

Screen failures are defined as participants who sign the ICF but fail to meet one or more criteria required for participation in the study or do not complete the screening process. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to competent authorities.

The following will be recorded in the electronic case report form (eCRF) for screen failures:

- Date of informed consent.
- Review of inclusion/exclusion criteria.
- Adverse events related to a study procedure during the screening period and any medications used to treat those adverse events.

Participants who do not meet the criteria for participation in this study (screen failure) cannot be rescreened. However, if vital signs measured as per protocol do not initially fulfil inclusion criterion, an unscheduled assessment is authorized after 10 minutes of rest without considering this as rescreening.

6. Study Treatment

6.1. Study Treatment(s) Administered

The study treatment is encorafenib, a novel, oral, highly selective ATP-competitive small molecule kinase inhibitor with potent and selective inhibitory activity against mutant BRAF kinase, a member of the RAS/RAF/MEK/ERK pathway, which plays a prominent role in controlling several key cellular functions including growth, proliferation and survival in tumor cells expressing metastatic *BRAF* V600E mutations, including melanoma and lung cell lines.

Encorafenib treatment details are provided in Table 5. Full information is provided in the Pharmacy Manual and the Investigator's Brochure for encorafenib.

Table 5: Detail of Study Treatment

Study treatment	Encorafenib
Code	PF-07263896 or W0090 (in Europe), LGX818 (in US), ONO-7702 (in Japan).
Pharmaceutical form	Hard capsule
Dosing regimen	Flat-fixed dose
Route of administration	Oral
Unit dose Components	Active ingredient: encorafenib. Inactive excipients: copovidone, poloxamer 188, succinic acid, microcrystalline cellulose, silica colloidal anhydrous, crospovidone, and magnesium stearate. The capsule shell is commercially available and contains: gelatin, titanium dioxide (E171), iron oxide red (E172), iron oxide yellow (E172), iron oxide black (E172), ink capsule shell (pharmaceutical glaze, iron oxide black (E172) propylene glycol).
Strength	75 mg
Dose	300 mg (4 × 75 mg)
Frequency	QD
Abbreviations: QD = once daily; US = United States.	

Encorafenib will be supplied by the sponsor and sent to a local facility (sponsor designee) for storage prior to onward distribution to each study site prior to, and during the study.

The study treatments will be packaged and labelled by the Investigational Medicinal Product Management Service of IRPF according to local requirements and local language(s). Each study treatment box is labelled, at a minimum, with the rules described in **Appendix 6**: Study Treatment labelling.

Encorafenib 75 mg will be packaged into a box of 120 hard capsules. This box will contain 20 blisters of six capsules.

Encorafenib will be orally self-administered. A fixed-flat dose of 300 mg PO encorafenib will be administered QD. Encorafenib should be taken daily in the morning at approximately the same time (± 2 hours) every day without regard to food. If a participant vomits at any time after dosing, the dose should not be re-administered. Doses of encorafenib that are omitted for adverse events or any other reason should not be made up during the day, or at the end of the dosing period.

The first dose of encorafenib will be taken on Cycle 1 Day 1 and will then be continuously self-administered in 28-day cycles until death, disease progression, one of the other criteria for study treatment discontinuation is met (see Section 7.1) or the participant is lost to follow-up (see Section 7.3). On Day 1 of each cycle the encorafenib dose will be administered at the study site.

Lifestyle considerations in relation to dosing are detailed in Section 5.3. There are no restrictions on dosing in relation to the timing of meals.

Participants will receive a diary to document self-administration of encorafenib to include the dose, date of dosing (and time if applicable), if the participant vomited after dosing, if any doses were missed and the reason for the missed dose. One diary will be provided per cycle. On the days when encorafenib is administered at the study site, these details will be recorded in the eCRF by the study site personnel.

Management of dose modifications (including dose interruptions and retreatment) are detailed in Section 6.6.

Continuing study treatment beyond disease progression for any participant is only to be considered under special circumstances when it is believed that the participant may clinically benefit from continued treatment beyond progression. If it is judged by the investigator (in consultation with the sponsor) to be in the best interest of the participant, the participant may remain on study treatment as long he/she continues to benefit from the study treatment according to the investigator's assessment. Special circumstances can be defined by e.g. mixed responses and appearance of new brain metastases (only) which is treatable with stereotactic radiotherapy or surgery but does not require whole brain radiotherapy.

Treatment beyond progression is not allowed in the following cases:

- Participants with clear evidence of disease radiographic and clinical progression at multiple sites or clear evidence of new lesions outside the central nervous system.
- Participants with rapid progression of disease at critical anatomical sites (e.g. cord compression) requiring urgent alternative medical treatment cannot be dosed beyond progression.
- Participants who have clinically relevant worsening of laboratory values.
- Participants who have a clinically significant decline in ECOG performance status at time of progression.

6.2. Preparation/Handling/Storage/Accountability/Return/Destruction

6.2.1. Accountability on Site and Return/Destruction

Before the start of the study, the sponsor or designee will supply the study site with the number of study treatments units required for the study using Interactive Response Technology (IRT).

Encorafenib will be supplied by the sponsor and sent to a local facility (sponsor designee) for storage prior to onward distribution to each study site prior to, and during the study. Full shipping, storage and handling details will be provided in the Pharmacy Manual.

- Labelled, packaged encorafenib will be shipped to each study site by the sponsor designee and will contain a temperature monitoring device. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Only participants enrolled in the study may receive study treatment and only authorized study site personnel may supply or administer study treatment. All study treatment must be stored according to Section 6.2.2.
- The investigator, institution or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation and record maintenance (dates and quantities of study treatment received, to whom study treatment is dispensed [participant-by-participant accounting] and accounts of returned and destroyed treatment).

  To ensure adequate records, all study treatment will be accounted for on an accountability inventory form as instructed by the sponsor according to Good Clinical Practice (GCP) (International Council on Harmonization [ICH] E6 (R2) [5.14]).

  Drug accountability must be performed by the clinical research associate (CRA) on a regular basis during the study according to the Monitoring Plan. The investigator must retain all unused or expired study treatment supplies until the CRA has confirmed the accountability records. If site policy prohibits holding study treatment supplies for CRA review, then a copy of the standard operating procedure for processing returns must be provided to the sponsor.
- At the end of the study, all used and unused study treatment including packaging should be noted and return/destruction is organized by the CRA. Further guidance and information for the final disposition of unused study treatments are provided in the Pharmacy Manual.

6.2.2. Storage

At the time of delivery to the site an accompanying letter will be provided with the details of storage conditions that should be respected.

As soon as the Pharmacist receives the study treatment, he/she will check the contents and immediately followed the instructions described in the Study Pharmacy Manual. Documents included in the parcel will be kept in the Investigator's file. .

At the time of delivery to the site an accompanying letter will be provided with the details of storage conditions that should be respected. The CRA will ensure during the initiation visit that study treatments have been received in good conditions and the acknowledgment of receipt has been returned adequately.

All study treatment must be stored in a secure, environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions and applicable regulatory requirements with access limited to the investigator and authorized study site personnel.

Storage conditions will be described on the medication label. Detailed instructions for storage and handling of encorafenib will be detailed in the Study Pharmacy Manual.

6.2.3. Expiry Date

The investigator or designee should ensure that the study treatment expiry date has not been exceeded. If the expiry date has been exceeded, then the affected study treatment supplies must be quarantined to prevent them from being used. Accountability and final disposition will follow the process in Section 6.2.1.

6.2.4. Return / destruction

At the end of the study, all used and unused study treatments, including packaging should be tracked, and their return/destruction will be arranged by the CRA.

The study treatment can be destroyed at the sponsor-designated local facilities or at a third party (on site) in accordance with local guidelines, as appropriate.

Further guidance and information for the final disposition of unused study treatments will be provided in the Study Pharmacy Manual.

6.2.5. Recall

In case of recall of study treatment (decided by the competent authorities or the sponsor), the investigator will be immediately informed by the sponsor. The investigator, in collaboration with the sponsor representatives (study manager, CRA) must urgently:

- Put all study treatments concerned by the recall in quarantine.
- Stop the administration of the concerned study treatments to the participants.

- Inform the concerned participants that they must immediately stop taking these study treatments and bring them back.

The study manager/CRA will organize the return of the recalled products to Pierre Fabre Médicament, according to the sponsor procedures.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Blinding and Randomization

This is an open-label, single-arm, non-randomized study therefore no procedures for blinding or randomization are applicable. All participants will receive the same study treatment.

6.3.2. Participant Numbering

A participant will be considered enrolled into the study as soon as he/she has signed the ICF. All participants who provide informed consent will be assigned a unique participant code by an Interactive Response Technology (IRT) system. Once a participant is enrolled, he/she will be identified only by the assigned participant code. Once assigned, a participant code must not be reused for any other participant.

The participant code will contain eight digits, corresponding to the country number, the site number and the participant's number according to chronological order (once having provided written informed consent).

6.3.3. Allocation of Study Treatment and Dispensing

Allocation of boxes of encorafenib to each participant will be controlled by the IRT system. Encorafenib will be allocated on Day 1 of each cycle during the treatment period. Returned encorafenib should not be re-dispensed.

Full information is described in the IRT Manual.

6.4. Study Treatment Compliance

As participants self-administer encorafenib at home, each participant will be reminded to bring back to the site any remaining encorafenib blisters and boxes (used or unused) from the previous cycle on Day 1 of the next cycle. Compliance with study treatment will be assessed on Day 1 of each cycle (from Cycle 2 onwards) by reviewing participant diary entries, accounting of returned study treatments and participant's interviews during the site visits and documented in the source documents and eCRF. Non-compliance from the prescribed dosage regimen should be recorded in the eCRF.

A record of the number of encorafenib capsules dispensed to and taken by each participant must be maintained and reconciled with study treatment and compliance records. The study treatment intake start and stop dates, including dates for study treatment delays and/or dose reductions will also be recorded in the eCRF.

6.5. Concomitant Medication and Therapeutic/Diagnostic Procedures

Any medication (including vaccines) other than study treatment (including non-prescription or prescription medicines or vitamins) taken in the period from 28 days before to the first administration of study treatment up to 30 days after the last dose of study treatment must be recorded. Any changes in dose of a medication during the study must also be recorded. The following information must be recorded in the eCRF:

- The name of the medication.
- The reason for prescription.
- The route of administration.
- The dose.
- The frequency.
- The duration (start date and end date).

The participant must be told to notify the study site about any new therapies and dietary supplements taken after the start of the study treatment.

Any therapeutic and diagnostic procedures (such as endoscopic examinations, diagnostics tests, ablation, surgical procedures, blood or platelet transfusions etc.) not planned by the study protocol must also be recorded. These procedures may be associated with events, in which case the condition that leads to the procedure must be reported in the appropriate section of the eCRF (adverse events, medical history). The following information must be noted in the eCRF:

- The name of the procedure.
- The indication.
- The duration (start date and end date).

Investigators should use caution when prescribing concomitant medications, as clinical experience with these compounds in participants with cancer is often limited. Investigators should contact the sponsor or designee when they are unsure whether a medication should be prescribed to a participant in the clinical study.

6.5.1. Authorized Medications, Therapeutic and Diagnostic Procedures

In general, the use of any concomitant medications deemed necessary for the care of the participant is permitted, unless otherwise specified. Additional information regarding concomitant medications is provided in the Investigator's Brochure.

Participants should be closely monitored for the occurrence of adverse events whilst taking permitted therapies requiring caution and/or action.

6.5.1.1. Authorized Therapies requiring Caution and/or Action

Participants should be closely monitored for the occurrence of adverse events whilst taking these therapies.

6.5.1.1.1. Cytochrome P450 and Uridine 5'-diphospho-glucuronosyltransferase Substrates and Inhibitors

Encorafenib is a reversible inhibitor of CYP2B6, CYP2C9, CYP3A4 and uridine 5'-diphospho-glucuronosyltransferase (UGT)1A1. It is also a time-dependent inhibitor of CYP3A4. Permitted medications to be used with caution in this study include those that are sensitive substrates of CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4 (see Table 11 and Table 12) and UGT1A1 (see Table 13) or those substrates that have a narrow therapeutic index.

There is a potential for encorafenib to induce CYP3A4, which may reduce the effectiveness of hormonal contraception methods. At least one form of non-hormonal contraception is therefore required during participation in this study (see Section 5.3.1). Caution should also be exercised in participants receiving concomitant treatment with other drugs that are substrates of CYP3A4 as the efficacy of these drugs could be reduced when administered with encorafenib.

Encorafenib has been identified in vitro to be metabolized by CYP3A4 and to a lesser extent by CYP2C19. The use of strong inhibitors of CYP3A4 is prohibited (see Section 6.5.2). Concomitant use of moderate CYP3A4 inhibitors (see Table 14) while on study should be avoided. If use of moderate CYP3A4 inhibitors is unavoidable and no alternatives are available, short-term use (≤30 days) following discussion with the sponsor may be permitted with accompanying dose reduction to one-half of the encorafenib dose before use of moderate CYP3A4 inhibitors (or as close as can be achieved without exceeding the target dose). The encorafenib dose that was taken before initiating the CYP3A4 inhibitor may be resumed after the inhibitor has been discontinued for three to five elimination half-lives. Strong inhibitors of CYP2C19 should be used with caution when coadministered with encorafenib.

6.5.1.1.2. Transporter Substrate and Inhibitors

In vitro data showed that encorafenib is a substrate of the transporter P-glycoprotein (P-gp) and a breast cancer resistance protein (BCRP) inhibitor. Use of medications that are known to inhibit or induce P-gp or BCRP should be used with caution (see Table 15). Encorafenib is also a potent inhibitor of the renal transporters, organic anionic transporter (OAT)1, OAT3 and organic cationic transporter (OCT)2 and the hepatic transporter organic anion-transporting peptide (OATP1)B1 and OATP1B3. The co-administration of drugs that are known to be sensitive or narrow therapeutic index substrates of BCRP, P-gp, OAT1, OAT3, OCT2, OATP1B1 and OATP1B3 should be used with caution (see Table 16).

6.5.1.1.3. Drugs with a Conditional or Possible Risk to Prolong the QT Interval and/or Induce Torsade de Pointes

Investigators should use caution when administering encorafenib with concomitant medications with a known, conditional or possible risk to prolong the QT interval and/or induce Torsade de Pointes (see Table 17**)**. Participants receiving such medications must be carefully monitored for potentiation of toxicity due to any individual concomitant medication and may require dose titration of the concomitant medication.

6.5.2. Prohibited Medications and Therapeutic/Diagnostic Procedures

The following therapies are prohibited during screening and the Treatment Period (unless otherwise noted). There are no prohibited therapies during the post-treatment Follow-up Period. None of the concomitant therapies and therapeutic/diagnostic procedures listed below are allowed during the treatment phase:

- Anticancer agents such as cytotoxic chemotherapy small-molecule targeted agents, biological agents, immune response modifiers or hormonal therapy.
- Local therapies which could interfere with treatment (e.g. surgical excision or ablation of lesions are not permitted without sponsor approval.
- Investigational drugs (other than study treatments) and devices.
- Radiation therapy (not including palliative radiotherapy at focal sites that covers ≤10% of the bone marrow reserve). Calculation of the percentage of active bone marrow reserve can be performed using information in **Table 6** [**Hindorf, 2010**].

  Note: The participant must have clear measurable disease outside the radiated field.

  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be considered on a case-by-case basis after consultation with the sponsor's medical monitor.

  Note: Administration of palliative radiation therapy will be considered clinical progression.
- Herbal preparations/medications. Participants should stop using herbal medications (including use of St. John’s Wort [hypericum perforatum] and traditional Chinese medicine

susceptible to be a moderate or strong inhibitor or inducer of CYP3A4/5) 7 days before the first dose of study treatment.

- Concomitant systemic strong CYP3A4 inhibitors or moderate/strong inducers which are likely to significantly increase or decrease respectively encorafenib exposure (listed in Table 18).

Table 6: The percentage of total red marrow present at different skeletal sites in a healthy adult

Skeletal site	Percentage of red marrow
Cranium	7.6
Mandible	0.8
Scapulae	2.8
Clavicles	0.8
Sternum	3.1
Ribs	16.1
Cervical vertebrae	3.9
Thoracic vertebrae	16.1
Lumbar vertebrae	12.3
Sacrum	9.9
Os coxae	17.5
Femora, upper half	6.7
Femora, lower half	0
Tibiae, fibulae, patellae	0
Ankle and foot bones	0
Humeri, upper half	2.3
Humeri, lower half	0
Ulnae, radii	0
Wrist and hand bones	0

If another therapy and/or therapeutic/diagnostic procedure has to be prescribed in the interests of the participant's health, the decision to discontinue the participant from the study should be taken by the investigator.

6.6. Dose Modification

Participants will be monitored for adverse events throughout the study. The severity of adverse events will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events NCI CTCAE Version 4.03 [NCI CTCAE 2010].

If a participant develops toxicity, the dose should be modified as outlined in Appendix 10.4. This table include criteria for interruption, reduction and discontinuation of study treatment. All dose modifications should be based on the worst preceding toxicity. All dosing interruptions and modifications must be recorded in the eCRF.

Individual decisions regarding dose modifications should be made using appropriate clinical judgment, considering relatedness of the adverse event to the study treatment and the participant's underlying condition. Adverse events that have a clear alternative explanation or are transient (≤72 hours) abnormal laboratory values without associated clinically significant signs or symptoms may be exempt from dose reduction rules. The investigator should follow the study site supportive guidelines for the management of these toxicities and prophylactic measures.

6.6.1. Dose Interruptions

Following initiation of therapy, treatment with encorafenib may be delayed to allow resolution of toxicity. Participants may resume treatment if no medical condition or other circumstance exists that, in the opinion of the investigator, would make the participant unsuitable for further participation in the study.

Dose interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study treatment (e.g. elective surgery, unrelated medical events, vacation, holidays). Participants should be resumed on study treatment within 2 weeks (14 days) of the scheduled interruption, unless otherwise discussed with the sponsor. The reason for interruption will be documented in the participant's medical file and in the eCRF.

If a participant misses >4 weeks (i.e. 28 consecutive days) of dosing with encorafenib, study treatment will be permanently discontinued (see **Section 7.1**).

6.6.2. Dose Reductions

The dose of encorafenib may be reduced for toxicity management as outlined in **Table 7** All dose modifications are based on the worst preceding toxicity. Dose reduction below 150 mg QD encorafenib is not allowed.

Table 7: Dose Reductions for Encorafenib

Dose Level	Encorafenib
0 (starting dose)	300 mg QD
-1	225 mg QD
-2	150 mg QD
Abbreviations: QD = once daily NOTE: Dose reduction should be based on the highest preceding toxicity	

If the event causing a dose reduction improves to the baseline level and remains stable for a minimum of 14 days, the dose can be re-escalated to the next dose level at the discretion of the investigator, provided there are no other concomitant toxicities that would prevent re-escalation. There is no limit to the number of times the participant can have their dose reduced or re-escalated (in increments specified in Table 7).

Following any dose reductions occurring due to toxicity, should investigators believe that it is the best interest of their patients, they may re-start and re-escalate doses, with close supervision and monitoring of their patients, except for the following circumstances of dose modification:

- No dose re-escalation of encorafenib is allowed after a dose reduction due to prolonged QTcF ≥ 501 msec
- No dose re-escalation is allowed after a dose reduction due to retinal toxicity ≥ Grade 2.

7. Discontinuation of Study Treatment and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Treatment for Individual Participants

7.1.1. Temporary Discontinuation and Rechallenge

Adverse events and clinically significant laboratory abnormalities leading to a dose interruption and the conditions for re-starting study treatment (rechallenge) are provided in Appendix 10.4.

A treatment interruption occurs if at least one study treatment administration is missed, followed by a restart of the study treatment.

It may be necessary for a participant to interrupt study treatment to allow for resolution of toxicity (see Section 6.6). Participants may resume treatment if no medical condition or other circumstance exists that, in the opinion of the investigator, would make the participant unsuitable for further participation in the study.

Dose interruptions are also permitted in the case of medical/surgical events or logistical reasons not related to study treatment (e.g. elective surgery, unrelated medical events, vacation, holidays). Participants should be resumed on study treatment within 2 weeks (14 days) of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption will be documented in the eCRF. Dose interruptions of >4 weeks (28 consecutive days) are not allowed unless approved by the sponsor's medical monitor and study treatment must be permanently discontinued (see **Section 7.1.2**).

7.1.2. Permanent Study Treatment Discontinuation

Study treatment is to be administered until any of the following criteria for permanent discontinuation is met:

- Disease progression, as defined by Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (continuation of treatment beyond progression is permitted in special circumstances, **see Section 6.1**).

- Clinical progression, as determined by the investigator in the absence of radiographic progression.
- Withdrawal of consent. Participants may choose to withdraw consent to continue study treatment but remain in the study to be followed for safety and disease progression. In this case, follow-up data will continue to be collected for this participant. Withdrawal of consent for study treatment may occur at any time without penalty of jeopardizing their healthcare or loss of benefits to which they are otherwise entitled. Participants who withdraw consent to study treatment and follow-up, will no longer receive study treatment or followed up within this study.
- Unacceptable adverse events or failure to tolerate study treatment:
  - Grade 4 or life-threatening adverse event as outlined in Appendix 10.4 (except with approval from the sponsor's medical monitor)
  - Toxicity requiring more than the allowed number of dose reductions for encorafenib, (see **Table 7**).
  - Occurrence of an adverse event that is related to study treatment and compromises the participant's ability to continue study-specific procedures according to investigator's judgement or is considered to not be in the participant's best interest. The medical monitor or delegate should immediately be informed by phone or e-mail and a report explaining the discontinuation will be forwarded to him/her as soon as possible.
- Initiation of subsequent anticancer therapy.
- Participant is non-compliant with study procedures or study treatment that in the judgment of the investigator or sponsor renders the participant unsuitable.
- Significant protocol deviation that, in the opinion of the investigator and/or sponsor, renders the participant unsuitable for further study treatment administration.
- Participant has missed >4 weeks (i.e., 28 consecutive days) of dosing (see Section 7.1.1).
- Participant becomes pregnant or begins breastfeeding.
- Participant is lost to follow-up.
- Defined end of the study (see Section 4.4)
- Termination of the study site or study by the sponsor/competent authority (described in **Appendix 10.1.2 and Appendix 10.1.10**).
- Physician decision.
- Other reasons (any unexpected event considered relevant by the investigator to be discussed case by case with the sponsor).

If a participant is withdrawn from study treatment, the date and reason of treatment discontinuation will be recorded in the eCRF. The participant will have an end of treatment visit followed by a 30-day safety follow-up assessment.

Data to be collected at the time of discontinuation of study treatment and follow-up and for any further evaluations that need to be completed are specified in Table 1. For participants who have discontinued study treatment for reasons other than disease progression, tumor assessments should continue to be performed (as per local review and standard of care) until the start of a new anticancer therapy, disease progression, death, loss to follow-up, participant's decision or withdrawal of consent whichever occurs first.

Participants who are discontinued from the study treatment due to a treatment-related adverse event will be followed until resolution to Grade ≤1 or stabilization.

7.2. Participant Discontinuation/Withdrawal from the Study

Participants may withdraw consent to the study treatment and follow-up at their own request or be withdrawn at the discretion of the investigator (e.g. for safety, behavioural, compliance or administrative reasons) at any time and for any reason without prejudice to their future medical care. This is expected to be uncommon. The participant will be permanently discontinued both from study treatment and from the study at that time.

At the time of withdrawing from the study, if possible, a 30-day safety follow-up visit should be conducted. Data to be collected at the time of discontinuation of study treatment and follow-up and for any further evaluations that need to be completed are specified Table 1.

In all cases, the investigator should attempt to contact the participant as soon as possible for a final assessment in order to:

- Obtain the reason(s) for withdrawal and report it/them with the discontinuation date in the eCRF, and in the participant's medical file.
- Evaluate the participant's clinical condition.
- If necessary, take appropriate therapeutic measures: management of an adverse effect or concomitant disease, prescription of another treatment.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. Any blood or tissue samples collected up to the date of withdrawal of consent will be analyzed. No further data, except data in the public domain, may be solicited from or collected on the participant.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- Study site personnel must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designated study site personnel must make every effort to regain contact with the participant (where possible, three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the schedule of activities (Table 1). Adherence to the study design requirements, including those specified in the schedule of activities, is essential and required for study conduct. Additional, unscheduled visits or procedures may be performed at the discretion of the investigator (including samples for safety reasons or because of technical issues with the samples). Details must be recorded in the eCRF.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. Protocol waivers or exemptions are not allowed. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (e.g. blood count) and obtained before provision of informed consent may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the schedule of assessments.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed one standard blood donation.

8.1. Screening Assessments and Procedures

Participants must undergo *BRAF* V600E local laboratory testing using an NMPA approved test prior to screening.

All eligible participants will then undergo screening in the 28 days before the start of study treatment. Participants must provide informed consent for the study before any screening procedures to determine eligibility for participation in the study are performed (see Appendix 10.1.4). Participants will be registered for the study using IRT after informed consent is obtained (see Section 6.3).

The following will be recorded at screening for all participants:

- Demographic variables (including age, sex and race).
- Disease history including stage, tumor location, organs involved and sites of metastases, baseline tumor mutation status including details of prior antineoplastic treatments including number of prior metastatic regimens.
- Other past and present medical history considered by the investigator to be significant.
- Smoking history.

- Prior medications/procedures (to cover the 28 days before the first dose of study treatment).

The following assessments will be performed:

- Physical examination, height and weight (see Section 8.3.2) and dermatological examination (see Section 8.3.3).
- Vital signs (see Section 8.3.6), ECG (see Section 8.3.7), cardiac function (see Section 8.3.8) tests and ECOG performance status (see Section 8.3.9).
- Local clinical laboratory blood tests:
  - Safety tests (hematology, clinical chemistry and coagulation) (see Section 8.3.4).
  - Viral serology tests for HBsAg and HCV Ab, (plus HIV in jurisdictions that specifically requiring it), and HBV DNA if HBsAg was positive or HCV RNA if HCV Ab positive.
  - Pregnancy test in WOCBP (see Section 8.3.5).
  - If required, analysis of follicle stimulating hormone (FSH) (see Appendix 10.2.1), to confirm postmenopausal status in females.

  Samples will be collected, handled and analyzed at the local laboratory according the study site's standard procedures.
- Urinalysis (see Section 8.3.4).
- Baseline tumor assessment of the chest, abdomen, pelvis and brain by CT/MRI plus bone or positron emission tomography (PET) scan if clinically indicated (see Section 8.2).

Participant eligibility will be verified against the inclusion and exclusion criteria once all screening procedures are completed. When a participant is confirmed as eligible, they will be assigned to study treatment.

8.2. Efficacy Assessments

This study is not intended to formally assess efficacy, however, some efficacy assessment is necessary for the Investigator to assess continued benefit.

Tumor response will be evaluated according to RECIST Version 1.1 (see Appendix 10.7). Tumor overall assessment (response, stable disease (SD), progressive disease (PD) will be determined locally by the investigator.

Baseline disease assessments (imaging with a preference for CT and /or calliper measurements) will be performed at screening (in the 28-days before the first dose of study treatment up to Day -1) and as close as possible to the start of treatment.

During the study, 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. A final assessment should be performed at the end of treatment visit, unless the previous assessment was performed in the last 30 days. More frequent radiological assessments may be performed if needed.

According to RECIST Version 1.1, responses (complete response or partial response) should be confirmed by a repeat radiographic assessment no sooner than 4 weeks after the first documented response and no later than the next per-protocol scheduled imaging, whichever is clinically indicated.

Additional imaging evaluations may be performed at any time if there is symptomatic evidence suggesting the possibility of disease progression based on clinical symptoms or physical examination. Following the 30-day safety follow up (when clinically appropriate) it is also recommended the participant be monitored with 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.

8.3. Safety Assessments

8.3.1. Adverse Events

Requirements for recording and reporting adverse events and SAEs are described in Section 8.4.

8.3.2. 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 treatment), 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 at each timepoint. 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.

All physical examinations must be performed prior to study treatment administration. Significant findings in the investigator's opinion must be included in on the medical history or adverse event eCRF pages.

8.3.3. Dermatological Examination

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 [Flaherty 2010, Kefford 2010, Robert 2011]. 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.

In case of occurrence of keratoacanthoma and/or squamous cell carcinoma, participants should undergo complete surgical excision of the skin lesion following study site standards. The evaluation may be done by the dermatologist if clinically indicated.

8.3.4. Clinical Safety Laboratory Assessments

Laboratory tests performed before the start of study treatment to determine eligibility or baseline status only (i.e. for viral serology and tests to confirm postmenopausal status for females) are detailed in Section 8.1. Pregnancy testing is detailed in Section 8.3.4.

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 treatment), 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 8.

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 Section 6.6) should be reviewed before study treatment administration.

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 the study site's standard procedures. Normal 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. The normal ranges will be provided to data management for all local laboratories in the study.

Table 8: Protocol-required Clinical Laboratory Safety Assessments

Hematology	Erythrocytes (RBC), hematocrit, hemoglobin, platelets Leukocytes (WBC) count with differential (absolute values): basophils, eosinophils, lymphocytes, monocytes, neutrophils
Clinical Chemistry[a]	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
Coagulation	aPTT, INR or PT
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: HBsAg, HBsAg antibody, hepatitis B core antibody, and HBV DNA if HBsAg or HBcAb was positive • HCV Ab and HCV RNA if HCV Ab was positive • 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 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.

The investigator must review the laboratory report, document this review and record any clinically relevant changes occurring during the study as an adverse event. The laboratory reports must be filed with the source documents. 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. An abnormal laboratory value that is not associated with an already reported adverse event is to be recorded as an adverse event only if an action on the study treatment is made as a result of the abnormality, if treatment for management of the abnormality is required or at the discretion of the investigator.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the aetiology should be identified, and the sponsor notified.

If laboratory values from non-protocol specified laboratory assessments performed at the study site's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g. adverse event, SAE or dose modification), then the results must be recorded in the eCRF.

8.3.5. Pregnancy Testing

Pregnancy tests will be performed on females determined to be WOCBP only (see Appendix 10.2.1). 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.

The pregnancy tests at screening and predose on Cycle 1 Day 1 must be negative for inclusion. Any positive pregnancy tests during the treatment period will result in immediate discontinuation of study treatment (see Section 7.1). If any urine test cannot be confirmed as negative (e.g. an ambiguous result), a serum pregnancy test is also required.

Pregnancies will be managed as defined in Section 8.4.5.

8.3.6. Vital Signs

Tympanic temperature, pulse rate, respiratory rate, systolic blood pressure and diastolic blood pressure 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. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g. television, cell phones). All assessments during the treatment phase should be made prior to study treatment administration and before blood collection for laboratory tests.

Any treatment-emergent abnormal findings should be recorded as adverse events.

8.3.7. Electrocardiograms

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.

Three serial ECGs will be conducted within approximately 5 to 10 minutes total time. 12-lead ECGs should be preceded by at least 5 minutes of rest for the participant in a quiet setting without

distractions (e.g. television, cell phones) after the participants has rested in the supine position for at least 5 minutes:

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

Interpretation of the tracing will be made by a qualified physician and documented in the eCRF. QT interval values will be corrected for pulse rate using the Fridericia formula (QTcF). Clinically significant abnormalities present at screening but prior to the first dose of study treatment should be recorded as medical history in the eCRF.

An abnormal 12-lead ECG (e.g. QTcF of >500 ms or with a change in QTcF from baseline of ≥60 ms) may be repeated if it cannot be interpreted by the investigator. ECG tracings will be made available if requested by the sponsor.

8.3.8. Cardiac Function

Participants who develop signs/symptoms of cardiac toxicity including congestive heart failure at any point during the study should be monitored according to study site guidelines.

8.3.9. Eastern Cooperative Oncology Group Performance Status

An assessment of ECOG performance status [Oken 1982] 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 9).

Table 9: 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

8.3.10. Other examinations/Chest, abdomen and pelvis CT scanner

Based on its mechanism of action, encorafenib may promote malignancies associated with activation of RAS through mutation or other mechanisms.
A head and neck examination, chest/abdomen computerized tomography (CT) scan, anal and pelvic examinations (for women) and complete blood cell counts prior to initiation will be performed during and at the end of treatment as clinically appropriate.

8.4. Adverse Events and Serious Adverse Events

Adverse events and SAEs are defined in Appendix 10.8. Events meeting these definitions are also specified.

8.4.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All adverse events will be collected from when the participant first provides informed consent until the 30-day safety follow-up visit. If the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study and he/she considers the event to be related to the study treatment or study participation, the investigator must promptly notify the sponsor.

8.4.2. Method of Detecting, Recording and Reporting Adverse Events and Serious Adverse Events

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate or the participant's legally authorized representative). Care will be taken not to introduce bias when detecting adverse events. Open-ended (participant’s spontaneous reporting) and non-leading verbal questioning of the participant are the preferred methods.

The investigator and designated study site personnel are responsible for detecting, documenting and recording events that meet the definition of an adverse event/SAE and remain responsible for following up events that are serious, considered related to the study treatment or study procedures, or that caused the participant to discontinue the study or study treatment (see Section 7).

The records of adverse events must describe the nature (diagnosis, signs and symptoms), intensity, date/time of onset, date/time of end, outcome and actions taken with study treatment, relationship to study treatment (in the investigator's opinion) and whether the event is serious or not.

The process of recording, evaluating and assessing adverse events/SAEs for intensity and causality is provided in Table 10.

Table 10: Process for Recording, Evaluating and Assessing Adverse Events and Serious Adverse Events

Recording
• When an adverse event/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory reports and diagnostics reports) related to the event. • For a recurrent adverse event (that resolves and subsequently recurs), each recurrence must be recorded as a separate adverse event. • For a continuous adverse event (i.e. unresolved between participant assessments), any change in intensity (improvement or worsening) or seriousness must be recorded with the indication of the start and (if applicable) the end of the change within the same adverse event report. • The investigator will then record all relevant adverse event/SAE information in the eCRF. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of adverse event/SAE eCRF pages. • There may be instances when copies of medical records for certain cases are requested by sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/SAE.
Assessment of Intensity
The investigator will make an assessment of intensity for each adverse event/SAE. Wherever possible this should be performed using the NCI CTCAE Version 4.03 scale [NCI CTCAE 2010]. For any term not specifically listed, intensity should be assigned as Grade 1 through 5 according to the following categories: • Grade 1 (mild): asymptomatic or mild symptoms; clinical or diagnostic observations only; treatment not indicated. • Grade 2 (moderate): minimal, local or non-invasive treatment indicated; limiting age-appropriate instrumental activities of daily living. • Grade 3 (severe or medically significant but not immediately life-threatening): hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living. • Grade 4 (life-threatening consequences): urgent treatment indicated. • Grade 5 (death related to adverse event). Note: An event is defined as 'serious' when it meets at least one of the predefined seriousness criteria (see Appendix 10.8.2) NOT when it is rated as severe.
Assessment of Causality
• The investigator is obligated to assess the relationship between study treatment and each occurrence of each adverse event/SAE. • A "reasonable possibility" of a relationship conveys that there are facts, evidence and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. • The investigator will also consult the Investigator's Brochure and/or locally-approved Product Information, for marketed products, in his/her assessment.

• For each adverse event/SAE, the investigator **must** document in the medical notes that he/she has reviewed the event and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Pierre Fabre Médicament Corporate Vigilances Division. However, it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the Pierre Fabre Médicament Corporate Vigilances Division. • The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.
Abbreviations: eCRF = electronic case report form; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; SAE = serious adverse event.

All events determined to be SAEs (irrespective of study treatment or causality) will be recorded and reported to the sponsor or designee immediately to facilitate the regulatory reporting requirements in Section 8.4.4. Under no circumstances should this exceed 24 hours.

The primary means for reporting SAEs to the sponsor's Corporate Vigilances Division is using the SAE form (pdf extension). The investigator will enter the SAE data (with all the available information about the event) into this enterable pdf SAE form, sign and transmit it within 24 hours of awareness SAE information to the Pierre Fabre Médicament Corporate Vigilances Division: PII

The SAE form (in pdf extension) template can be downloaded from the eCRF.

If enterable pdf SAE form is unavailable, the paper SAE form available at site will be used and filled in English Language.

SAE Reporting to Pierre Fabre via paper SAE form
• E-mail transmission of the paper SAE form, within 24 hours (with all the available information about the event) is the preferred method to transmit this information to Pierre Fabre Corporate Vigilances Division. • Contacts for SAE reporting : **HQ.pharmacovigilance@pierre-fabre.com** • In rare circumstances notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE form within the designated reporting time frames.

In case of pregnancy, see **Section 8.4.5** for reporting procedures.

8.4.3. Follow-up of Adverse Events and Serious Adverse Events

The investigator is obligated to proactively follow-up all adverse events and perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by sponsor or designee to elucidate the nature and/or causality of the event as fully as possible. This may include additional laboratory tests or investigations, histopathological

examinations or consultation with other health care professionals. If a participant dies during participation in the study or during the follow-up period, the investigator will provide the sponsor with a copy of any post-mortem findings, including histopathology.

All SAEs will be followed until resolution, stabilization, the event is otherwise explained or the participant is lost to follow-up (as defined in Section 7.3).

The investigator will submit any new or updated SAE data to the sponsor's Corporate Vigilances Division within 24 hours receipt of the information. New or updated information will be entered on the SAE eCRF page (or provided on a new paper SAE form, if required).

8.4.4. Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify the competent authority about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific requirements relating to safety reporting to the competent authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) and investigators.

An SAE is determined to be a suspected unexpected serious adverse reactions (SUSAR) if it meets all the following criteria:

- Unexpected (i.e. nature or severity of which is not consistent with the study treatment description [e.g. Investigator's Brochure for an unapproved investigational product or locally approved Product Information for a marketed product]).
- Serious.
- Assessed to be related to study treatment.

Safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives a safety report describing a SAE or other specific safety information (e.g. summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5. Pregnancy

Contraceptive requirements for female and male participants are specified in Section 5.3.1.

The investigator will attempt to collect pregnancy information on any female participant or male participant's female partner who becomes pregnant while the participant is in the study, during or after exposure to study treatment.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy.

The primary means for reporting pregnancies to the sponsor's Corporate Vigilances Division is using the pregnancy form (pdf extension). The investigator will enter the pregnancy data (with all available information about the event) into this enterable pdf pregnancy form, sign and transmit it within 24 hours of awareness pregnancy information to the Pierre Fabre Médicament Corporate Vigilances Division PII [redacted] within 24 hours of awareness.

The pregnancy form (in pdf extension) template can be downloaded from the eCRF.

If enterable pdf pregnancy form is unavailable, the paper pregnancy form available at site will be used and filled in English Language.

Pregnancy Reporting to Pierre Fabre via paper Pregnancy form
• E-mail transmission of the pregnancy form, within 24 hours, is the preferred method to transmit this information to the Pierre Fabre Corporate Vigilances Division. • Contacts for pregnancy reporting: PII [redacted] • In rare circumstances notification by telephone is acceptable with a copy of the pregnancy data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the pregnancy form within the designated reporting time frames.

- Additional informed consent will be sought (required within 72 hours) from female study participants to follow the pregnancy to outcome. Likewise, informed consent to follow the pregnancy will be sought from a pregnant female partner of a male study participant) (see Appendix 10.1.4). Once informed consent is provided, additional pregnancy information will be submitted to the sponsor on a pregnancy form following the process above.
- The pregnant female will be followed until the completion/termination of the pregnancy. Information on the status of the mother and the neonate will be forwarded to the sponsor using pregnancy form. Follow-up will be performed for as long as necessary beyond the delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Abnormal pregnancy outcomes (e.g. spontaneous abortion [occurring at <22 weeks gestational age], stillbirth (occurring at >22 weeks gestational age), fetal death, congenital anomalies, ectopic pregnancy) are always considered to be an SAEs (see Appendix 10.8.2).

- Any poststudy pregnancy-related SAE considered related to the study treatment by the investigator will be reported to the sponsor as described in Section 8.4.2. While the investigator is not obligated to actively seek this information in former study participants, he/she or she may learn of an SAE through spontaneous reporting.

If pregnancy is suspected during treatment period, the study treatment(s) should be temporarily discontinued (see Section 7.1.1) immediately until the result of the pregnancy testing is known. If pregnancy is confirmed, then the study treatment should be permanently discontinued (see Section 7.1.2) in an appropriate manner and the participant discontinued from the study.

8.4.6. Cardiovascular and Death Events

Cardiovascular and death events will be recorded and reported as specified in Section 8.4.1 to Section 8.4.4.

8.4.7. Disease-related Events and/or Disease-related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

Progression of malignancy (including fatal outcomes) will be documented as part of the efficacy assessment (see definition of an adverse event in Appendix 8) and will not be reported according to the standard process for recording and reporting of adverse events unless either of the following conditions applies, then the event must be recorded and reported as an adverse event (instead of a disease-related event):

- The event is, in the investigator's opinion, of greater intensity, frequency or duration than expected for the individual participant.

OR

- The investigator considers that there is a reasonable possibility that the event was related to study treatment.

8.4.8. Adverse Events of Special Interest

Adverse events of special interest will be defined in the Statistical Analysis Plan (SAP).

8.5. Overdose

Any dose of study treatment greater than the participant's assigned dose according to protocol recommendations will be considered an overdose. The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator or designated physician should:

19. Contact the medical monitor immediately.
20. Monitor renal function as well as adverse reactions.
21. In the absence of seriousness criteria, the overdose, and associated adverse events if any, are reported only on the adverse event eCRF page. **If the definition** of seriousness criteria **is met**, the SAE eCRF page must be also completed and transmitted to the sponsor.
22. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.6. Pharmacokinetics

8.6.1. Pharmacokinetic Samples

Blood samples of approximately 4 mL 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 (total 10 samples per participant). Each blood sample will be drawn by direct venipuncture or via an indwelling catheter: If an indwelling catheter is used for blood collection, approximately 1 mL will be drawn and discarded before sampling. Care must be taken to collect blood slowly without causing hemolysis.

The following will be recorded:

- Cycle 1 Day 1: date and time of the first encorafenib dose and exact date and time of each sample.
- Cycle 2 Day 1: date and time of the last previous encorafenib dose before Cycle 2 Day 1 (i.e. Cycle 1 Day 28) dosing and the current day's encorafenib dose and exact date and time of each sample.

Study visits for PK sampling should be scheduled in the morning so that correct predose and postdose PK blood samples can be collected. The encorafenib dose on PK visit days **should be taken at the study site, only after collecting the predose PK sample**.

If a participant experiences an adverse event that results in an unscheduled visit or meets the criteria for an SAE, a further blood sample should be collected, if feasible, if less than 24 hours have elapsed since the last dose. On Cycle 1 Day 1 and Cycle 2 Day 1, if vomiting occurs, the exact time of the first vomiting episode within the first 4 hours postdose on that day must be noted. If a vomiting episode occurs within the first 4 hours postdose of encorafenib during the day of the last dose prior to collection of PK samples (except for Cycle 1 Day1), the exact time (whenever possible) must be noted in the eCRF.

Each sample will be divided into aliquots (for primary aliquots for PK analysis and back-ups). Samples will be stored at the study site at -20°C. Primary aliquots will be shipped to central laboratory on the day of collection and back-ups within 28 days of collection.

Complete information regarding blood sample collection and processing, handling and shipment will be provided in the Laboratory Manual. The primary and back-up aliquots will be shipped separately. The samples will be stored at the central laboratory at -70°C until transfer to the third-party bioanalytical laboratory for analytical determination.

8.6.2. Analytical Determination

Analytical determination of plasma concentrations of encorafenib and LHY746 will be carried out at a designated third-party bioanalytical laboratory using validated liquid chromatography tandem mass spectrometry (LC/MS-MS) methods.

8.6.3. Pharmacokinetic Analysis

Encorafenib and LHY746 concentrations will be transmitted by the bioanalytical laboratory to the subcontractor in charge of PK analysis. Non-compartmental (e.g. area under the curve [AUC], maximum concentration [C_{max}] and minimum concentration [C_{min}]) and population PK analyses (as appropriate) will be performed (see Section 9.4.3.2).

8.7. Pharmacodynamics

Not applicable. Pharmacodynamics will not be assessed in the study.

8.8. Pharmacogenomics

Not applicable. Pharmacogenomics will not be assessed in the study.

8.9. Other Exploratory Biomarker Assessment

Not applicable. Biomarkers will not be assessed in the study.

9. Statistical Considerations

This section presents a summary of the planned statistical analyses. Statistical analysis will be performed under the supervision of the study statistician at the Biometry Department, Pierre Fabre Médicament.

9.1. 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.

9.2. Sample Size Determination

The planned sample size is up to six evaluable participants based on a 3+3 design (see Section 4.1.1). 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 4.1.1).

9.3. Populations for Analyses

The following populations will be analyzed:

Population	Description
Safety Set (SAF)	All participants who receive at least one dose of encorafenib (partial or full).
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.
Pharmacokinetics Set (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.

9.4. Statistical Analyses

9.4.1. General Considerations

All data will be listed. This section summarizes the descriptive analyses planned on these data.

A SAP will be prepared by the sponsor (or designee) and finalized prior to first participant first visit. This plan will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses. Any major modifications will also be described in a protocol amendment.

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

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, mean, standard deviations, median, quartiles, minimum and maximum. 95% CIs will be presented if relevant.
- Categorical data will be summarized using number of observations, frequencies, percentages and number of 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 if not otherwise specified in the SAP.

Baseline is defined as the last completed and available assessment prior to date of first dose of study treatment. 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.

The Clinical Study Report will be written based on all data at the end of the study.

9.4.2. Primary Endpoint

The primary endpoint is the incidence of DLTs experienced during Cycle 1 of encorafenib treatment. 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 4 (see Section 4.1.1).

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

9.4.3. Secondary Endpoints

9.4.3.1. Safety

All safety analyses will be performed on the SAF.

9.4.3.1.1. Study Treatment Exposure

The duration of study treatment exposure in weeks, actual and relative dose intensity will be summarized. The number of participants with dose modifications will be presented. The actual daily doses and reasons for dose modification will be listed.

Further details will be provided in the SAP.

9.4.3.1.2. Adverse Events

All analyses of adverse events will be further detailed in the SAP.

The occurrence of an adverse event 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). All adverse events will be coded using the MedDRA terminology according to Appendix 10.1.8.3.4 and the verbatim term, system organ class (SOC) and preferred term presented.

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).

Incidence tables will display the number and percentage of participants with TEAEs and number of TEAEs by SOC and preferred term. Further summaries will be provided by maximum severity (based on NCI CTCAE grades, where applicable) and relationship to study treatment. 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.

Summaries of Grade 3 and 4 TEAEs, SAEs and adverse events resulting in study treatment discontinuation, study treatment modification or study discontinuation and adverse events leading to additional therapy will also be separately presented by SOC and preferred term.

Summaries for deaths on-study will be provided.

Adverse events of special interest will be identified, defined in the SAP and summarized. Such categories consist of 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 treatment. For each specific category, number and percentage of participants with at least one event will be reported, if relevant. Additional analyses may be defined.

9.4.3.1.3. Clinical Safety Laboratory Evaluation

Clinical safety laboratory parameters will be graded using graded using NCI CTCAE Version 4.03, where possible and presented in shift tables or scatterplots of baseline grade versus maximum grade on study, if relevant. For laboratory parameters that cannot be graded using NCI CTCAE Version 4.03, shift tables of normal-abnormal will be provided. Summaries of 'clinically notable' measurements will also be provided. The definitions of 'clinically notable' will be provided in the SAP.

For other laboratory parameters that cannot be graded using NCI CTCAE, shift tables of normal-abnormal will be presented.

9.4.3.1.4. Other Safety Data

Vital signs, physical examination, dermatological examination, ECG and ECOG performance status data will be summarized descriptively over time for values and changes from baseline and/or with shift tables or scatterplots, if relevant. Summaries of clinically notable measurements will also be provided. Definitions will be detailed in the SAP.

Results for each ECG parameter will be summarized and reviewed for clinically notable abnormalities according to predefined criteria as outlined in the SAP.

9.4.3.2. **Pharmacokinetics**

PK analyses will be performed on the PK Set.

Descriptive statistics of encorafenib and LHY746 plasma concentrations will be reported and presented graphically. A non-compartmental analysis will be performed (e.g. AUC, C_{max} and C_{min}). Descriptive statistics of non-compartmental PK parameters of encorafenib and LHY746 will be reported. Details of the analyses will be included in the SAP or in a PK Analysis Plan.

If appropriate and possible, the generated PK data will be pooled with data from other studies to enrich the full population PK analysis planned for encorafenib. Details of these analyses will be provided in a specific standalone modelling plan. The modelling results will be reported in a separate report.

9.4.4. Other Analyse(s)

Concomitant medications/therapies will be summarized by Anatomical Therapeutic Classification System term and preferred term. Analyses will be performed on the SAF. The number of participants with at least one concomitant procedure will be tabulated by summarized by SOC and preferred term, if applicable.

Summaries will include those medications/therapies and therapeutic/diagnostic procedures starting on or after the start of study treatment or starting before the start of study treatment and continuing after the start of study treatment.

Any other medication or procedure starting and ending before the first study treatment administration will be listed.

Other analyses will be described in the SAP.

9.5. Compliance

Compliance is described in Section 6.4.

9.6. Interim/Initial Analyses

There are no interim analyses planned.

9.7. Trial Steering Committee

The TSC will analyse 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.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines.
  - Applicable ICH GCP Guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator's Brochure and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants. In that case, an amendment will be submitted within the period defined by local regulations.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable) and all other applicable local regulations.
- The screening of participants does not start before the approval of the IRB/IEC has been obtained and the study authorized by the competent authority (or notified to the competent authority, depending on the national regulations).

10.1.2. Early Study Termination

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the competent authorities and any Contract Research Organizations (CRO[s]) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.2.1. Early Study Termination decided by the Sponsor

The sponsor may discontinue the study at any time for any of the following reasons:

- Emerging adverse events of such a serious nature that continuation of the study becomes unacceptable.
- Recruitment rate too low to expect completion of the study in its present form within the period foreseen for inclusions.
- Deviations from ICH GCP and/or regulations.
- Decision to stop development of the study treatment.

If the study is prematurely discontinued, all study data must be returned to Pierre Fabre Médicament. In addition, the study site must conduct final disposition of all unused study treatments in accordance with study procedures.

10.1.2.2. Early Study Termination decided by the Competent Authorities

The competent authorities may suspend or prohibit a study if it considers that the conditions of authorization are not being met or has doubt about the safety or scientific validity of the study.

10.1.3. Financial Disclosure

Investigators and co-investigators will provide the sponsor with sufficient, accurate financial information (as requested) to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate competent authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

The funding of research is supported by the sponsor (e.g. investigator fees, study costs, participant compensation for travel expenses).

By signing the protocol, the investigator declares no conflict of interest.

10.1.4. Informed Consent Process

- Written information about the study must be given to each participant and/or their legally authorized representative before his/her decision to participate or abstain from participation. This information is based on the elements set out in the Declaration of Helsinki and ICH GCP. It must also describe the measures taken to safeguard participant's privacy and protection of personal data, according to the European Union (EU) General Data Protection Regulation (2016/679).
- The investigator or designated study site personnel will explain the nature of the study, including the restraints and risks, to the participant or his/her legally authorized representative and answer all questions regarding the study. They will be given a sufficient time to consider the study before consenting.
- Participants must be informed that taking part in the study is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, the IRB/IEC or study site and EU General Data Protection Regulation (2016/679). Participants will provide written informed consent before any study-specific procedures are carried out.
- The medical records must include statements that the applicable written informed consent was obtained for screening and the dates obtained. The investigator or his/her designee obtaining the informed consent must also sign the ICFs.
- The participant must be reconsented to confirm his/her agreement to continue participating if the written information is amended during the study due to new information becoming available that may be relevant to the participant's willingness to continue participating or due to amendments to the protocol.
- Participants that are re-screened must also be re-consented.
- The information and consent documents are prepared in duplicate: the original copy is kept by the investigator and the other copy is given to the participant.
- As soon as consent is signed, the participant will be given a personal card to be kept all along the study duration and providing the following information: participant's name, sponsor's name, study code, (if applicable), date of start and expected date of end of the study (if applicable), complete address of the study site with the name and emergency phone number of the Investigator.
- In the event of pregnancy during the study additional informed consent will be sought (required within 72 hours) from the pregnant female (female study participant or partner of a male study participant) to allow the investigator to follow the pregnancy to outcome and to provide pregnancy information to the sponsor.

10.1.5. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law and EU General Data Protection Regulation (2016/679). The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the ICF.

The participant must be informed that his/her medical records may be examined by clinical quality assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members and by inspectors from competent authorities.

10.1.6. Communication with Sites

Sites will be updated regularly about study status. Relevant information and important decisions regarding the study will be communicated to all sites in parallel in writing in a timely manner.

In case of emergency requiring implementation of urgent measures with regards to participant safety, the sites will first be contacted by telephone by the sponsor medical monitor or designee, with the information confirmed in writing. A Safety Monitoring Plan will be also written with regards to SAE management and communication.

10.1.7. Dissemination of Clinical Study Data

Information concerning the study, patent applications, processes, scientific data or other pertinent information is confidential and remains the property of the sponsor. The investigator may use this information for the purposes of the study only.

It is understood by the investigator that the sponsor will use information obtained in this clinical study in connection with the clinical development program and therefore may disclose it as required to other clinical investigators and to regulatory authorities. In order to allow the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide complete test results and all data obtained during this study to the sponsor.

Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with written consent from the sponsor.

Clinical Study Report:

Data analysis and Clinical Study Report writing are the sponsor's responsibility.

Upon completion of the data analysis, a final report, including a review of the objectives and methods, a presentation and discussion of the results are drawn up according to ICH Guidelines (Structure and Content of Clinical Study Reports, ICH E3, CPMP/ICH/137/95).

The report is a clinical, statistical and PK integrated report. It must be signed by the sponsor's medically qualified representative signatory and the co-ordinating investigator.

Study Results Communication:

Within a maximum period of 12 months after study completion, global results of the research are communicated to the investigator.

The participant can ask the investigator for the results, according to local regulations.

For clinical studies that are part of a marketing authorization application, the results have to be published on the Chinese website www.chinadrugtrials.org.cn within 12 months of completion of the clinical study (at a minimum, the clinical study results information shall include synopsis content of the Clinical Study Report as specified in ICH E3) as per Center of Drug Evaluation regulation "Regulations for the registration and information publicity of drug clinical trials" (2020 NO. 9) and on the European Medicines Agency (EMA) website. In that case, the documents will be anonymized to ensure data protection of individuals according to legislation (EMA/90915/2016).

The final Clinical Study Report, if part of a Common Technical Document dossier, will be anonymized as part of data protection regulations for further public communication to the EMA gate.

A lay summary of the study results will be authored in local languages as part of the EU regulation 536/2014.

10.1.8. Data Quality Assurance

All participant data relating to the study will be recorded in an eCRF unless transmitted to the sponsor or designee electronically (e.g. central laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The sponsor assumes accountability for actions delegated to other individuals (e.g. CROs).

10.1.8.1. Audit

The investigator must permit study-related monitoring, audits, IRB/IEC review and competent authority inspections.

The purpose of a sponsor's audit, independent of and separate from monitoring or quality control activities, is to evaluate study conduct and compliance with the protocol, sponsor's standard operating procedures, ICH GCP and the applicable regulatory requirements. Audits may be conducted by the sponsor's Clinical Quality Assurance Department or designee at each relevant location where activities dedicated to the clinical study are performed: for example at sponsor's site(s), at the investigational site(s), at CRO(s) site(s) and laboratory(ies) if applicable. All study-related documentation must be directly accessible to auditors. The practical conditions for the audit are discussed between the auditees and the sponsor's Clinical Quality Assurance Department or designee.

10.1.8.2. Inspection

The competent authority may inspect any study site or the sponsor during the course of the study or after its completion, to verify the conduct of the study and quality of the data. The investigator must agree to provide direct access to source documents.

10.1.8.3. Data Management

The sponsor or designee is responsible for the data management of this study, including quality checks of the data. Data management will be subcontracted to a CRO under the supervision of the sponsor's data manager of the Pierre Fabre Médicament Biometry Department. All clinical data related to the study will be collected and saved in a computerized database according to the procedures in Appendix 10.1.8.3.1 to Appendix 10.1.8.3.6. Full details are provided in the Data Management Plan.

10.1.8.3.1. Electronic Case Report Form

An eCRF will be developed for this study. The eCRF (Medidata Rave®) will be used to record all participant data required by the protocol. The hosting of this web-based electronic data capture will be subcontracted to Medidata Solutions, Inc.

The eCRF should be compliant with local regulations, compliant with 21CFR Part 11, fully validated and include an access control and a traceability system for data corrections (audit trail).

Before the start of the study, the investigator will complete a Delegation of Significant Study-related Duties Form. The signature and initials of all persons in charge of eCRF completion should be recorded on this form. Each person involved in eCRF completion, review, correction and/or validation will be trained and then will have an individual login and access code to the eCRF. An eCRF user guide will be available for investigators/study site personal involved in eCRF completion and CRAs.

Data from study assessments and procedures outlined in Section 8 will be recorded in the source documents and the eCRF by the investigator and designated study site personnel. All information entered into the eCRF will be recorded from source documents. The investigator is responsible for the management and accuracy of the information entered into the eCRF.

An eCRF must be completed for each participant enrolled in the study (i.e. ICF signed).

10.1.8.3.2. Central/External Data

Results of local laboratory testing will be entered into the eCRF.

The following electronic data are not reported in the eCRF by the investigator and will be transferred to data management for validation and integration into the study database according to the specifications given by the data manager. These data will be captured and handled in accordance with ICH GCP guidelines:

- Centrally analyzed PK samples:

  Actual dates and times of blood collections will be entered in the eCRF. Validated results from bioanalysis of encorafenib concentrations in plasma will be transmitted by the third-party bioanalytical laboratory to the subcontractor in charge of PK analysis. The encorafenib concentrations and final PK parameters will be uploaded in the final database from an electronic data file respectively provided by the bioanalytical laboratory and the subcontractor.

10.1.8.3.3. Data Cleaning

Manual and electronic edit checks used for data cleaning are described in the study Data Validation Plan. Upon approval, the edit checks and listings will be programmed. The CRO data management will follow the cleaning of the data over the course of the study. The investigator will be asked to resolve queries by making changes directly into the eCRF. The system's automatic audit trail will record the date, time and author of the changes.

10.1.8.3.4. Data Coding

Adverse events, concomitant diseases, concomitant therapeutic/diagnostic procedures and medical/surgical histories will be coded using MedDRA (latest version in use) and prior and concomitant medications will be coded using the World Health Organization (WHO) DRUG GLOBAL dictionary (latest version in use), plus the respective user guides and sponsor specific guidelines. The coding will be validated by a CRO physician and the sponsor's medical monitor.

10.1.8.3.5. Database Lock

Analysis will be based either on database lock or database snapshot.

A snapshot consists of a stable view of the data i.e. an extract of the database done at a specific timepoint. The specific timepoint will be defined in the TSC Charter as well as the list of critical variables.

As data will not be locked in the eCRF, entry of additional data and changes in eCRF will be deemed possible after the timepoint the snapshot was made. These changes will not be tracked.

All snapshots will be stored in SAS® format on a sponsor-dedicated secured server.

The validated database will be locked upon request of the sponsor's data manager following the completion of all steps required, i.e. entry, reception and check of all data, resolution of all queries, validation of the coding, clinical and safety databases reconciliation and data review/Validation Committee meeting performed.

Subsequent changes to the database will then only be made only by written agreement of the sponsor.

10.1.8.3.6. Data Storage

Data, as well as their modifications, will be saved and kept available upon request of the sponsor. The sponsor's data manager will assume storage of the locked clinical database in SAS® format on a secured server.

Electronic capture of all eCRFs will be sent in portable document format (PDF) format to the sponsor and then stored on a dedicated secured server by the sponsor.

A CD-ROM (or similar storage support) containing the PDF version of all eCRFs of the site (including audit trail) will be archived by the study site.

10.1.8.4. **Study Monitoring**

Monitoring details describing strategy (e.g. risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of non-compliance issues and monitoring techniques (central, remote or on-site monitoring) are provided in Monitoring Plan.

Representatives of the sponsor will perform ongoing source data verification to confirm that data entered into the eCRF by authorized study site personnel are accurate, complete and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP and all applicable regulatory requirements.

On-site visits will be carried out by a representative of the sponsor (CRA and/or study manager) before study initiation and at regular intervals (as defined in the Monitoring Plan) throughout the study. Additional visits and communication by telephone, fax or meeting may be performed if necessary. Any site visit performed by representatives of the sponsor will be recorded in the investigator's site file.

10.1.8.4.1. Site Pre-selection Visit

Before selecting a study site for the study, a visit will be carried out by the CRA and/or the study manager to ensure that the investigator has the necessary capacities (availability, recruitment, environment), technical means and study site personnel to carry out the study. This includes a check that the study site has all the necessary equipment to conduct the study (e.g. sample processing and storage, study treatment storage, ECGs) and where applicable, appropriate calibration has been performed.

10.1.8.4.2. Initiation Visit

Before the start of the study at all investigation sites, an initiation visit will be carried out by the CRA to check at least that:

- The investigator has received:
  - The protocol, administrative and financial agreement signed by all parties.
  - The written statement of IRB/IEC approval and the list of its members and their functions.
  - The written statement of competent authority approval.
- The original signed and dated curriculum vitae of the investigator(s) has been collected.
- Local laboratory normal ranges have been collected.
- All study materials are available at the study site.
- All participants agree with the monitoring procedures and know the study procedures.
- All participants are aware of a possible audit or inspection.

The CRA will also provide training on the study protocol requirements and study specific procedures.

10.1.8.4.3. Routine Monitoring Visits

Throughout the study, regular monitoring visits will be carried out by the CRA to check compliance with ICH GCP, participant informed consent, strict application of the protocol, conformity of the data entered in the eCRF with the source documents and ensure its correct completion, adverse event reporting, proper retention, storage and management of the study treatment as well as the source and other study-related documents.

10.1.8.4.4. Close-out Visit

At the end of the study, a final visit will be carried out by the CRA to:

- Verify that the eCRFs are complete and all queries are resolved.

- Control the accountability of intact and used study treatment units and destroy or return them to Pierre Fabre Médicament, or delegated warehouse, for destruction.
- Obtain the last data clarifications and/or solutions if any.
- Make an on-site review of all study documentation and complete it if necessary.
- Remind the investigator of his regulatory obligations, study document archiving process and duration.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion unless local regulations or study site policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.9. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the study site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Current medical records must also be available.
- Definition of what constitutes source data can be found in the Source Data Agreement.

In accordance to the requirements of ICH GCP, all sponsor representatives (study manager, CRA and auditors) have to be given a direct access to all source and study data to perform quality monitoring/audit, thus ensuring accuracy and completeness of data.

Investigators are reminded that all sponsor representatives keep professional confidentiality with regards to the participant data.

10.1.10. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed (see Appendix 10.1.8.4.4).

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures or ICH GCP guidelines.
- Inadequate recruitment of participants by the investigator.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IRB/IEC, the competent authorities, and any CROs used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.11. Publication Policy

The results of this study, which are the property of the sponsor and considered as confidential, may be published or presented at scientific meetings. The investigator must agree to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments. Publication or communication relating to results of the study, in written or oral form, shall comply with the following provisions:

- Any communication or publication project must be provided to the sponsor for review at least 60 days before the expected date of submission to the intended publisher or of planned presentation.
- If requested by the sponsor, the communication or publication project shall be withheld for an additional 60 days, to allow the filing of a patent application or to allow the sponsor to take any measures he deems appropriate to establish and preserve his proprietary rights.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a co-ordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. In case of a multicenter study, the sponsor shall determine the author’s list and their appearance order within the publication project according to their participation in the design of the protocol as well as their recruitment of eligible and analysable participants.

10.1.12. Insurance Policy

In accordance with the provisions of the law and ICH GCP, the sponsor has an insurance policy intended to guarantee against possible damage resulting from the research.

The studies and/or experiments performed on behalf of the sponsor are specifically and expressly guaranteed.

It is advisable to underline that non-compliance with the research legal conditions is a cause for guarantee exclusion.

Unintentional infringements and vicarious liability are covered by the sponsor's insurance**.**

10.2. Appendix 2: Contraceptive Guidance

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. The following guidance is adapted from the guidelines of the Clinical Trials Facilitation Group [CTFG 2014].

10.2.1. Definition of a Woman of Childbearing Potential and Fertile Men

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (e.g. amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study treatment, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal.
2. Premenopausal female with one of the following:
    - Documented hysterectomy.
    - Documented bilateral salpingectomy.
    - Documented bilateral oophorectomy.

    For participants with permanent infertility due to an alternate medical cause other than the above, (e.g. mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

    Note: Documentation can come from the study site personnel's: review of the participant's medical records, medical examination or medical history interview.
3. Postmenopausal female:
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - High FSH levels in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one measurement is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

For the purpose of this guidance, a man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

10.2.2. Contraceptive Guidance

For the purpose of this guidance, methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral.
  - Intravaginal.
  - Transdermal.
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral.
  - Injectable.
  - Implantable.
- Intrauterine device.
- Intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Vasectomized partner.
- Sexual abstinence.

Acceptable birth control methods that result in a failure rate of more than 1% per year include:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action.
- Male or female condom with or without spermicide.
- Cap, diaphragm or sponge with spermicide.

NOTE: Due to the potential of encorafenib to induce CYP3A4, hormonal agents (including but not limited to birth control patch, vaginal ring, oral, injectable or implanted contraceptives) are permissible only when combined with other highly effective or acceptable methods of contraception.

10.3. Appendix 3: Non-exhaustive List of Concomitant Medications

These lists are not all inclusive. Please refer to the following websites provided for further guidance:

- https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers
- https://drug-interactions.medicine.iu.edu/MainTable.aspx

Table 11: List of Cytochrome P450 Substrates to be used with Caution (CYP2C8, CYP2C9, CYP2C19 and CYP3A)

CYP2C8	CYP2C9	CYP2C19	CYP3A	
Amodiaquine	Acenocoumarol	Clopidogrel	Alfentanil[a],[b]	Ergotamine[b]
Cerivastatin	Celecoxib	Diazepam	Alpha-dihydroergocryptine[a]	Everolimus[a]
Repaglinide	Diclofenac	Esoprazole	Alprazolam	Felodipine[a]
Rosiglitazone	Glipizide	Lansoprazole	Amlodipine	Fentanyl[b]
Torasemide	Irbesartan	Moclobemide	Aplaviroc	Fluticasone[a]
	Losartan	Omeprazole	Aprepitant[a]	Indinavir[a]
	Phenytoin[b]	Pantoprazole	Aripiprazole	Lopinavir[a]
	Piroxicam	Phenobarbitone	Atorvastatin	Lovastatin[a]
	S-ibuprofen	Phenytoin[b]	Boceprevir	Maraviroc[a]
	Sulfamethoxazole	Proguanil	Brecanavir	Midazolam[a]
	Tolbutamide	Rabeprazole	Brotizolam[a]	Nifedipine
	Torasemide	S-mephenytoin	Budesonide[a]	Nisoldipine
			Buspirone[a]	Nitrendipine
			capravirine	Perospirone[a]
			casopitant	Quinine
			Conivaptan[a]	Saquinavir[a]
			Cyclosporine[b]	Sildenafil[a]
			Darifenacin[a]	Simvastatin[a]
			Darunavir[a]	Sirolimus[a],[b]
			Diazepam	Telaprevir
			Diergotamine[b]	Tipranavir[a]
			Diltiazem	Tolvaptan
			Ebastine[a]	Triazolam[a]
			Eletriptan[a]	Verapamil
			Eplerenone[a]	

Abbreviations: CYP = cytochrome P450; FDA = Food and Drug Administration; US = United States.

*Table was compiled from the Indiana University School of Medicine's "Clinically Relevant" table, a list by the US FDA) (http://.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm) and the University of Washington's Drug Interaction Database. The list is not necessarily exhaustive of every possible substrate.

[a] Sensitive substrates: Drugs whose plasma area under concentration-time curve values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor of the respective enzyme.

[b] Substrates with narrow therapeutic index: Drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g. Torsade de Pointes).

Table 12: List of Cytochrome P450 substrates to be used with Caution (CYP2B6)

CYP2B6*
bupropion[a]
Cyclophosphamide
Efavirenz[a]
Ifosfamide
Methadone
Thiotepa
Abbreviations: CYP = cytochrome P450; FDA = Food and Drug Administration; US = United States. *Table was compiled from the Indiana University School of Medicine's "Clinically Relevant" table, a list by the US FDA (http:// fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499 htm) and the University of Washington's Drug Interaction Database. The list is not necessarily exhaustive of every possible substrate. [a] Sensitive substrates: The area under the concentration-time curves of these substrates were not increased by 5-fold or more with a CYP2B6 inhibitor, but they represent the most sensitive substrates studied with available inhibitors evaluated to date.

Table 13: List of Inhibitors of Uridine Diphosphate-glucuronosyl Transferase 1A1 to be used with Caution

Inhibitors of UGT1A1	Atazanavir, erlotinib, flunitrazepam, gemfibrozil, indinavir, ketoconazole, nilotinib, pazopanib, propofol, regorafenib, sorafenib
Abbreviations: UGT1A1 = Uridine diphosphate-glucuronosyl transferase.	

Table 14: Moderate Cytochrome P450 3A4 inhibitors to be Administered with Caution when co-administered with Encorafenib

Ciprofloxacin	Erythromycin
Fluconazole	Amprenavir
Verapamil	Imatinib
Atazanavir	Schisandra sphenanthera
Aprepitant	Casopitant
Cyclosporine	Cimetidine
Tofisopam	Dronedarone
Fosamprenavir	Darunavir
Diltiazem	
Reproduced from http://.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499 htm	

Table 15: Breast Cancer Resistance Protein and P-glycoprotein inhibitors/inducers to be used with caution

Transporter	Gene	Inhibitor[a]	Induce[b]
BCRP	ABCG2	Cyclosporine, elacridar (GF120918), eltrombopag, gefitinib	Not known
P-gp	ABCB1	Amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir and ritonavir, quercetin, quinidine, ranolazine, verapamil	Avasimibe, carbamazepine, phenytoin, rifampin, St John's wort, tipranavir/ritonavir

Abbreviations: BCRP = breast cancer resistance protein; P-gp = P-glycoprotein.

Reproduced from http://.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499 htm

[a] Inhibitors listed for P-gp are those that showed >25% increase in digoxin area under the concentration-time curve or otherwise indicated if substrate is other than digoxin.

[b] Inducers listed for P-gp are those that showed >20% decrease in digoxin area under the concentration-time curve orotherwise indicated if substrate is other than digoxin.

Table 16: Substrates of Breast Cancer Resistance Protein, Organic Anionic Transporters, Organic Anion Transporting Polypeptides, Organic Cationic Transporters and P-glycoprotein, to be administered with caution

BCRP	Imatinib, irinotecan, lapatinib, methotrexate, mitoxantrone, rosuvastatin, sulfasalazine, topotecan
P-gp	Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan
OCT2	Amantadine, amiloride, cimetidine, dopamine, famotidine, memantine, metformin, pindolol, procainamide, ranitidine, varenicline, oxaliplatin
OAT1	Adefovir, captopril, furosemide, lamivudine, methotrexate, oseltamivir, tenofovir, zalcitabine, zidovudine
OAT3	Acyclovir, bumetanide, ciprofloxacin, famotidine, furosemide, methotrexate, zidovudine, oseltamivir acid, (the active metabolite of oseltamivir), penicillin G, pravastatin, rosuvastatin, sitagliptin
OATP1B1	Atrasentan, atorvastatin, bosentan, ezetimibe, fluvastatin, glyburide, SN-38 (active metabolite of irinotecan), rosuvastatin, simvastatin acid, pitavastatin, pravastatin, repaglinide, rifampin, valsartan, olmesartan
OATP1B3	Atorvastatin, rosuvastatin, pitavastatin, telmisartan, valsartan, olmesartan

Abbreviations: BCRP= breast cancer resistance protein; OAT = organic anion transporter, organic anion transporting polypeptide; organic cationic transporter; P-gp = P-glycoprotein.

Reproduced from http://.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499 htm

Table 17: List of Potential QT Prolonging Drugs

Drug	QT Risk	Comment
Alfuzosin	Possible risk	
Amantadine	Possible risk	
Amiodarone	Known risk	Females>Males, TdP risk regarded as low
Amitriptyline	Conditional risk	Risk of TdP with overdosage. Substrate of CYP2C19
Arsenic trioxide	Known risk	
Astemizole	Known risk	Not available in China. Substrate for CYP3A4
Atazanavir	Possible risk	
Azithromycin	Possible risk	Rare reports
Bepridil	Known risk	Females>Males
Chloral hydrate	Possible risk	
Chloroquine	Known risk	
Chlorpromazine	Known risk	
Ciprofloxacin	Conditional risk	Drug metabolism inhibitor; risk for drug interactions
Cisapride	Known risk	Substrate for CYP3A4
Citalopram	Known risk	
Clarithromycin	Known risk	Substrate for CYP3A4
Clomipramine	Conditional risk	
Clozapine	Possible risk	
Desipramine	Conditional risk	Risk of TdP with overdosage
Diphenhydramine	Conditional risk	Risk of QT increase/TdP in overdosages
Disopyramide	Known risk	Females>Males
Dofetilide	Known risk	
Dolasetron	Possible risk	
Domperidone	Known risk	
Doxepin	Conditional risk	
Dronedarone	Possible risk	Substrate for CYP3A4
Droperidol	Known risk	
Eribulin	Possible risk	
Erythromycin	Known risk	Females>Males. Substrate for CYP3A4
Escitalopram	Possible risk	
Famotidine	Possible risk	
Felbamate	Possible risk	
Fingolimod	Possible risk	
Flecainide	Known risk	

Drug	QT Risk	Comment
Fluconazole	Conditional risk	Drug metabolism inhibitor; risk for drug interactions
Fluoxetine	Conditional risk	
Foscarnet	Possible risk	
Fosphenytoin	Possible risk	
Galantamine	Conditional risk	
Gatifloxacin	Possible risk	
Gemifloxacin	Possible risk	
Granisetron	Possible risk	
Halofantrine	Known risk	Females>Males
Haloperidol	Known risk	When given intravenously or at higher than recommended doses, risk of sudden death, QT prolongation and torsades increases. Substrate for CYP3A4
Ibutilide	Known risk	Females>Males
Imipramine	Conditional risk	Risk of TDP in overdosage
Indapamide	Possible risk	
Isradipine	Possible risk	
Itraconazole	Conditional risk	Drug metabolism inhibitor-risk for drug interactions
Ketoconazole	Conditional risk	Drug metabolism inhibitor
Levofloxacin	Possible risk	
Levomethadyl	Known risk	Not available in the US.
Lithium	Possible risk	
Mesoridazine	Known risk	
Methadone	Known risk	Females>Males. Substrate for CYP3A4
Moexipril/HCTZ	Possible risk	
Moxifloxacin	Known risk	
Nicardipine	Possible risk	
Nortriptyline	Conditional risk	
Octreotide	Possible risk	
Ofloxacin	Possible risk	
Ondansetron	Possible risk	
Oxytocin	Possible risk	
Paliperidone	Possible risk	
Paroxetine	Conditional risk	
Pentamidine	Known risk	Females>Males
Perflutren lipid microspheres	Possible risk	
Pimozide	Known risk	Females>Males. Substrate for CYP3A4

Drug	QT Risk	Comment
Probucol	Known risk	
Procainamide	Known risk	
Protriptyline	Conditional risk	
Quetiapine	Possible risk	Substrate for CYP3A4
Quinidine	Known risk	Females>Males. Substrate for CYP3A4
Ranolazine	Possible risk	
Risperidone	Possible risk	
Ritonavir	Conditional risk	Substrate for CYP3A4
Roxithromycin	Possible risk	
Sertindole	Possible risk	
Sertraline	Conditional risk	
Solifenacin	Conditional risk	
Sotalol	Known risk	Females>Males
Sparfloxacin	Known risk	
Tacrolimus	Possible risk	Substrate for CYP3A4
Telithromycin	Possible risk	Substrate for CYP3A4
Terfenadine	Known risk	Substrate for CYP3A4
Thioridazine	Known risk	
Tizanidine	Possible risk	
Trazodone	Conditional risk	Substrate for CYP3A4
Trimethoprim-Sulfa	Conditional risk	
Trimipramine	Conditional risk	
Vandetanib	Known risk	
Vardenafil	Possible risk	Substrate for CYP3A4
Venlafaxine	Possible risk	
Voriconazole	Possible risk	
Ziprasidone	Possible risk	

Abbreviations: CYP = cytochrome P450; TDP = Torsades de Pointes; US = United States.
Additional agents can be found at https://www.crediblemeds.org
Classification according to the Qtdrugs.org Advisory Board of the Arizona CERT.

Table 18: Strong Cytochrome P450 3A4 Inhibitors and Strong/moderate Cytochrome P450 Inducers to be Prohibited when Co-administered with Encorafenib

Strong Inhibitors	
boceprevir	nefazodone
Clarithromycin	Nelfinavir
Conivaptan	Posaconazole
Indinavir	Ritonavir
Itraconazole	Saquinavir
Ketoconazole	Telithromycin
Lopinavir	Troleandomycin
Telaprevir	Grapefruit juice (citrus paradisi fruit juice)
Mibefradil	Voriconazole
Strong Inducers	
Avasimibe	Rifampin
Carbamazepine	St. John's wort
Phenytoin	
Moderate Inducers	
Bosentan	Efavirenz
Etravirine	Modafinil
Reproduced from https://fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499 htm	

10.4. Appendix 4: Dose Modifications for Encorafenib-related Adverse Events

Table 19: Recommended Dose Modifications for Encorafenib-related Adverse Events

Worst Toxicity NCI CTCAE Version 4.03 Grade (unless otherwise specified)	Dose Modification for Encorafenib
Eye disorders - Posterior uveitis (including iritis and iridocyclitis) **Any visual acuity impairment at screening should be documented and should be considered as baseline.**	
Grade 1 or 2	Treat with specific (e.g. topical) ocular therapy. If uveitis does not respond, interrupt dosing of encorafenib and repeat ophthalmic monitoring including visual acuity assessment within 10 days. If resolved to baseline or ≤Grade 1 resume study treatment at the same dose. If posterior uveitis lasts >6 weeks, permanently discontinue encorafenib.
Grade 2	Treat with specific (e.g. topical) ocular therapy. If uveitis does not respond, interrupt dosing of encorafenib and repeat ophthalmic monitoring including visual acuity assessment within 10 days. If resolved to ≤Grade 1, resume study treatment at one reduced dose level of encorafenib[a]. If posterior uveitis lasts >6 weeks, permanently discontinue encorafenib and ophthalmic monitoring should be repeated.
Grade 3	Interrupt dosing of encorafenib and repeat ophthalmic monitoring including visual acuity assessment within 10 days. If resolved to ≤Grade 1, resume study treatment at one reduced dose level of encorafenib[a]. If posterior uveitis lasts >6 weeks, permanently discontinue encorafenib and ophthalmic monitoring should be repeated.
Grade 4	Permanently discontinue encorafenib and immediately follow-up with ophthalmic monitoring[b]
Liver-related adverse events	
Grade 1 AST or ALT >ULN to 3 × ULN	Maintain dose level of encorafenib.
Grade 2 AST or ALT >3 to 5.0 × ULN or 3 × baseline value[c] **AND** **blood total bilirubin** **≤2.0 × ULN**	Maintain dose level of encorafenib. If not resolved in ≤14 days, interrupt dose of encorafenib until resolved to Grade≤1 (or Grade ≤2 in case of liver metastasis), then resume study treatment at current dose level of encorafenib. <u>If additional occurrence:</u> Interrupt dosing of encorafenib until resolved to Grade ≤1 (or Grade ≤2 in case of liver metastasis), then resume study treatment at one reduced dose level[a] of encorafenib.
AST or ALT 3.0 to 5.0 × ULN **AND** **blood total bilirubin** **>2.0 × ULN**	Interrupt dosing of encorafenib until resolved to Grade ≤1, then: • If resolved in ≤7 days, resume study treatment at one reduced dose level[a] of encorafenib. • If not resolved in ≤7 days, permanently discontinue encorafenib.

Worst Toxicity **NCI CTCAE Version 4.03 Grade (unless otherwise specified)**	**Dose Modification for Encorafenib**
Grade 3 AST or ALT >5.0 to 8.0 × ULN **AND** **blood total bilirubin** **≤2.0 × ULN**	Interrupt dosing of encorafenib until resolved to Grade ≤1 (or Grade ≤2 in case of liver metastasis), then: • If resolved in ≤14 days, resume study treatment at current dose level of encorafenib. • If not resolved in ≤14 days, resume study treatment at one reduced dose level[a] of encorafenib. If additional occurrence: Interrupt dosing of encorafenib until resolved to Grade ≤1 (or Grade ≤2 in case of liver metastasis), then resume treatment at one reduced dose level[a] of encorafenib.
AST or ALT >8 × ULN AND blood total bilirubin ≤2.0 × ULN	Permanently discontinue encorafenib.
AST or ALT >5.0 × ULN AND blood total bilirubin >2.0 × ULN	Permanently discontinue encorafenib.
Grade 4 AST or ALT >20.0 × ULN	Permanently discontinue encorafenib.
Cardiac investigation – Prolongation of QT interval QTcF value	
QTcF >500 ms during treatment and change from pre-treatment value remains ≤60 ms	Participants should have regular ECG monitoring (continuous where appropriate) until an adequately trained physician (such as a cardiologist or internist) has reviewed the data. Electrolyte abnormalities including magnesium should be corrected and cardiac risk factors for QT prolongation (e.g. congestive heart failure, bradyarrhythmias) should be controlled. 1st occurrence: Temporarily interrupt dosing of encorafenib until QTcF <500 ms. Then resume treatment at one reduced dose level[a] of encorafenib. 2nd occurrence: Temporarily interrupt dosing of encorafenib until QTcF <500 ms. Then resume treatment at one reduced dose level[a] of encorafenib. If a participant restarts encorafenib following resolution of Grade 3 QTcF prolongation event, the participant should be evaluated with triplicate predose ECGs on Day 1 of the next cycle, followed by a single postdose ECG and a single predose ECG on Day 15, as well as single predose ECG and a single postdose ECG on Day 1 of the subsequent cycle (2nd cycle after the Grade 3 QT prolongation event). 3rd occurrence: Permanently discontinue encorafenib.
QTcF increase during treatment is both >500 ms and >60 ms change from pre-treatment values	Participants should have regular ECG monitoring (continuous where appropriate) until an adequately trained physician (such as a cardiologist or internist) has reviewed the data. Electrolyte abnormalities including magnesium should be corrected and cardiac risk factors for QT prolongation (e.g. congestive heart failure, bradyarrhythmias) should be controlled. Permanently discontinue encorafenib.

Worst Toxicity **NCI CTCAE Version 4.03 Grade (unless otherwise specified)**	**Dose Modification for Encorafenib**
Rash	
Grade 1	Maintain dose level of encorafenib. Initiate Initial Rash Treatment regimen if it was not already started and rash should be closely monitored.
Grade 2	Maintain dose level of encorafenib. Initiate Initial Rash Treatment regimen if it was not already started and rash should be closely monitored. Reassess within ≤14 days. If rash worsens or does not improve, interrupt dosing of encorafenib until resolved to Grade≤1. Then resume study treatment at current dose level of encorafenib. For dermatitis acneiform, treatment with encorafenib may be maintained if, in the judgment of the investigator, the rash is considered to be unrelated to encorafenib. If treatment with encorafenib was maintained and no improvement within 8 days, interrupt dosing of encorafenib.
Grade 3	1st occurrence: Interrupt dosing of encorafenib until resolved to Grade≤1. Reassess weekly. Then resume treatment at current dose level of encorafenib. Consider referral to dermatologist and manage rash per dermatologist's recommendation. 2nd occurrence: Interrupt dosing of encorafenib until resolved to Grade≤1. Then resume study treatment at one reduced dose level[a] of encorafenib unless in the judgment of the investigator, the rash is considered to be unrelated to encorafenib then study treatment can be resumed at the same dose level. Consider referral to dermatologist and manage rash per dermatologist's recommendation.
Grade 4	Permanently discontinue encorafenib[e].
HFSR/PPE syndrome[d]	
Grade 1	Maintain dose of encorafenib. Promptly institute supportive measures, such as topical therapy, for symptomatic relief. Give instruction on lifestyle modifications.
Grade 2	1st occurrence: Maintain dose of encorafenib and HFSR should be closely monitored. Promptly institute supportive measures, such as topical therapy, for symptomatic relief. Give instruction on lifestyle modifications. If no improvement ≤14 days, interrupt dosing of encorafenib until resolved to Grade ≤1. Resume treatment with encorafenib at current dose level. Continue supportive measures, such as topical therapy, for symptomatic relief. Give instruction on lifestyle modifications. Additional occurrence: Treatment with encorafenib may be maintained or interrupted based upon the investigator's discretion. Continue supportive measures, such as topical therapy, for symptomatic relief. Give instruction on lifestyle modifications. If dosing is interrupted, interrupt until resolved to Grade ≤1. Resume study treatment at the same dose level or one reduced dose level[a] of encorafenib at the investigator's discretion.

Worst Toxicity **NCI CTCAE Version 4.03 Grade (unless otherwise specified)**	**Dose Modification for Encorafenib**
Grade 3	1st to 3rd occurrence: Interrupt dosing of encorafenib until resolved to Grade ≤1. Promptly initiate supportive measures, such as topical therapy, for symptomatic relief. Give instruction on lifestyle modifications. Reassess the participant weekly. Then resume treatment at one reduced dose level[a] of encorafenib. Consider referral to dermatologist and manage HFSR per dermatologist's recommendation. >3rd occurrence: Interrupt dosing of encorafenib until resolved to Grade ≤1, decision to resume treatment with encorafenib at one reduced dose level[a] or permanently discontinue encorafenib should be based upon the investigator's discretion.
SCC, KA and any Other Suspicious Skin Lesion	
Grade ≤3	Maintain dose of encorafenib. Treatment of SCC, KA and any other suspicious skin lesion (e.g. new primary melanoma) should occur based upon study site standards.
Diarrhea. Treatment should be based on study site practice	
Uncomplicated Grade 1 or 2	Maintain dose of encorafenib.
Complicated Grade 1 or 2	Consider temporary interruption of encorafenib until resolved to Grade ≤1. Then resume treatment at current dose level.
Grade 3 or 4	Interrupt dosing of encorafenib until resolved to Grade ≤1. Then resume treatment at current dose level of encorafenib if, in the judgment of the investigator, the toxicity is considered to be unrelated to encorafenib, or at one reduced dose level[a].
Nausea/vomiting	
Grade 1 or 2	Maintain dose level of encorafenib. Promptly institute antiemetic measure.
Grade 3	Interrupt dosing of encorafenib until resolved to Grade ≤1. Then resume treatment at one reduced dose level[a] of encorafenib. Note: Interrupt dosing of encorafenib for ≥Grade 3 vomiting or Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetics (based on study site standards).
Grade 4	Permanently discontinue encorafenib[e].
All other adverse events (suspected to be related to encorafenib)	
Grade 1 or 2	If the event is a persistent Grade 2 adverse event not responsive to a specific therapy, consider interruption or reduction of encorafenib, as applicable
Grade 3	Interrupt dosing of encorafenib until resolved to Grade ≤1 or to pretreatment/baseline level. If the event resolves ≤21 days, then encorafenib may be resumed at one reduced dose level[a] based upon the investigator's discretion.
Grade 4	Permanently discontinue encorafenib[e].
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; HFSR = hand-foot skin reaction; KA = keratoacanthoma; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PPE = Palmar-plantar erythrodysesthesia; QTcF = QT interval corrected for heart rate using Fridericia's formula; SCC = squamous cell carcinoma; ULN = upper limit of normal. [a] Dose reduction below 150 mg QD is not allowed.	

Worst Toxicity NCI CTCAE Version 4.03 Grade (unless otherwise specified)	Dose Modification for Encorafenib
[b] Ophthalmic monitoring mandated for posterior uveitis: further evaluation with specialized retinal imaging in addition to basic assessment (e.g. best corrected visual acuity testing, slit lamp examination, intraocular pressure and dilated fundoscopy). Any diagnosis of retinal events must be supported by presence or absence of symptoms and visual acuity assessment as well as any other document findings. [c] For participants enrolled with liver metastases and baseline liver function test elevations. [d] Disorder characterized by redness, marked discomfort, swelling and tingling in the palms of the hands or the soles of the feet. [e] A participant with a Grade 4 adverse event may resume encorafenib at the lower dose level if the event recovers to Grade ≤1 within 28 days of discontinuing study treatment and, if in the opinion of the investigator and medical monitor, the event is not life-threatening and the participant can be managed and monitored for recurrence of the event. Any participants requiring a dose interruption of duration >28 days must discontinue encorafenib permanently.	

10.5. Appendix 5: Snellen Equivalence (Visual Acuity Conversion Chart)

Taken from Holladay 2004.

				Distance				Near					
					Snellen Equivalent								
Line Number	Visual Angle (min)	Spatial Frequency (Cyc/deg)	LogMAR	% Central Visual Efficiency	Feet 20/	Meter 6/	Decimal	% Central Visual Efficienty	Inches (14/)	Centimeters (35/)	Revised Jaeger Standard	American Point-Type	"M" Notation
−3	0.50	60.00	0.30	100	10	3.0	2.00	100	7.0	17.5	—	—	0.20
−2	0.63	48.00	0.20	100	12.5	3.8	1.60	100	8.8	21.9	—	—	0.25
−1	0.80	37.50	0.10	100	16	4.8	1.25	100	11.2	28.0	—	—	0.32
0	1.00	30.00	0.00	100	20	6.0	1.00	100	14.0	35.0	1	3	0.40
1	1.25	24.00	−0.10	95	25	7.5	0.80	100	17.5	43.8	2	4	0.50
—	1.50	20.00	−0.18	91	30	9.0	0.67	95	21.0	52.5	3	5	0.60
2	1.60	18.75	−0.20	90	32	9.6	0.63	94	22.4	56.0	4	6	0.64
3	2.00	15.00	−0.30	85	40	12.0	0.50	90	28.0	70.0	5	7	0.80
4	2.50	12.00	−0.40	75	50	15.0	0.40	50	35.0	87.5	6	8	1.0
—	3.00	10.00	−0.48	67	60	18.0	0.33	42	42.0	105.0	7	9	1.2
5	3.15	9.52	−0.50	65	63	18.9	0.32	40	44.1	110.3	8	10	1.3
—	3.50	8.57	−0.54	63	70	21.0	0.29	32	49.0	122.5	—	—	1.4
6	4.00	7.50	−0.60	60	80	24.0	0.25	20	56.0	140.0	9	11	1.6
7	5.00	6.00	−0.70	50	100	30.0	0.20	15	70.0	175.0	10	12	2.0
—	5.70	5.26	−0.76	44	114	34.2	0.18	12	79.8	199.5	11	13	2.3
8	6.25	4.80	−0.80	40	125	37.5	0.16	10	87.5	218.8	12	14	2.5
—	7.50	4.00	−0.88	32	150	45.0	0.13	6	105.0	262.5	—	—	3.0
9	8.00	3.75	−0.90	30	160	48.0	0.13	5	112.0	280.0	13	21	3.2
10	10.00	3.00	−1.00	20	200	60.0	0.10	2	140.0	350.0	14	23	4.0
11	12.50	2.40	−1.10	17	250	75.0	0.08	0	175.0	437.5	—	—	5.0
—	15.00	2.00	−1.18	16	300	90.0	0.07	0	210.0	525.0	—	—	6.0
12	16.00	1.88	−1.20	15	320	96.0	0.06	0	224.0	560.0	—	—	6.4
13	20.00	1.50	−1.30	10	400	120.0	0.05	0	280.0	700.0	—	—	8.0
16	40.00	0.75	−1.60	5	800	240.0	0.03	0	560.0	1400.0	—	—	16.0
20	100.00	0.30	−2.00	0	2000*	600.0	0.01	0	1400.0	3500.0	—	—	40.0
30	1000.00	0.03	−3.00	0	20000†	6000.0	0.001	0	14000.0	35000.0	—	—	400.0

Bold values are standard logMAR progression.
LogMAR = logarithm of the minimum angle of resolution
*20/2000 is equivalent to counting fingers @ 2 feet
†20/20000 is equivalent to hand motion @ 2 feet

10.6. Appendix 6: Study Treatment labelling

Study treatment unit kit box and blisters will be labelled in compliance with local requirements, according to the following rules:

Study Treatment unit kit box labelling:

a) Name and address of the sponsor
b) Pharmaceutical dosage form, route of administration, quantity of dosage units, name/identifier and strength/potency
c) Packaging batch number
d) Trial reference code allowing identification of the study (Protocol number)
e) Treatment number
f) Name of the investigator (will be added at time of shipment)
g) Directions for use (reference may be made to the IB or other explanatory document intended for the trial participant or person administering the product)
h) "FOR CLINICAL TRIAL USE ONLY"
i) Storage conditions
j) Expiry date as month/year (MM/YYYY) or (YYYY/MM)
k) "Keep out of reach and sight of children"

The kit box labelling contains a tear-off flap with the following information: Name of sponsor, Protocol number, Packaging batch number and Treatment number.

Study Treatment blisters:

a) Name of the sponsor
b) Pharmaceutical dosage form, quantity of dosage units, name/identifier and strength/potency
c) Packaging batch number
d) Protocol number
e) Treatment number
f) Expiry date as month/year (MM/YYYY) or (YYYY/MM)

Additional mentions will be added according to local authority requirements.

Symbols or pictograms may be included to clarify certain information mentioned above. Additional information, warnings and/or handling instructions may be displayed.

10.7. Appendix 7: Response Evaluation Criteria in Solid Tumors Version 1.1

Taken from Eisenhaur 2009.

10.7.1. 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 treatment 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 complete response (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 partial response (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.

10.7.2. Measurability of Tumor at Baseline

10.7.2.1. 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.

10.7.2.2. 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.

10.7.3. 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 Appendix 10.7.2.1).

10.7.3.1. 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 x 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').

10.7.3.2. **Response Criteria**

Tumor 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 3studies 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 fluorodeoxyglucose-positron emission tomography (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 20.

Table 20: 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 time point response. This would be most likely to happen in the case of PD.

Evaluation of Best Overall Response

The best overall response (BOR) is the best response across all timepoints recorded from the start of the study treatment until the end of treatment (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 posttreatment 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.

*For example, a participant who has SD at first assessment, PR at second assessment and PD on last assessment has a best overall response of PR. When SD is believed to be the best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best timepoint response, the participant's best response depends on the subsequent assessments. For example, a participant who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same participant lost to follow-up after the first SD assessment would be considered not evaluable.

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 treatment 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 treatment. Symptomatic deterioration is *not* a descriptor of an objective response: it is a reason for stopping study treatment. 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.

10.8. Appendix 8: Adverse Event Definitions

10.8.1. Definition of an Adverse Event

Adverse Event Definition
An adverse event is any untoward medical occurrence from signature of informed consent in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. NOTE: An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease (new or exacerbated) temporally associated with the use of study treatment.

Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (e.g. haematology, clinical chemistry or urinalysis) or other safety assessments (e.g. ECG, radiological scans, vital signs measurements), including those that worsen from ICF signature, considered clinically significant in the medical and scientific judgment of the investigator (i.e. not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after ICF signature even though it may have been present before the start of the study. • Signs, symptoms or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. The event of an overdose itself meets the definition of an adverse event and should be reported as an adverse event/SAE. • Progression of malignancy (including fatal outcomes), if documented by use of appropriate method as part of the efficacy assessment will be designated as progression of disease in the eCRF and should not be reported as adverse events unless a causal relationship to study treatment is suspected. • "Lack of efficacy", "disease progression" or "failure of expected pharmacological action" per se will not be reported as an adverse event/SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or SAE if they fulfil the definition of an adverse event/SAE. • Adverse events specifically related to subsequent anticancer therapy and hospitalizations necessary for the administration of such therapy before the 30-day safety follow-up visit.

Events NOT Meeting the Adverse Event Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g. endoscopy, appendectomy): the condition that leads to the procedure is the adverse event. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

Events NOT Meeting the Adverse Event Definition
• Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.8.2. Definition of a Serious Adverse Event

If an event is not an adverse event according to the definition in Section 10.8.1, then it cannot be an SAE even if serious conditions are met (e.g. hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:	
a	**Results in death**
b	**Is life-threatening** The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c	**Requires inpatient hospitalization or prolongation of existing hospitalization** • In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event. • Any hospitalization or prolongation of hospitalization due to the circumstances listed below will not be notified as a SAE to the sponsor by the investigator: - Planned (according to the protocol) medical/surgical procedure including 24 hours hospitalization after the first treatment administration. - Preparation for routine health assessment/procedure (e.g. routine colonoscopy). - Planned medical/surgical admission (planned before entry into the study; appropriate documentation is required). - Administrative or social reasons (e.g. lack of housing, economic inadequacy, care-giver respite, family circumstances).
d	**Results in persistent disability/incapacity** • The term disability means a substantial disruption of a participant's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e	**Is a congenital anomaly/birth defect**

A SAE is defined as any untoward medical occurrence that, at any dose:

f Other situations:

- Medical or scientific judgment should be exercized in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical treatment to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of drug dependency or drug abuse.

10.9. Appendix 9: Abbreviations

Abbreviation	Definition
Ab	Antibody
AIDS	Acquired Immunodeficiency Syndrome
Anti-CTLA-4	Antibody against the cytotoxic T-lymphocyte antigen
ATP	Adenosine Triphosphate
AUC	Area under the Curve
BCRP	Breast Cancer Resistance Protein
BOR	Best Overall Response
BRAF	B-RAF Proto-oncogene, Serine/threonine Kinase
BRAF V600	B-RAF Proto-oncogene, Serine/threonine Kinase V600 Mutant
BRAF V600E	B-RAF Proto-oncogene, Serine/threonine Kinase V600E Mutant
BRAF V600E/K	B-RAF Proto-oncogene, Serine/threonine Kinase V600E or K Mutant
CFR	Code of Federal Regulations
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	Maximum Concentration
C_{min}	Minimum Concentration
cORR	Confirmed Overall Response Rate
CR	Complete Response
CRA	Clinical Research Associate
CRO	Contract Research Organization
CT	Computed Tomography
CYP	Cytochrome P450
DDS	Dose-determining Set
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Co-operative Oncology Group
eCRF	Electronic Case Report From
EMA	European Medicines Agency
ERK	Extracellular Signal-related Kinase
EU	European Union
FDG-PET	Fluorodeoxyglucose-positron Emission Tomography
FSH	Follicle-stimulating Hormone
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus

Abbreviation	Definition
HCG	human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HFSR / PPE syndrome	Hand-foot Skin Reaction / Palmar-Plantar Erythrodysesthesia syndrome
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HRT	Hormone Replacement Therapy
ICF	Informed Consent Form
ICH	International Council on Harmonization
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IRT	Interactive Response Technology
LC/MS-MS	Liquid Chromatography Tandem Mass Spectrometry
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated Protein Kinase Kinase
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NMPA	National Medical Products Administration
NSCLC	Non-small Cell Lung Cancer
OAT	Organic Anionic Transporter
OATP	Organic Anion-transporting Peptide
OCT	Organic Cationic Transporter
ORR	Overall Response Rate[a]
OS	Overall Survival
PD	Progressive Disease
PDF	Portable Document Format
PET	Positron Emission Tomography
PFS	Progression-free Survival
P-gp	P-glycoprotein
PK	Pharmacokinetics
PO	Per Oral
PPE syndrome / HFSR	Palmar-Plantar Erythrodysesthesia syndrome / Hand-foot Skin Reaction
PR	Partial Response
QD	Once Daily
QTcF	QT interval corrected for pulse rate using Fridericia's formula
RAF	Proto-oncogene Serine/threonine-Protein Kinase
RAS	Rat Sarcoma Viral Oncogene Homologue
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid

Abbreviation	Definition
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAS®	Statistical Analysis Software
SD	Stable Disease
SOC	System Organ Class
SUSAR	Suspected, Unexpected, Serious Adverse Reaction
TEAE	Treatment emergent Adverse Event
$T_{1/2diss}$	Dissociation half-life
TSC	Trial Steering Committee
UGT	5'-diphospho-glucuronosyltransferase
ULN	Upper Limit of Normal
US	United States
WHO	World Health Organization
WOCBP	Women of Childbearing Potential
[a] This may also refered to as 'objective response rate' in some protocols or publications	

10.10. Appendix 10: Protocol Amendment History

Document version	Date of Issue	Type (subst / non subst)	Application area Global / Local (Country: C / Sites: S)	Country (ies) and site (s) concerned	Description of changes
Proto V1.0	23OCT2020	NA	Global	All	First version of the protocol
Proto V2.0	04AUG2021	Non substantial	Global	All	Bicarbonate assessments removed to the protocol according to sites practices in China.
Proto V3.0	30SEP2021	Non substantial	Global	All	Creatine Kinase assessment have been updated in Clinical Chemistry in accordance with the safety follow-up to perform during encorafenib treatment + clarification of active hepatitis definition according to cdc.gov + update to eligibility approval check, in IRT functionality, for clarification.

10.11.Sponsor Personnel

PII

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11. References

American Cancer Society. Cancer Facts & Figures 2012.
Atlanta: American Cancer Society; 2012.

Ascierto PA, McArthur GA, Dréno B et al.
Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial.
Lancet Oncol. 2016; 17: 1248-1260.

Baik CS, Myall NJ, Wakelee HA.
Targeting BRAF-mutant non-small cell lung cancer: From molecular profiling to rationally designed therapy.
The Oncologist 2017;22:786–796.

Barlesi F, Mazieres J,Merlio JP et al.
Routine molecular profiling of patients with advanced non-small cell lung cancer: results of a 1-year nationwide programme of the French Cooperative Thoracic Intergroup (IFCT).
Lancet 2016;387:1415-1426.

Bray F, Ferlay J, Soerjomataram I et al.
Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries.
CA Cancer J Clin 2018;68(6):394-424.

Cao M and Chen W.
Epidemiology of lung cancer in China.
Thoracic Cancer. 2019 Jan;10(1):3-7.

Cardarella S, Ogino A, Nishina M et al.
Clinical, pathological and biological features associated with BRAF mutations in non-small cell lung cancer.
Clin Cancer Res. 2013; 19(16): 4532-4540.

Cetin K, Ettinger D, Hei YJ, O'Malley C.
Survival by histologic subtype in Stage IV non-small cell lung cancer based on data from the Surveillance, Epidemiology and End Results Program.
Clinical Epidemiology 2011;3:139-148.

Chapman PB, Hauschild A, Robert C et al.
Improved survival with vemurafenib in melanoma with BRAF V600E mutation.
N Engl J Med 2011;364(26):2507-2516.

Chapman PB, Robert C, Larkin J et al.
Vemurafenib in patients with BRAFV600 mutation-positive metastatic melanoma: final overall survival results of the randomized BRIM-3 study.
Ann Oncol. 2017;28:2581-2587.

National Health Commission of the People's Republic of China
Chinese guidelines for diagnosis and treatment of melanoma 2018 (English version).
Chinese J Cancer Res. 2019;31(4):578-585.

Corcoran RB, Ebi H, Turke AB, et al.
EGFR-mediated reactivation of MAPK signaling contributes to insensitivity of BRAF-mutant colorectal cancers to RAF inhibition with vemurafenib.
Cancer Discov 2012;2(3):227-235.

Couraud S, Barlesi F, Fontaine-Delaruelle C, et al.
Clinical outcomes of non-small-cell lung cancer patients with BRAF mutations: results from the French Cooperative Thoracic Intergroup biomarkers France study.
European Journal of Cancer 201911686-97

Heads of Medicines Agencies, Clinical Trials Facilitation Group (CTFG).
Recommendations related to contraception and pregnancy testing in clinical trials. Final Version 2014.
http://www.hma.eu/fileadmin/dateien/Human_Medicines/01About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

Delord JP, Robert C, Nyakas M et al.
Phase I dose-escalation and -expansion study of the BRAF inhibitor encorafenib (LGX818) in metastatic BRAF-mutant melanoma.
Clin Cancer Res. 2017;23(17):5339-5348.

Ding X, Zhang Z, Jiang T et al.
Clinicopathologic characteristics and outcomes of Chinese patients with non-small-cell lung cancer and BRAF mutation.
Cancer Medicine. 2017; Mar; 6(3):555–562.

Dudnik E, Peled N, Nechushtan H et al.
BRAF Mutant Lung Cancer: Programmed Death Ligand 1 Expression, Tumor Mutational Burden, Microsatellite Instability Status, and Response to Immune Check-Point Inhibitors.
J Thorac Oncol 2018;13(8):1128-1137.

Dummer R, Robert C, Nyakas M, et al.
Initial results from a phase I, open-label, dose escalation study of the oral BRAF inhibitor LGX818 in patients with BRAF V600 mutant advanced or metastatic melanoma.
J Clin Oncol 2013;31: suppl;abstr 9028.

Dummer R, Ascierto PA, Gogas HJ et al.
Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial.
Oncol 2018a;19(5):603-615.

Dummer R, Ascierto PA, Gogas HJ et al.
Overall survival in patients with BRAF-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): a multicentre, open-label, randomised, phase 3 trial.
Lancet Oncol 2018b;19(10):1315-1327.

Eisenhauer EA, Therasse P, Bogaerts J.
New response evaluation criteria in solid tumours: revised RECIST guideline (Version 1.1).
Eur J Cancer 2009; 45(2):228-247.

Feng RM, Zong YN, Cao SM et al.
Current cancer situation in China: good or bad news from the 2018 Global Cancer Statistics?
Cancer Commun. 2019;39:22

Ferlay J, Shin HR, Bray F, et al*Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008.*
Int J Cancer. 2010 Dec 15;127(12):2893-917.

Flaherty KT, Puzanov I, Kim KB et al.
Inhibition of mutated, activated BRAF in metastatic melanoma.
N Engl J Med 2010;363:809-819.

Flaherty KT, Infante JR, Daud A et al.
Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations.
N Engl J Med 2012;367(18):1694-1703.

Gautschi O, Milia J, Cabarrou B et al.
Targeted Therapy for Patients with BRAF-Mutant Lung Cancer: Results from the European EURAF Cohort.
J Thorac Oncol. 2015;10:1451–1457.

Globocan 2018.
Colorectal Cancer.
WHO International Agency for Research on Cancer.
http://gco.iarc.fr/today/data/factsheets/cancers/10_8_9-Colorectum-fact-sheet.pdf Accessed April 2020.

Gomez-Roca CA, Delord J, Robert C, et al.
Encorafenib (LGX818), an oral BRAF inhibitor, in patients (pts) with BRAF V600E metastatic colorectal cancer (mCRC): Results of dose expansion in an open-label, phase 1 study.
Ann Oncol 2014;25(suppl 4):iv167-iv209.

Gou LY, Wy YL.
Prevalence of driver mutations in non-small-cell lung cancers in the People's Republic of China.
Lung cancer: Targets and Therapy 2014; 5:1-9.

Herbst R, Morgensztern D and Boshoff C.
The biology and management of non-small cell lung cancer.
Nature 2018;553, 446–454.

Hindorf C, Glatting G, Chiesa C, Lindén O, Flux G;
EANM Dosimetry Committee. EANM Dosimetry Committee guidelines for bone marrow and whole-body dosimetry.
Eur J Nucl Med Mol Imaging. 2010;37(6):1238-1250. doi:10.1007/s00259-010-1422-4

Holladay JT.
Visual acuity measurements.
J Cataract Refact Surg 2004;30:287-290.

Jemal A, Saraiya M, Patel P, et al.
Recent trends in cutaneous melanoma incidence and death rates in the United States, 1992-2006.
J Am Acad Dermatol. 2011 Nov;65(5 Suppl 1):S17-25.e1-3.

Joshi M, Rice SJ, Liu X et al.
Trametinib with or without Vemurafenib in BRAF Mutated Non-Small Cell Lung Cancer.
PLoS ONE. 2015;10(2):e0118210.

Kefford R, Arkenau H, Brown MP, et al.
Phase I/II study of GSK2118436, a selective inhibitor of oncogenic mutant BRAF kinase, in patients with metastatic melanoma and other solid tumors.
J Clin Oncol 28(Suppl.): abstract 10523.2010.

Koelblinger P, Thuerigen, O and Dummer, R.
Development of encorafenib for BRAF-mutated advanced melanoma.
Current Opin Oncol. 2018; 30: 125-133

Kopetz S, Grothey A, Yaeger, R et al.
Encorafenib, binimetinib, and cetuximab in BRAF V600E–mutated colorectal cancer.
New Engl J Med 2019;381:1632-1643.

Larkin J, Ascierto PA, Dréno B et al.
Combined vemurafenib and cobimetinib in BRAF-mutated melanoma.
N Engl J Med. 2014;371(20):1867-1876.

Li S, Li L, Zhu Y et al.
Coexistence of EGFR with KRAS, or BRAF, or PIK3CA somatic mutations in lung cancer: a comprehensive mutation profiling from 5125 Chinese cohorts.
Br J Cancer. 2014; 110(11): 2812-2820.

Li Z, Jiang L, Bai H et al.
Prevalence and clinical significance of BRAF V600E in Chinese patients with lung adenocarcinoma.
Thorac Cancer. 2015;6:269-274

Lin Q, Zhang H, Ding H et al.
The association between BRAF mutation class and clinical features in BRAF-mutant. Chinese non-small cell lung cancer patients.
J Translational Medicine. 2019; 17: 298

Long GV, Stroyakovskiy H, Gogas E et al.
Combined BRAF and MEK Inhibition versus BRAF Inhibition Alone in Melanoma.
N Engl J Med. 2014;371:1877-1888.

Long GV, Hauschild A, Santinami Mario
Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma
N Engl J Med 2017;377:1813-1823

Marchetti A, Felicioni L, Malatesta S et al.
Clinical Features and Outcome of Patients With Non–Small-Cell Lung Cancer Harboring BRAF Mutations.
J Clin Oncol. 2011;29 (26):3574-3579.

Mazieres J, Drilon A, Mhanna L et al.
Efficacy of immune-checkpoint inhibitors (ICI) in non-small cell lung cancer (NSCLC) patients harboring activating molecular alterations (ImmunoTarget).

J Clin Oncol 2018;36, Suppl 15:9010 (abst).

National Cancer Institute Common Terminology Criteria for Adverse Events Version 4 (published 28 May 2009; Version 4.03 14 June 2010).

Oken MM, Creech RH, Tormey DCet al.
Toxicity and response criteria of the Eastern Cooperative Oncology Group.
Am J Clin Oncol ;19825:649-655.

Planchard D, Kim TM, Mazieres J et al.
Dabrafenib in patients with BRAF(V600E)-positive advanced non-small-cell lung cancer: a single-arm, multicentre, open-label, phase 2 trial.
Lancet Oncol 2016;17(5):642-650.

Planchard D, Besse B, Groen HJM et al.
DaBRAFenib plus trametinib in patients with previously treated $BRAF^{V600E}$-mutant metastatic non-small cell lung cancer: an open-label, multicenter phase 2 trial.
Lancet Oncol. 2016b; 17(7): 984-993

Planchard D, Besse B, Kim TM et al.
Updated survivals of patients (pts) with previously treated $BRAF^{V600E}$-mutated advanced non-small cell lung cancer (NSCLC) who received daBRAFenib (D), D + Trametinib (T) in the phase II BRF113928 study.
J Clin Oncol 2017a;35,15 Suppl:9075 (abst)

Planchard D, Smit EF, Groen HJM et al.
DaBRAFenib plus trametinib in patients with previously untreated $BRAF^{V600E}$-mutant metastatic non-small cell lung cancer: an open-label, multicenter phase 2 trial.
Lancet Oncol. 2017b:18(10):307-316

Rihawi K, Giannarelli D, Galetta D et al.
BRAF Mutant NSCLC and Immune Checkpoint Inhibitors: Results from a Real-World Experience.
J Thorac Oncol 2019;14(3):e57-e59.

Robert C, Karaszewska B, Schachter J et al.
Two-year estimate of overall survival in COMBI-v, a randomized, open-label, phase III study comparing the combination of dabrafenib (D) and trametinib (T) with vemurafenib (Vem) as first-line therapy in patients (pts) with unresectable or metastatic BRAF V600E/K mutation- positive cutaneous melanoma.
Euro J Cancer 2015;51(Suppl 3):S663.

Robert C, Karazewska B, Schachter J et al. *Three-year estimate of overall survival in COMBI-v, a randomized phase 3 study evaluating first-line dabrafenib (D) + trametinib (T) in patients (pts) with unresectable or metastatic BRAF V600E/K-mutant cutaneous melanoma.*
Ann Oncol. 2016;27(6):LBA40 (abst).

Robert C, Arnault JP, Mateus C.
RAF inhibition and induction of cutaneous squamous cell carcinoma.
Current Opinion in Oncology 2011;23(2):177-182.

Si L, Kong Y, Xu X et al.

Prevalence of BRAF V600E mutation in Chinese melanoma patients: Large scale analysis of BRAF and NRAS mutations in a 432-case cohort.
Euro J Cancer. 2012;48:94-100.

Si L, Zhang X, Xu Z et al.
Vemurafenib in Chinese patients with BRAFV600 mutation–positive unresectable or metastatic melanoma: an open-label, multicenter phase I study.
BMC Cancer. 2018;18:520.

Sosman JA, Kim KB, Schuchter L et al.
Survival in BRAF V600–Mutant Advanced Melanoma Treated with Vemurafenib.
N Engl J Med 2012;366:707-714.

Stuart DD, Li N, Poon DJ, et al. *Preclinical profile of LGX818: a potent and selective RAF kinase inhibitor [abstract]*.
In: Proceedings of the 103rd Annual Meeting of the American Association for Cancer Research; 2012 Mar 31-Apr 4; Chicago, IL. Philadelphia (PA): AACR.
Cancer Res 2012;72(8 Suppl):Abstract nr 3790.

Subbiah V, Gervais R, Rieley G et al.
Efficacy of Vemurafenib in Patients With Non–Small-Cell Lung Cancer With BRAF V600 Mutation: An Open-Label, Single-Arm Cohort of the Histology-Independent VE-BASKET Study.
JCO Precision Oncol. 2019; 3 1-9.

Tan I, Stinchcombe T, Ready N et al.
Therapeutic outcomes in non-small cell lung cancer with BRAF mutations: a single institution, retrospective cohort study.
Transl Lung Cancer Res 2019;8(3):258-267

Turski M, Vidwans SJ, Janku F et al.
Genomically Driven Tumors and Actionability across Histologies: BRAF-Mutant Cancers as a Paradigm.
Molecular Cancer Ther. 2016;15:533-547.

Zeng H, Chen W, Zheng R et al.
Changing cancer survival in China during 2003–15: a pooled analysis of 17 population-based cancer registries.
Lancet Glob Health. 2018; 6: e555-567