CLINICAL STUDY PFIZER C4221008/ARRAY-818-202

Protocol Title:

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

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study protocol.

Abbreviation or special term	Explanation
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the curve
BCRP	breast cancer resistance protein
β-HCG	beta human chorionic gonadotropin
BID	twice daily
BUN	blood urea nitrogen
BRAF	serine/threonine-protein kinase B-Raf
BRAF	B-RAF proto-oncogene, serine/threonine-protein kinase
C1D1	Cycle 1 Day 1
CDx	companion diagnostic
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CK or CPK	creatine (phospho)kinase
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete response
CRF	case report form
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA

Abbreviation or special term	Explanation
CYP	cytochrome P450 enzyme (2B6, 2C9, 2C19, 3A4 refer to isoforms)
DCR	disease control rate
DILI	drug-induced liver injury
dL	deciliter(s)
DMC	Data Monitoring Committee
DOR	duration of response
DVT	deep vein thrombosis
EC	ethics committee (includes institutional review board, research ethics board, and institutional ethics committee)
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperation Oncology Group
eCRF	electronic case report form
EDP	exposure during pregnancy
EGFR	epidermal growth factor receptor
EDC	electronic data capture
EOT	end of treatment
ERK	extracellular signal-related kinase
ESMO	European Society of Medical Oncology
EU	European Union
EUA	Emergency Use Authorization
FAS	Full Analysis Set
FDA	US Food and Drug Administration
FDG	fluorodeoxyglucose
FNA	fine needle aspiration
FSH	follicle stimulating hormone
g	gram(s)
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
h	hour(s)
HBV	hepatitis B virus
HCV	hepatitis C virus
HFSR	hand-foot skin reaction
HIPAA	Health Information Portability and Accountability Act of 1996

Abbreviation or special term	Explanation
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	independent ethics committee
INR	international normalized ratio
IPM	Investigational Product Manual
IRB	institutional review board
IRR	independent radiology review
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IWRS	Interactive Voice/Web Response System
L	liter(s)
LDH	lactate dehydrogenase
LFT	liver function test
LLN	lower limit of normal
LVEF	left ventricular ejection fraction
m	meter(s)
MedDRA	Medical Dictionary for Regulatory Activities
MEK	mitogen-activated protein kinase
min	minute(s)
mg	milligram(s)
mL	milliliter(s)
mmHg	millimeters of mercury
MRI	magnetic resonance imaging
ms	millisecond(s)
MUGA	multigated acquisition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGS	next-generation sequencing
NSAID	nonsteroidal anti-inflammatory drug

Abbreviation or special term	Explanation
NSCLC	non-small cell lung cancer
OAT	organic anion transporter (1 and 3 refer to family members)
OATP	organic anion transporting polypeptide (1B1, 1B3 refer to family members)
OCT	organic cation transporter (2 refers to family member)
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death protein ligand 1
PDF	portable document format
PE	pulmonary embolism
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
pH	hydrogen ion concentration
PK	pharmacokinetic(s)
PKS	Pharmacokinetics (PK) Set
PPS	Per-protocol Set
PR	partial response
PS	performance status
PT	prothrombin time
PTT	partial thromboplastin time
PVC	premature ventricular contraction
Q8W	every 8 weeks
Q12W	every 12 weeks
QD	once daily
QT	QT interval
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula.
RBC	red blood cell(s)
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RPED	retinal pigment epithelial detachment
RVO	retinal vein occlusion

Abbreviation or special term	**Explanation**
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV2	severe acute respiratory syndrome coronavirus 2
SD	stable disease
SoA	schedule of activities
SS	Safety Set
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
TDP	Torsades de Pointes
TPS	tumor proportion score
TTR	Time to response
UGT	uridine 5'-diphospho-glucuronosyltransferase (1A1 refers to family member)
ULN	upper limit of normal
v	version
WBC	white blood cell(s)
WOCBP	woman of childbearing potential

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

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

Protocol Number: Pfizer C4221008/ARRAY-818-202

Rationale:

Approximately 1% to 8% of patients with NSCLC have mutations in *BRAF* (Barlesi et al, 2016; Davies et al, 2002; Cardarella et al, 2013; Baik et al, 2017; Lin et al, 2014), with half of these driven by the *BRAF*^{V600E} mutation (Zheng et al, 2015). Based on a parallel-group trial of the BRAF inhibitor dabrafenib with or without the MEK inhibitor trametinib, the combination of dabrafenib plus trametinib is now a standard-of-care regimen for the treatment of this molecular subtype of NSCLC either as first-line therapy for metastatic disease, or after progression on first-line platinum-based therapy with or without a PD-1/PD-L1 inhibitor (Planchard et al, 2017; NCCN Guidelines; Planchard et al, 2018). In this study, for patients treated with the combination of dabrafenib plus trametinib, the confirmed ORR for both treatment-naïve patients (64% [95% CI 46, 79]) and patients who progressed following first-line platinum-based therapy (63.2% [95% CI 49.3, 75.6]) was nearly twice that of those treated with dabrafenib monotherapy (33% [95% CI 23, 45]) (Planchard et al, 2016a; Planchard et al, 2016b; Planchard et al, 2017). The median DOR for patients who were previously treated was 9.0 months (95% CI 6.9, 18.3), and 10.4 months (95% CI 8.3, 17.9) for treatment-naïve patients (Planchard et al, 2016a; Planchard et al, 2017). PFS and OS results were similarly better for combination therapy as compared to dabrafenib monotherapy (Planchard et al, 2017).

Nonclinical data have demonstrated the enhanced activity of combining BRAF and MEK inhibition in *BRAF*^{V600}-driven tumors (Stuart et al, 2012; Flaherty et al, 2012; Joshi et al, 2015; Khunger et al, 2018). This combination has been validated clinically by the efficacy observed for the combination in *BRAF*^{V600E}-mutant NSCLC (Planchard et al, 2017), and also in the treatment of *BRAF*$^{V600E/K}$-mutant melanoma where the combination of BRAF and MEK inhibition is an established standard-of-care based on 4 pivotal trials of various BRAF/MEK inhibitor combinations (Long et al, 2014; Ascierto et al, 2016; Robert et al, 2016; Dummer et al, 2018a).

Encorafenib is a potent and selective BRAF inhibitor and binimetinib is a potent and selective MEK inhibitor. In a Phase 3 study of encorafenib with or without binimetinib compared to vemurafenib (a standard-of-care BRAF inhibitor comparator) in patients with advanced *BRAF*$^{V600E/K}$-mutant melanoma (Study CMEK162B2301; COLUMBUS trial), the combination was shown to improve PFS, OS and ORR compared to vemurafenib treatment (Dummer et al, 2018a; Dummer et al, 2018b). Median PFS, median OS and confirmed ORR for the combination of encorafenib plus binimetinib were 14.9 months (95% CI 11.0, 18.5), 33.6 months (95% CI 24.4, 39.2) and 63.0% (by central review; 95% CI 55.8, 69.9)/75.0%

(by local review; 95% CI 68.3, 81.0), respectively. These results compared favorably to the PFS, OS and ORR of 7.3 months (95% CI 5.6, 8.2), 16.9 months (95% CI 14.0, 24.5) and 40.3% (by central review; 95% CI 33.3, 47.6)/49.0% (by local review; 95% CI 41.9, 56.5), respectively, for vemurafenib, which performed almost identically on all endpoints compared to its performance in other pivotal trials in *BRAF*^{V600}-mutant melanoma where it was used as a control (Larkin et al, 2014; Robert et al, 2015). These data compare favorably with results from trials of dabrafenib plus trametinib in a similar melanoma setting, with median PFS of 11.4 months, median OS of 25.6 months (95% CI 23.1, 34.3) and ORR of 64% by local review (95% CI 59, 69) for the combination of dabrafenib plus trametinib and median PFS of 7.3 months, median OS of 18 months (95% CI 15.6, 20.7) and ORR of 51% by local review (95% CI 46, 97) for vemurafenib (Robert et al, 2015; Robert et al, 2016).

Although the combination of encorafenib plus binimetinib was not studied in direct comparison to the combination of dabrafenib plus trametinib in melanoma, the numerically superior outcomes with encorafenib plus binimetinib, particularly when compared to results from trials that incorporated a common control arm (vemurafenib) that performed similarly across trials, provides reassurance that there is at least comparable efficacy in the setting of melanoma. These results also suggest that the efficacy of encorafenib plus binimetinib in other *BRAF*^{V600}-driven settings such as *BRAF*^{V600E} NSCLC may be similar or potentially superior to that observed with dabrafenib and trametinib.

Importantly, the combination of encorafenib plus binimetinib has a different safety and tolerability profile (Flaherty et al, 2017) from dabrafenib plus trametinib. Pyrexia, manifesting as a distinctive recurrent febrile syndrome refractory to NSAIDs and associated in a minority of patients with chills, dehydration and renal failure, is a significant toxicity associated with dabrafenib and trametinib, and is seen in over 50% of patients (Long et al, 2014). Treatment with encorafenib and binimetinib was associated with a lower incidence of pyrexia (18% of patients) in the COLUMBUS trial and these events were generally low grade, nonrecurrent and not associated with other manifestations (Dummer et al, 2018a; Dummer et al, 2018b); 64% of patients with previously untreated *BRAF*-mutant metastatic NSCLC, and 46% of patients with previously treated *BRAF*-mutant advanced NSCLC who received dabrafenib plus trametinib reported pyrexia (Planchard et al, 2016a; Planchard et al, 2017).

Therefore, encorafenib plus binimetinib may represent an alternative BRAF/MEK inhibitor combination regimen for the treatment of *BRAF*^{V600E}-mutant NSCLC, and potentially for other V600 Class 1 *BRAF* mutations (e.g. K or D), though very rare. Encorafenib plus binimetinib has a differentiated safety profile and may have enhanced efficacy based on results observed in the treatment of *BRAF*^{V600}-mutant melanoma. This study seeks to generate data to explore the efficacy and safety of this new combination in NSCLC.

Objectives and Endpoints:

Table 1 presents the primary and major/select secondary objectives and endpoints.

Table 1. Primary and Select Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of encorafenib + binimetinib in treatment-naïve and previously treated patients with *BRAF*^{V600E}-mutant NSCLC as measured by ORR	• ORR defined as the proportion of patients who have achieved a confirmed best overall response (CR or PR) as determined by IRR per RECIST v1.1 in the treatment-naïve setting • ORR defined as the proportion of patients who have achieved a confirmed best overall response (CR of PR) as determined by IRR per RECIST v1.1 in the previously treated setting
Secondary	
• To evaluate the efficacy of encorafenib + binimetinib in treatment-naïve and previously treated patients with *BRAF*^{V600E}-mutant NSCLC as measured by DOR, DCR, PFS, and TTR	• Confirmed ORR by Investigator per RECIST v1.1 • DOR (by IRR and by Investigator) defined as the time from the date of the first documented response (CR or PR) that is subsequently confirmed (by IRR and by Investigator, respectively) to the earliest date of disease progression, per RECIST v1.1, or death due to any cause • DCR (by IRR and by Investigator), defined as the proportion of patients who have a confirmed CR or confirmed PR, or SD per RECIST v1.1 • PFS (by IRR and by Investigator), defined as the time from the date of first dose of study drug to the earliest date of disease progression, per RECIST v1.1, or death due to any cause • TTR (by IRR and Investigator), defined as the time from the date of first dose to the first documentation of objective response (CR or PR) which is subsequently confirmed (by IRR and by Investigator, respectively)
• To evaluate the efficacy of encorafenib + binimetinib in treatment-naïve and previously treated patients with *BRAF*^{V600E}-mutant NSCLC with respect to OS	• OS defined as the time from the date of first dose of study drug to the date of death due to any cause
• To evaluate the safety and tolerability of encorafenib + binimetinib in treatment-naïve and previously treated patients with *BRAF*^{V600E}-mutant NSCLC	• Incidence and severity of AEs graded according to the NCI CTCAE v4.03 and changes in clinical laboratory parameters, vital signs, ECGs and ECHO/MUGA scans

Overall Design:

Table 2 presents the study design elements.

Table 2. Study Design Elements

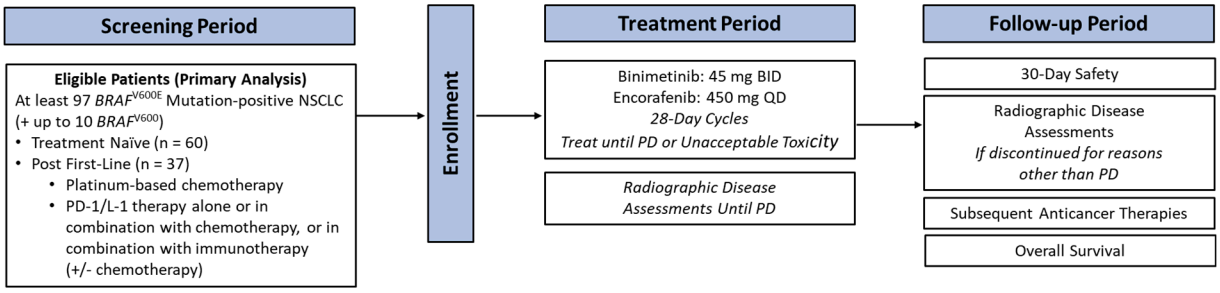
Study Phase	2
Type of Design	Open-label, multicenter, non-randomized study
Primary Purpose	Treatment: combination treatment with encorafenib + binimetinib in patients with *BRAF*^{V600E} NSCLC
Intervention Model	Single Group
Clinical Indication	*BRAF*^{V600}mutant NSCLC
Population	Male and female patients at least 18 years of age who have metastatic *BRAF*^{V600}-mutant NSCLC who are either 1) treatment-naïve, OR who have received 2) first-line treatment with platinum-based chemotherapy, OR 3) first-line treatment with an anti-PD-1/PD-L1 inhibitor given alone, or in combination with platinum-based chemotherapy, or in combination with immunotherapy (e.g., ipilimumab) with or without platinum-based chemotherapy.
Number of Patients	At least 60 treatment-naïve patients, and 37 previously treated patients with the locally confirmed *BRAF*^{V600E} mutation will be enrolled and treated. It is not expected that more than 107 patients with any *BRAF*^{V600} mutation will be enrolled and treated. Up to 10 additional patients who have a *BRAF*^{V600} mutation other than *BRAF*^{V600E} (*BRAF*^{V600x}) can be enrolled and treated.
Study Design	This is an open-label, multicenter, non-randomized, Phase 2 study of the combination of encorafenib and binimetinib in patients with *BRAF*^{V600E}-mutant metastatic NSCLC. Although very rare in NSCLC, patients with other V600 Class 1 BRAF mutations (e.g. K or D) are also allowed. Treatment will be administered in 28-day cycles and will continue until disease progression, unacceptable toxicity, withdrawal of consent, initiation of subsequent anticancer therapy, death, or the defined end of the study. Once the patient discontinues study treatment, the treatment period will end, and the patient will enter the follow-up period.
Treatment Regimens	Study treatment with encorafenib and binimetinib will be self-administered orally without regard to food. Patients will receive the following per 28-day (± 3 days) cycle: • Encorafenib: 450 mg (6 × 75 mg capsule) QD • Binimetinib: 45 mg (3 × 15 mg tablet) BID **Alternate starting doses may also be explored based on safety of the combination regimen. For an individual patient, the dose of study**

Table 2. Study Design Elements

	treatment may be reduced or interrupted as appropriate based on protocol-defined treatment modifications.
Estimated Duration of Study Patients	After the signing of the ICF, screening assessments may be completed over a period of up to 28 days. Patients may continue treatment in consecutive 28-day (± 3 days) cycles provided the patient is receiving benefit and have not met criteria for study withdrawal. If the patient discontinues study treatment, then the treatment period will end, and the patient will enter the follow-up period for safety, disease assessments (if applicable), subsequent anticancer therapies, and survival. Study participation, including post-treatment follow-up is expected to average approximately 12-18 months per individual patient. The end of study will occur 2 years after treatment initiation of the last enrolled patient or the point at which all patients have died or withdrawn consent or have been lost to follow up, whichever occurs first. Any patients still receiving study treatment at the end of the study may be allowed to continue treatment in accordance with local regulations and requirements at the discretion of the Investigator as long as none of the treatment discontinuation criteria have been met.

1.2. Study Schema

Figure 1. Overall Study Design



1.3. Schedule of Activities (SoA)

Table 3. Schedule of Activities

Evaluation/ Window	Screening	Treatment Period						Post-Treatment Period			Notes/Protocol Section
	Screening	Cycle 1		Cycle 2	Subsequent Cycles	Every 8 Weeks	Every 12 Weeks	EOT	Safety Follow-up	Survival Follow-up	
	Day -28 to -1	Day 1	Day 15	Day 1 ± 3D	Day 1 ± 3D	± 7D	± 7D	± 3D	30 Days ± 7D	Q12W ± 7D	
Administrative Procedures											
Informed Consent	X										See Sections 7.1 and 9.4
Inclusion/exclusion criteria	X										See Sections 5.1 and 5.2
Demography and medical history	X										See Sections 7.3.1 and 7.3.2
Local documentation of *BRAF*^{V600} mutation status	X										See Section 7.1.1.1
Prior/concomitant medication	X	Assess continuously									See Section 6.5
Contact IWRS	X	X		X	X			X			See Section 6.3
Dispense encorafenib (with dosing diary)		X		X	X						See Sections 6.1 and 7.4.1
Dispense binimetinib (with dosing diary)		X		X	X						See Sections 6.1 and 7.4.1
Assess study treatment compliance		X		X	X						See Section 6.4
Document subsequent therapies									X	X	See Sections 7.1.4.1 and 7.1.4.3
Survival status									X	X	See Section 7.1.4.3

Table 3. Schedule of Activities

Evaluation/ Window	Screening	Treatment Period						Post-Treatment Period			Notes/Protocol Section
	Screening	Cycle 1		Cycle 2	Subsequent Cycles	Every 8 Weeks	Every 12 Weeks	EOT	Safety Follow-up	Survival Follow-up	
	Day -28 to -1	Day 1	Day 15	Day 1 ± 3D	Day 1 ± 3D	± 7D	± 7D	± 3D	30 Days ± 7D	Q12W ± 7D	
Clinical Procedures/Assessments											
Tumor tissue sample	X										Central laboratory testing to confirm *BRAF*^{V600} status. See Section 7.1.1.1
Physical exam	X	X		X	X			X	X		See Section 7.3.3
Vital signs	X	X		X	X			X	X		See Section 7.3.6
Dermatologic exam	X	X				X		X	X		Post-treatment follow-up required. See Section 7.3.4.
ECOG performance status	X	X		X	X			X	X		See Section 7.2.5
Full ophthalmic exam	X	Full ophthalmic exams are required only if clinically indicated									see Section 7.3.5
Visual acuity exam		X		X	X						see Section 7.3.5
Triplicate 12-lead ECG	X	X									Predose only. See Section 7.3.7 and Table 10
Single 12-lead ECG		X		X			X	X			C1D1 2.0 h (± 0.5 h) after administration of study treatment. See Section 7.3.7 and Table 10
ECHO/MUGA	X			X			X	X			See Section 7.3.8

Table 3. Schedule of Activities

Evaluation/ Window	Screening	Treatment Period						Post-Treatment Period			Notes/Protocol Section
	Screening	Cycle 1		Cycle 2	Subsequent Cycles	Every 8 Weeks	Every 12 Weeks	EOT	Safety Follow-up	Survival Follow-up	
	Day -28 to -1	Day 1	Day 15	Day 1 ± 3D	Day 1 ± 3D	± 7D	± 7D	± 3D	30 Days ± 7D	Q12W ± 7D	
Tumor radiographic assessment	X					X		Patients who discontinue treatment for reasons other than PD will continue to have radiographic assessments Q8W until PD or meet any of the criteria in Section 7.1.4.2			Q8W for 12 months then Q12W thereafter. See Sections 7.2.1, 7.2.2 and 7.2.3
Adverse event assessment	X	Assess continuously									See Section 7.5
Laboratory Assessments											
Hematology	X	X		X	X			X	X		See Section 7.3.9 and Table 11
Chemistry	X	X		X	X			X	X		See Section 7.3.9 and Table 11
Coagulation	X	Patients on anticoagulation treatment should have parameters monitored throughout the study as clinically indicated									See Section 7.3.9 and Table 11
Serum pregnancy test	X							X			See Section 7.3.9.2 and Table 11
Urine pregnancy test		Performed locally on Day 1 of each cycle; or as clinically indicated; or per country-specific requirement									See Section 7.3.9.2 and Table 11
Urinalysis	X										See Section 7.3.9 and Table 11
HBV and HCV serology testing and HIV where applicable	X										See Section 7.3.9.1 and Table 11

Table 3. Schedule of Activities

Evaluation/ Window	Screening	Treatment Period						Post-Treatment Period			Notes/Protocol Section
	Screening	Cycle 1		Cycle 2	Subsequent Cycles	Every 8 Weeks	Every 12 Weeks	EOT	Safety Follow-up	Survival Follow-up	
	Day -28 to -1	Day 1	Day 15	Day 1 ± 3D	Day 1 ± 3D	± 7D	± 7D	± 3D	30 Days ± 7D	Q12W ± 7D	
PK assessments (for patients enrolled under Protocol Versions 0 to 3)		X	X	X							See Section 7.8 and Table 12
PK assessments (for patients enrolled under Protocol Version 4 or later)		X		X	X (Cycles 3-6)						Predose sample only See Section 7.8 and Table 13
ctDNA blood sample	X			X	X			X			See Section 7.10.1
ctDNA blood sample for biomarkers (for patients enrolled under Protocol Version 4 or later)	X										See Section 7.10.1
Proteomic/Metabolic serum sample (for patients enrolled under Protocol Version 4 or later)		X		X	X (Cycle 3 only)			X			See Section 7.10.2

2. INTRODUCTION

2.1. Background

2.1.1. Overview of Non-small Cell Lung Cancer

Lung cancer is the most commonly occurring cancer in men and the third most commonly occurring cancer in women. Worldwide, the World Health Organization (WHO 2018) reports the incidence of lung cancer will be about 2.09 million cases in 2018, resulting in an expected 1.76 million deaths. More than 40% of NSCLC patients have Stage IV disease at initial diagnosis. The 5-year survival rate for those diagnosed with Stage IVMa (e.g., separate tumor nodules in a contralateral lobe, tumor with pleural nodules or malignant pleural [or pericardial] effusion), lung cancer is approximately 10% and is < 1% for Stage IVMb (e.g., distant metastasis in extra-thoracic organs). More than half of people newly diagnosed with lung cancer can be expected to die within 1 year of diagnosis (U.S. National Institute of Health, National Cancer Institute 2015).

NSCLC is the most common type of lung cancer, accounting for 80% to 85% of all lung cancer diagnoses. As with other cancers, NSCLC is a heterogeneous disease comprised of an expanding number of biologically distinct and clinically relevant molecular subsets (Jordan et al, 2017; Kris et al, 2014). Approximately 1% to 8% of patients with NSCLC have mutations in *BRAF* (Barlesi et al, 2016; Davies et al, 2002; Cardarella et al, 2013; Baik et al, 2017; Lin et al, 2014), with half of these driven by the $BRAF^{V600E}$ mutation (Class 1) and the other half driven by non-V600E mutations distributed throughout exons 11 and 15 collectively (Class 2 and 3) (Zheng et al, 2015). In 2018, recognizing rapid advances in the field of molecular pathology and new options for targeted therapy, updated recommendations from several professional organizations included a consensus statement that *BRAF* testing should be performed on all patients with advanced lung adenocarcinoma, irrespective of clinical characteristics (Kalemkerian et al, 2018; Lindeman et al, 2018).

2.1.2. Treatment of *BRAF*-mutant Non-small Cell Lung Cancer

Before the advent of targeted and immune therapies for NSCLC, the ORR for first-line platinum-based chemotherapy for Stage IV NSCLC was approximately 30% to 40% with a mean survival time of 8 to 10 months (Non-small Cell Lung Cancer Collaborative Group 1995). The development and application of antibodies targeting PD-1 (nivolumab and pembrolizumab) and PD-L1 (atezolizumab, avelumab and durvalumab) have advanced the treatment of cancer (Ribas and Wolchok, 2018; Sun et al, 2018). PD-1/PD-L1 inhibitors in combination with chemotherapy have recently been approved for the first-line treatment of NSCLC patients (KEYTRUDA® [pembrolizumab] prescribing information; TECENTRIQ® [atezolizumab] prescribing information), and has led to changes in the recommended treatment algorithms for NSCLC (NCCN Guidelines; Planchard et al, 2018). However, PD-1/PD-L1 inhibitors produce durable responses in only about 20% of patients with advanced NSCLC (Brahmer et al, 2010; Topalian et al, 2012; Gettinger and Herbst, 2014; Herbst et al, 2014). The response rate is higher when patients are stratified by partial or complete membrane staining for PD-L1 (tumor proportion score, TPS) (Aguilar et al, 2018; Gandhi et al, 2018).

Recently, molecular characterization of a NSCLC tumor has become a key tool for facilitating treatment decisions and the clinical management of NSCLC patients (Tsoulos et al, 2017). Identification of the unique molecular drivers and development of highly effective genotype-specific therapies have transformed the natural history of disease for select subgroups of NSCLC patients (Hyman et al, 2018; Leduc et al, 2017; Lee et al, 2017). Experience with *BRAF*^{V600E} melanoma and its treatment with BRAF/MEK inhibitors has influenced the treatment of *BRAF*^{V600E} NSCLC (Khunger et al, 2018). Based on a parallel-group trial of the BRAF inhibitor dabrafenib with or without the MEK inhibitor trametinib, the combination of dabrafenib plus trametinib is now a standard-of-care regimen for the treatment of this molecular subtype of NSCLC either as first-line therapy for metastatic disease, or after progression on first-line platinum-based therapy with or without a PD-1/PD-L1 inhibitor (Planchard et al, 2017; NCCN Guidelines; Planchard et al, 2018).

In this study, for patients treated with the combination of dabrafenib plus trametinib, there was no statistically significant difference in ORR for treatment-naïve patients (64% [95% CI 46, 79]) versus patients who progressed following first-line platinum-based therapy (63.2% [95% CI 49.3, 75.6]) (Planchard et al, 2016a; Planchard et al, 2016b; Planchard et al, 2017). Additionally, for patients treated with the combination, the confirmed ORR for both treatment-naïve patients and patients who progressed following first-line platinum-based therapy was nearly twice that of those treated with dabrafenib monotherapy (33% [95% CI 23, 45]). PFS and OS results were similar for patients treated with the combination regardless if they were treatment-naïve or progressed following first-line platinum-based therapy (Planchard et al, 2017). The median PFS and median OS were 10.9 months (95% CI 7.0, 16.6) and 24.6 months (95% CI 12.3, not estimable), respectively, for treatment-naïve patients and were 10.2 months (95% CI 6.9, 16.7) and 18.2 months (95% CI 14.3, not estimable), respectively, for patients who progressed on first-line platinum-based therapy. Median PFS and median OS results were also better for combination therapy as compared to dabrafenib monotherapy, with PFS and OS of 5.5 months (95% CI 2.8, 7.3) and 12.7 months (95% CI 7.3, 16.3), respectively, for monotherapy (Planchard et al, 2017). The median DOR for patients who were treatment naïve was 10.4 months (95% CI 8.3, 17.9) and was 9.0 months (95% CI 6.9, 18.3) for patients who were previously treated.

Some advanced NSCLC patients may be treated with platinum-based chemotherapy with or without a PD-1/PD-L1 inhibitor as first-line therapy prior to analysis of their tumor tissue for *BRAF*^{V600E} mutation status. Clinical outcomes for patients with *BRAF*^{V600E} mutations who have progressed on a PD-1/PD-L1 inhibitor regimen is unknown and warrant further clinical investigation so it follows that these patients should be studied in future clinical trials of BRAF/MEK inhibitor combinations.

2.1.3. Overview of Encorafenib and Binimetinib

Encorafenib is a potent and selective ATPcompetitive inhibitor of *BRAF*^{V600}-mutant kinase. Mutations in the *BRAF* gene, such as *BRAF*^{V600E}, can result in constitutively activated BRAF kinase that may stimulate tumor cell growth. Encorafenib inhibited in vitro growth of tumor cell lines expressing *BRAF* V600 E, D and K mutations.

Binimetinib is a potent and selective allosteric, ATP-uncompetitive inhibitor of MEK1/2. MEK proteins are upstream regulators of the ERK pathway. In vitro, binimetinib inhibited

ERK phosphorylation in cell-free assays as well as viability and MEK-dependent phosphorylation of *BRAF*-mutant human melanoma cell lines. Binimetinib also inhibited in vivo ERK phosphorylation and tumor growth in *BRAF*-mutant murine xenograft models.

Encorafenib and binimetinib target 2 different kinases in the RAS/RAF/MEK/ERK pathway. Compared with either drug alone, co-administration of encorafenib and binimetinib resulted in greater anti-proliferative activity in vitro in *BRAF* mutation-positive cell lines and greater anti-tumor activity with respect to tumor growth inhibition in $BRAF^{V600E}$-mutant human melanoma xenograft studies in mice. Additionally, the combination of encorafenib and binimetinib delayed the emergence of resistance in $BRAF^{V600E}$-mutant human melanoma xenografts in mice compared to either drug alone.

Encorafenib 450 mg orally QD in combination with binimetinib 45 mg orally BID have received marketing approval in several jurisdictions, including the US and EU (BRAFTOVI™ [encorafenib] prescribing information; MEKTOVI® [binimetinib] prescribing information). Regulatory approval of encorafenib and binimetinib in combination was based on the Phase 3 COLUMBUS study (Study CMEK162B2301; randomized, 2-part, open-label, multicenter, international clinical study) (Dummer et al, 2018a; Dummer et al, 2018b). Detailed information regarding nonclinical studies and clinical PK are presented in the respective Investigator's Brochures for encorafenib and binimetinib.

2.1.4. Clinical Safety of Encorafenib in Combination with Binimetinib

COLUMBUS results demonstrated improved tolerability in the encorafenib 450 mg QD + binimetinib 45 mg BID arm compared with single-agent encorafenib 300 mg QD (Dummer et al, 2018a; Dummer et al, 2018b). This is consistent with a body of literature that suggests the combination of a BRAF inhibitor and a MEK inhibitor results in improved tolerability compared with either agent alone (Flaherty et al, 2012; Long et al, 2014; Robert et al, 2015; Larkin et al, 2014; Ascierto et al, 2016).

Among patients receiving encorafenib plus binimetinib combination therapy in the COLUMBUS study, the most common adverse reactions (≥ 20% of patients, all grades) were fatigue (43%), nausea (41%), diarrhea (36%), vomiting (30%), abdominal pain (28%), arthralgia (26%), myopathy (23%), hyperkeratosis (23%), rash (22%), headache (22%), constipation (22%), visual impairment (20%) and serous retinopathy (20%). Most of these toxicities were generally reversible and manageable by supportive medical care, dose modifications or discontinuation. Other clinically important adverse reactions occurring in < 10% of patients were facial paresis, pancreatitis, panniculitis, drug hypersensitivity and colitis. The most common laboratory abnormalities (≥ 2%, Grade 3 or 4) were increased GGT (11%), increased ALT (6%), increased creatine phosphokinase (5%), increased fasting glucose (5%), increased creatinine (4%), anemia (4%), hyponatremia (4%), increased AST (3%), neutropenia (3%) and lymphopenia (2%). Detailed information regarding clinical safety is presented in the respective Investigator's Brochures for encorafenib and binimetinib.

Important potential adverse effects associated with the administration of the combination of encorafenib and binimetinib established primarily from safety data from the COLUMBUS study and, where indicated, from other studies of the combination, include:

- **New primary malignancies:** Based on its mechanism of action, encorafenib may promote malignancies associated with activation of *RAS* through mutation or other mechanisms. Cutaneous and non-cutaneous malignancies occurred in patients, including cutaneous squamous carcinoma/keratoacanthoma (2.6%; median time to first occurrence of 5.8 months) and basal cell carcinoma (1.6%).

- **Left ventricular dysfunction:** Symptomatic or asymptomatic decreases in ejection fraction occurred in 7% of patients, with Grade 3 left ventricular dysfunction occurring in 1.6% of patients.

- **Hemorrhage:** Hemorrhage occurred in 19% of patients, with events ≥ Grade 3 occurring in 3.2% of patients. Fatal intracranial hemorrhage in the setting of new or progressive brain metastases occurred in 1.6% of patients. The most frequent hemorrhagic events were gastrointestinal, including rectal hemorrhage (4.2%), hematochezia (3.1%), and hemorrhoidal hemorrhage (1%).

- **Venous thromboembolism:** Occurred in 6% of patients, including 3.1% of patients who developed pulmonary embolism.

- **Ocular toxicities:** Serous retinopathy is a class effect of MEK inhibitors. It is generally asymptomatic or mildly symptomatic and reversible (Urner-Bloch et al, 2016). Serous retinopathy occurred in 20% of patients. Symptomatic serous retinopathy occurred in 8% of patients with no cases of blindness. The median time to onset of the first event of serous retinopathy (all grades) was 1.2 months. RVO is a known class-related adverse reaction of MEK inhibitors and may occur in patients treated with binimetinib in combination with encorafenib. In patients with *BRAF* mutation-positive melanoma across multiple clinical trials, 0.1% of patients experienced RVO.

- **Pneumonitis/Interstitial Lung Disease**: Pneumonitis occurred in 0.3% of patients with *BRAF* mutation-positive melanoma across multiple clinical trials.

- **Hepatotoxicity:** The incidence of Grade 3 or 4 increases in liver function laboratory tests was 6% for ALT, 2.6% for AST and 0.5% for alkaline phosphatase. No patient experienced Grade 3 or 4 serum bilirubin elevation.

- **CK Elevation/Rhabdomyolysis**: Asymptomatic elevations of laboratory values of serum CK occurred in 58% of patients. Rhabdomyolysis was reported in 0.1% of patients with *BRAF* mutation-positive melanoma across multiple clinical trials.

- **QTc Prolongation:** QT prolongation has been observed in patients treated with BRAF inhibitors. Encorafenib is associated with dose-dependent QTc interval prolongation in some patients. In the COLUMBUS study, an increase in QTcF to > 500 ms was measured in 0.5% of patients.

- **Embryo-Fetal Toxicity:** Encorafenib or binimetinib can cause fetal harm when administered to pregnant women.

2.1.5. Clinical Safety of Encorafenib

The maximum well-tolerated dose of encorafenib when given as a single agent is 300 mg QD. Encorafenib 300 mg QD as a single agent is associated with an increased risk of certain AEs compared to when used in combination with binimetinib. For example, Grade 3 or 4 dermatologic reactions in the COLUMBUS study occurred in 21% of patients treated with single-agent encorafenib compared to 2% of patients treated with encorafenib in combination with binimetinib.

Among patients receiving single-agent encorafenib 300 mg QD across multiple clinical trials including COLUMBUS, the most common AEs (≥ 20%, all grades) were alopecia (50%), palmar-plantar erythrodysesthesia syndrome (48%), arthralgia (43%), hyperkeratosis (42%), nausea (35%), dry skin (29%), fatigue (28%), myalgia (28%), headache (27%), vomiting (25%), rash (23%) and palmoplantar keratoderma (22%).

Encorafenib is primarily metabolized and eliminated by the liver; patients with mild to severe hepatic impairment may have increased exposure over the range of inter-patient variability exposure.

Detailed information regarding clinical safety of encorafenib used as a single agent is presented in the encorafenib Investigator's Brochure.

2.2. Benefit/Risk Assessment

Data from the COLUMBUS study and preclinical and exposure-response data for encorafenib and binimetinib demonstrate that both agents in combination contribute to observed efficacy (Dummer et al, 2018a; Dummer et al, 2018b). Co-administration of encorafenib 450 mg QD with binimetinib 45 mg BID reduces the incidence of safety findings of interest for binimetinib (acneiform dermatitis, peripheral edema and rash) and encorafenib (arthralgia, myalgia, vomiting, headache, rash and palmoplantar keratoderma). The reduction of encorafenib toxicity with the addition of binimetinib enables a higher dose of encorafenib, as well as fewer dose interruptions and reductions, which may enhance the efficacy of the combination.

The primary risks of the combination of encorafenib plus binimetinib treatment are well characterized and include known class effects of BRAF and MEK inhibitors (see Sections 2.1.4 and 2.1.5). The combination of encorafenib plus binimetinib has a lower frequency and severity of pyrexia and photosensitivity reactions than the dabrafenib plus trametinib and vemurafenib plus cobimetinib combinations, respectively. Pyrexia was infrequent with the combination of encorafenib plus binimetinib, not complicated by chills,

dehydration or renal failure and generally not recurrent. Almost all cases of pyrexia presenting as an SAE were associated with secondary causes of infection of progressive melanoma. Photosensitivity was infrequent (4.7%) in the encorafenib 450 mg QD plus binimetinib 45 mg BID arm of the COLUMBUS study.

2.3. Study Rationale

Nonclinical data have demonstrated the enhanced activity of combining BRAF and MEK inhibition in *BRAF*^{V600}-driven tumors (Stuart et al, 2012; Flaherty et al, 2012; Joshi et al, 2015; Khunger et al, 2018). In a *BRAF*^{V600E} NSCLC mouse xenograft model, administration of encorafenib (20 mg/kg QD) in combination with binimetinib (3.5 mg/kg BID) demonstrated enhanced anti-tumor activity (see Figure 2 and Table 4), with respect to tumor regression and tumor regrowth delay after dosing cesssation, compared to the single-agent activity of each drug. This combination has been validated clinically by the efficacy observed for the combination in *BRAF*^{V600E}-mutant NSCLC (Planchard et al, 2017), and also in the treatment of *BRAF*^{V600}-mutant melanoma where the combination of BRAF and MEK inhibition is an established standard-of-care based on 4 pivotal trials of various BRAF/MEK inhibitor combinations (Long et al, 2014; Ascierto et al, 2016; Robert et al, 2016; Dummer et al, 2018a).

Figure 2. Effects of Encorafenib and Binimetinib in DFCI-306 Mice (*BRAF* V600E, EGFR del19, T790M)

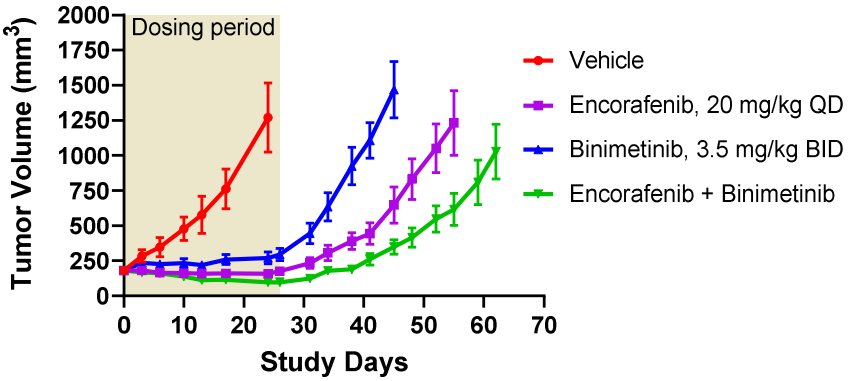


Table 4. Anti-tumor Activity of Encorafenib and Binimetinib in *BRAF* V600E Xenograft Model

Treatment	% Tumor Growth Inhibition	Maximum Regression	Days to 400% Target Tumor Volume
Vehicle	-		16.2
Encorafenib 20 mg/kg QD	100%	13.0%	47.1
Binimetinib 3.5 mg/kg BID	91.7%	0%	36.2

Table 4. Anti-tumor Activity of Encorafenib and Binimetinib in *BRAF* V600E Xenograft Model

Treatment	% Tumor Growth Inhibition	Maximum Regression	Days to 400% Target Tumor Volume
Encorafenib + Binimetinib 20 mg/kg QD, 3.5 mg/kg BID	100%	45.7%	56.0

Although the current approved BRAF/MEK inhibitor combination of dabrafenib plus trametinib has transformed the standard-of-care treatment for NSCLC in patients who have the $BRAF^{V600E}$ mutation, it has liabilities (e.g., pyrexia) that could limit effectiveness suggesting that additional therapeutic options are needed. $BRAF^{V600E}$ NSCLC remains an aggressive disease that portends a poor prognosis and there remains a need to develop new treatment regimens to expand the therapeutic options for patients.

In the Phase 3 COLUMBUS study of encorafenib with or without binimetinib compared to vemurafenib (a standard-of-care BRAF inhibitor comparator) in patients with advanced $BRAF^{V600E/K}$mutant melanoma, the combination was shown to improve PFS, OS and ORR compared to vemurafenib treatment (Dummer et al, 2018a; Dummer et al, 2018b). Median PFS, median OS and confirmed ORR for the combination of encorafenib plus binimetinib were 14.9 months (95% CI 11.0, 18.5), 33.6 months (95% CI 24.4, 39.2) and 63.0% (by central review; 95% CI 55.8, 69.9)/75.0% (by local review; 95% CI 68.3, 81.0), respectively. These results compared favorably to the PFS, OS and ORR of 7.3 months (95% CI 5.6, 8.2), 16.9 months (95% CI 14.0, 24.5) and 40.3% (by central review; 95% CI 33.3, 47.6)/51.0% (by local review; 95% CI 41.9, 56.5), respectively, for vemurafenib, which performed almost identically on all endpoints compared to its performance in other pivotal trials in $BRAF^{V600}$mutant melanoma where it was used as a control (Larkin et al, 2014; Robert et al, 2015). These data compare favorably with results from trials of dabrafenib plus trametinib in a similar melanoma setting, with median PFS of 11.4 months, median OS of 25.6 months (95%CI 23.1, 34.3) and ORR of 64% by local review (95% CI 59, 69) for the combination of dabrafenib plus trametinib and median PFS of 7.3 months, median OS of 18 months (95% CI 15.6, 20.7) and ORR of 51% by local review (95% CI 46, 97) for vemurafenib (Robert et al, 2015; Robert et al, 2016).

Although encorafenib plus binimetinib was not studied in direct comparison to dabrafenib plus trametinib in melanoma, the numerically superior outcomes with encorafenib plus binimetinib, particularly when compared to results from trials that incorporated a common control arm (vemurafenib) that performed similarly across trials, provides reassurance that there is at least comparable efficacy in the setting of melanoma and suggest that the efficacy of encorafenib plus binimetinib in other $BRAF^{V600}$-driven settings such as $BRAF^{V600E}$ NSCLC may be similar or potentially superior to that observed with dabrafenib and trametinib.

Importantly, encorafenib plus binimetinib has a different safety and tolerability profile (Flaherty et al, 2017) from dabrafenib plus trametinib. Pyrexia, manifesting as a distinctive recurrent febrile syndrome refractory to NSAIDs and associated in a minority of patients with chills, dehydration and renal failure, is a significant toxicity associated with dabrafenib

and trametinib, and is seen in over 50% of patients (Long et al, 2014). Treatment with encorafenib and binimetinib was associated with a lower incidence of pyrexia (18% of patients) in the COLUMBUS trial and these events were generally low grade, nonrecurrent and not associated with other manifestations (Dummer et al, 2018a; Dummer et al, 2018b); 64% of patients with previously untreated *BRAF*-mutant advanced NSCLC, and 46% of patients with previously treated *BRAF*-mutant metastatic NSCLC who received dabrafenib plus trametinib reported pyrexia (Planchard et al, 2016a; Planchard et al, 2017). Therefore, encorafenib plus binimetinib may represent an alternative BRAF/MEK inhibitor combination regimen for the treatment of $BRAF^{V600E}$-mutant NSCLC. Encorafenib plus binimetinib has a differentiated safety profile and may have enhanced efficacy based on results observed in the treatment of $BRAF^{V600}$-mutant melanoma. This study seeks to generate data to explore the efficacy and safety of this new combination in NSCLC.

3. OBJECTIVES AND ENDPOINTS

Table 5. Objectives and Endpoints

Primary Objective	Primary Endpoint
• To evaluate the efficacy of encorafenib + binimetinib in treatment-naïve and previously treated patients with *BRAF*^{V600E}-mutant NSCLC as measured by ORR	• ORR defined as the proportion of patients who have achieved a confirmed best overall response (CR or PR) as determined by IRR per RECIST v1.1 in the treatment-naïve setting • ORR defined as the proportion of patients who have achieved a confirmed best overall response (CR or PR) as determined by IRR per RECIST v1.1 in the previously treated setting.
Secondary Objectives	**Secondary Endpoints**
• To evaluate the efficacy of encorafenib + binimetinib in treatment-naïve and previously treated patients with *BRAF*^{V600E}-mutant NSCLC as measured by DOR, DCR, PFS, and TTR	• Confirmed ORR by Investigator per RECIST v1.1 • DOR (by IRR and by Investigator) defined as the time from the date of the first documented response (CR or PR) that is subsequently confirmed (by IRR and by Investigator, respectively) to the earliest date of disease progression, per RECIST v1.1, or death due to any cause • DCR (by IRR and by Investigator), defined as the proportion of patients who have a confirmed CR or confirmed PR, or SD per RECIST v1.1 • PFS (by IRR and by Investigator), defined as the time from the date of first dose of study drug to the earliest date of disease progression, per RECIST v1.1, or death due to any cause • TTR (by IRR and Investigator), defined as the time from the date of first dose to the first documentation of objective response (CR or PR) which is subsequently confirmed (by IRR and by Investigator, respectively)
• To evaluate the efficacy of encorafenib + binimetinib in treatment-naïve and previously treated patients with *BRAF*^{V600E}-mutant NSCLC with respect to OS	• OS defined as the time from the date of first dose of study drug to the date of death due to any cause
• To evaluate the safety and tolerability of encorafenib + binimetinib in treatment-naïve and previously treated patients with *BRAF*^{V600E}-mutant NSCLC	• Incidence and severity of AEs graded according to the NCI CTCAE v4.03 and changes in clinical laboratory parameters, vital signs, ECGs and ECHO/MUGA scans
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate the PK of encorafenib and its metabolite LHY746 and binimetinib in in patients with *BRAF*^{V600}-mutant NSCLC	• Plasma concentration-time profiles and PK parameter estimates for encorafenib and its metabolite LHY746 and binimetinib

Table 5. Objectives and Endpoints

• To assess blood ctDNA mutation status	• Genomic analysis of ctDNA in blood samples

4. STUDY DESIGN

4.1. Overall Design

This is an open-label, multicenter, non-randomized, Phase 2 study to determine the safety, tolerability and efficacy of encorafenib given in combination with binimetinib in treatment-naïve and previously treated patients with *BRAF*^{V600E}-mutant metastatic NSCLC. Although very rare in NSCLC, patients with other V600 Class 1 *BRAF* mutations (e.g., K or D) are also allowed. Patients who are either treatment-naïve, OR who have received 1) first-line treatment with standard platinum-based chemotherapy, OR 2) first-line treatment with an anti-PD-1/PD-L1 inhibitor given alone, or in combination with platinum-based chemotherapy, or in combination with immunotherapy (e.g., ipilimumab) with or without platinum-based chemotherapy will be enrolled. Treatment will be administered in 28-day (± 3 days) cycles and will continue until the patient meets the protocol-defined criteria for treatment withdrawal (see Section 6.7). Once the patient discontinues study treatment, the treatment period will end, and the patient will enter the follow-up period for safety, subsequent anticancer therapy, disease status, and survival status (see Section 7.1.4).

4.2. Discussion of Study Design

Due to the rarity of the *BRAF* mutations in patients with NSCLC (see Section 2.1.1), as well as the commercial availability of a BRAF/MEK combination, an adequately powered randomized clinical trial is not feasible. Because spontaneous remission is rare, ORR provides clear evidence of antitumor activity. Recent advances in the treatment of NSCLC patients with unique molecular drivers (e.g., ROS1 rearrangements and *BRAF* ^{V600E}-mutations), has been founded on regulatory approvals based on non-randomized clinical trials demonstrating clinically meaningful and durable ORR (Shaw et al, 2016; Planchard et al, 2016). Thus, the primary endpoint of the study is ORR, defined as the proportion of patients with CR or PR according to RECIST v1.1 (Eisenhauer et al, 2009).

The patient population was selected based on the mechanisms of action of both encorafenib and binimetinib (see Section 2.1.3) that might result in a potentially therapeutic approach for the treatment of NSCLC patients with a *BRAF*^{V600E} mutation. Inclusion of patients who had progressed on or after prior first-line immunotherapy was based on recent approvals of PD-1/PD-L1 antibodies and their progressive use as first-line treatment (see Section 2.1.2).

4.3. Justification for Dose

The regulatory approved dose and administration schedule of encorafenib 450 mg orally QD in combination with binimetinib 45 mg orally BID will be used in this study. Regulatory approval of encorafenib and binimetinib in combination was based on the Phase 3 COLUMBUS study (Dummer et al, 2018a; Dummer et al, 2018b; see Sections 2.1.4, 2.2, 2.3).

4.4. Duration of Treatment and Patient Participation

After signing the ICF, screening assessments may be completed over a period of up to 28 days. Patients may continue to receive study treatment until they meet any of the protocol-defined criteria for treatment withdrawal (see Section 6.7). If the patient discontinues study treatment, then the treatment period will end, and the patient will enter the follow-up period for safety, disease assessments (if applicable), subsequent anticancer therapies, and survival (see Section 7.1.4). Study participation, including post-treatment follow-up is expected to average approximately 12-18 months per individual patient.

4.5. End of Study Definition

The end of study will occur 2 years after treatment initiation of the last enrolled patient or the point at which all patients have died or withdrawn consent or have been lost to follow up, whichever occurs first. At the end of the study, access to study treatment will be provided in accordance with applicable regulations and requirements to all patients who have not met the protocol-defined criteria for treatment withdrawal (see Section 6.7).

4.6. Study Termination

The Investigator retains the right to terminate study participation at any time, according to the terms specified in the study contract. The Investigator is to notify the IRB/IEC in writing of the study's completion or early termination, send a copy of the notification to the Sponsor or designee, and retain a copy for the site study regulatory file.

The Sponsor will assess the benefits and risks associated with the study on a continuous basis based on information from the study, as well as from routine pharmacovigilance activities for encorafenib and binimetinib, and may terminate the study electively if the balance of risks and benefits no longer supports continuation of the study, if required by regulatory decision or for other reasons (e.g., poor recruitment, changing scientific or clinical landscape). If the study is terminated prematurely, the Sponsor will notify the Investigators, the IRB/IEC and regulatory bodies of the decision and reason for termination of the study.

5. STUDY POPULATION

Questions regarding patient eligibility should be addressed to the Sponsor or Sponsor's designated agent prior to enrollment. Patients must fulfill all of the following inclusion criteria and none of the exclusion criteria to be eligible for enrollment in the study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted as they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, and/or patient safety.

5.1. Inclusion Criteria

Patients must meet all of the following criteria to be eligible for enrollment in the study:

1. Able to provide written informed consent. Adult patients under guardianship may participate with the consent of their legally authorized guardian if permitted by local regulations.

2. Age ≥ 18 years at the time of informed consent.

3. Histologically confirmed diagnosis of NSCLC that is currently Stage IV (M1a M1b, M1c- AJCC 8th edition).

4. Presence of a *BRAF*^{V600E} mutation tumor tissue or blood (e.g., ctDNA genetic testing) as determined by a local laboratory assay. Other Class 1 *BRAF*^{v600} mutations (e.g., K or D) will be permitted with prior discussion with the Sponsor.
   Note: Patients must have written documentation from a previous local pathology report of *BRAF*^{V600} mutation in tumor tissue or blood.
   Note: Only PCR and NGS-based local assay results for tumor tissue or blood will be acceptable.

5. The Investigator must obtain prior to enrollment adequate tumor tissue for submission to a central laboratory for confirmation of *BRAF*^{V600} mutation status.
   Note: Tumor tissue collected after the patient was diagnosed with metastatic disease is preferred.
   Note: Tumor tissue sample must not be from locations previously radiated.
   Note: Tumor sample must be 1 block or a minimum of 8 unstained slides of analyzable tissue is required (up to 15 unstained slides is preferred).

   Note: Tumor cells from pleural fluid are permitted provided the sample has been centrifuged to generate a formalin-fixed, paraffin-embedded block with sufficient tumor nuclei (i.e. >20% tumor nuclei). Liquid samples are not permitted. One block or a minimum of 8 unstained slides is required (up to 15 unstained slides is preferred).

   Note: FNA is permitted provided sufficient material (1 block or a minimum of 8 unstained slides is required [up to 15 unstained slides is preferred]) from the same sample used to obtain the local BRAF positive result can be sent to the central laboratory.

6. Patients who are either treatment-naïve (e.g., no prior systemic therapy for advanced/metastatic disease), OR who have received 1) first-line platinum-based chemotherapy OR 2) first-line treatment with an anti-PD-1/PD-L1 inhibitor given alone, or in combination with platinum-based chemotherapy, or in combination with or in combination with immunotherapy (e.g., ipilimumab) with or without platinum-based chemotherapy.
   Note: Alternative chemotherapy regimens are acceptable if the patient was platinum intolerant or ineligible.
   Note: Patients with early stage disease (e.g., Stages I-III) who have had surgery followed by chemotherapy, radiation therapy and/or immunotherapy (e.g., treatment in the adjuvant setting), and present with new lesions or evidence of disease recurrence (e.g., metastatic disease), within 12 months of completing adjuvant treatment would be considered as having received treatment in the first-line setting for metastatic disease. These patients will start treatment with encorafenib/binimetinib in the previously treated setting.
   Note: Maintenance therapy given after first-line therapy in the metastatic setting will

not be considered a separate regimen, provided there was no documentation of disease progression between completion of first-line therapy and the start of maintenance therapy.

7. Presence of measurable disease based on RECIST v1.1.
   Note: Tumor lesions situated in a previously irradiated area, or in an area subjected to other locoregional therapy, are not considered measurable unless there has been documented progression of the lesion.
   Note: If baseline scans from an institution other than the investigational site are used, the site must obtain copies of the scans prior to enrollment of the patient, or the scans must be repeated at the investigational site and submitted for independent review (see Section 7.2.4).

8. ECOG performance status of 0 or 1.

9. Adequate bone marrow function characterized by the following at screening:

   a. ANC $\geq 1.5 \times 10^9$/L;

   b. Platelets $\geq 100 \times 10^9$/L;

   c. Hemoglobin ≥ 8.5 g/dL (with or without blood transfusions).

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

    a. Total bilirubin $\leq 1.5 \times$ ULN
       Note: Patients with documented Gilbert syndrome or hyperbilirubinemia due to non-hepatic cause (e.g., hemolysis, hematoma) may be enrolled following discussion and agreement with the Sponsor.

    b. ALT and AST $\leq 2.5 \times$ ULN, or $\leq 5 \times$ ULN in presence of liver metastases;

    c. Serum creatinine $\leq 1.5 \times$ ULN; or calculated creatinine clearance ≥ 50 mL/min by Cockcroft-Gault formula; or estimated glomerular filtration rate > 50 mL/min/1.73m^2.

11. Able to swallow, retain and absorb oral medications.

12. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests and other study procedures.

13. Female patients of childbearing potential as described in Appendix 1, must have a negative serum βHCG test result.

14. Female patients of childbearing potential must agree to use methods of contraception that are highly effective or acceptable, as described in Appendix 1, and to not donate ova from Screening until 30 days after the last dose of study treatment.

15. Male patients must agree to use methods of contraception that are highly effective or acceptable, as described in Appendix 1, and to not donate sperm from Screening until 90 days after the last dose of study drug.

5.2. Exclusion Criteria

Patients meeting any of the following criteria are ineligible for enrollment in the study.

1. Patients who have documentation of any of the following: EGFR mutation, ALK fusion oncogene or ROS1 rearrangement.

2. Patients who have received more than 1 prior line of systemic therapy in the advanced/metastatic setting. Prior therapies can be reviewed with the Sponsor.
   Note: Generally, treatments that are separated by an event of progression are considered to represent another line of therapy.
   Note: Any therapeutic intervention including systemic therapy, surgery concurrent with or followed by systemic therapy, radiation concurrent with systemic therapy, or stereotactic radiation/radiosurgery, initiated or added to an existing therapy for oligometastatic disease will be considered a new line of therapy.
   Note: Palliative radiation to solitary lesions is permitted and will not be considered a new line of therapy.
   Note: Surgery/radiosurgery for CNS metastases is permitted and will not be considered a line of therapy as long as the surgery/radiosurgery was not given with systemic therapy (neoadjuvant or adjuvant).
   Note: Surgery followed by chemotherapy in the metastatic setting will be considered a line of therapy.

3. Previous treatment with any BRAF inhibitor (e.g., dabrafenib, vemurafenib, XL281/BMS-908662, etc.), or any MEK inhibitor (e.g., trametinib, cobimetinib, selumetinib, RDEA119, etc.) prior to screening and enrollment.

4. Receipt of anticancer medications or investigational drugs within the following intervals before the first administration of study treatment:

   a. ≤ 14 days for chemotherapy, targeted small-molecule therapy, radiation therapy, immunotherapy, or antineoplastic biologic therapy (e.g., erlotinib, crizotinib, bevacizumab, etc.).

   b. ≤ 14 days or 5 half-lives (minimum of 14 days) for investigational agents or devices. For investigational agents with long half-lives (e.g., > 5 days), enrollment before the fifth half-life requires medical monitor approval. (

   Note: COVID-19 vaccinations approved under an Emergency Use Authorization (EUA) (or equivalent) are **not** considered investigational products by regulatory authorities.

   c. Palliative radiation therapy must be complete 7 days prior to the first dose of study treatment.

5. Patients who have had major surgery (e.g., inpatient procedure with regional or general anesthesia) ≤ 6 weeks prior to start of study treatment.

6. Patient has not recovered to ≤ Grade 1 from toxic effects of prior therapy and/or complications from prior surgical intervention 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 a prohibited medication (including herbal medications, supplements or foods), as described in Section 6.5.2, or use of a prohibited medication ≤ 1 week prior to the start of study treatment.

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)
    ≤ 6 months prior to start of study treatment;

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

    c. LVEF < 50% as determined by MUGA or ECHO;

    d. Uncontrolled hypertension defined as persistent systolic blood pressure ≥ 150 mmHg or diastolic blood pressure ≥ 100 mmHg despite optimal therapy;

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

    f. Triplicate average baseline QTcF interval ≥ 480 ms or a history of prolonged QT syndrome.

10. History of thromboembolic or cerebrovascular events ≤ 12 weeks prior to the first dose of study treatment. Examples include transient ischemic attacks, cerebrovascular accidents, hemodynamically significant (i.e. massive or sub-massive) deep vein thrombosis or pulmonary emboli.
    Note for all countries except Korea: Patients with either deep vein thrombosis or pulmonary emboli that do not result in hemodynamic instability are allowed to enroll if they are stable, asymptomatic and on stable anticoagulants for at least 2 weeks.
    Note: Patients with thromboembolic events related to indwelling catheters or other procedures may be enrolled.

11. History or current evidence of RVO or current risk factors for RVO (e.g., uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes); history of retinal degenerative disease.

12. Concurrent neuromuscular disorder that is associated with the potential of elevated CK (e.g., inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy).

13. Evidence of active noninfectious pneumonitis or history of interstitial lung disease.

14. Evidence of HBV or HCV infection.
    Note: Patients with laboratory evidence of cleared HBV or HCV infection may be enrolled.
    Note: Patients with no prior history of HBV infection who have been vaccinated against HBV and who have a positive antibody against hepatitis B surface antigen as the only evidence of prior exposure may enroll.

15. Known history of a positive test for HIV or known AIDS. Testing for HIV must be performed at sites where mandated locally.

16. Active infection requiring systemic therapy.

17. Patients with symptomatic brain metastasis, leptomeningeal disease or other active CNS metastases are not eligible.
    Note: Patients with previously treated brain metastases may participate provided they are stable for at least 28 days prior to the first dose of study treatment and any neurologic symptoms must have returned to baseline. Patients with untreated brain metastases may participate provided the lesions are < 5 mm and are clinically stable and asymptomatic.
    Note: Patients must have no evidence of new or enlarging brain metastases or CNS edema.

18. Concurrent or previous other malignancy within 2 years of study entry, except curatively treated basal or squamous cell skin cancer, prostate intraepithelial neoplasm, carcinoma in-situ of the cervix, Bowen's disease and Gleason ≤ 6 prostate cancer. Patients with a history of other curatively treated cancers must be reviewed with the Sponsor prior to entering the study.

19. Known sensitivity or contraindication to any component of study treatment (binimetinib and encorafenib), or their excipients.

20. Pregnancy or breastfeeding or patients who plan to become pregnant during the duration of the study.

21. Other severe, acute or chronic medical or psychiatric condition(s) or laboratory abnormality that may increase the risk associated with study participation or study treatment administration or that may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient an inappropriate candidate for the study.

5.3. Lifestyle Considerations

Please refer to Appendix 1 for guidance on contraceptive use for males and females of childbearing potential.

5.3.1. Meals and Dietary Restrictions

Patients must avoid consumption of grapefruit, pomegranates, star fruits, Seville oranges or products containing the juice of each during the entire study and preferably 7 days before the first dose of study drugs, due to potential CYP3A4 interaction with encorafenib (see Section 6.5.1.1). Orange juice is allowed.

5.3.2. Activity

Strenuous physical activities, such as competitive sports, can result in significant increases in CK levels while on binimetinib treatment. Patients should be cautioned not to start a new strenuous exercise regimen after first dose of study treatment.

5.4. Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failures to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Tests with results that fail eligibility requirements may be repeated during Screening if the Investigator believes the result to be in error. Additionally, a patient who fails Screening (screen failure) may repeat the Screening process 1 time if the Investigator believes that there has been a change in eligibility status.

6. STUDY TREATMENT

Study treatment refers to encorafenib and binimetinib. Detailed information regarding the study treatment can be found in Table 6 and in the IPM. Detailed information on study drug preparation, handling, storage and accountability will be provided in the Pharmacy Manual.

Alternate starting doses may also be explored based on the observed safety of the combination regimen in NSCLC patients. For an individual patient, the dose of study treatment may be reduced or interrupted as appropriate based on protocol-defined treatment modifications (see Section 6.6).

6.1. Study Treatments Administered

6.1.1. Encorafenib

Encorafenib will be self-administered orally without regard to food. Encorafenib should be taken daily in the morning at approximately the same time (± 2 hours) every day. Patients should be directed to take encorafenib and binimetinib together as applicable. Patients will swallow the study intervention whole, and will not manipulate by, for example, opening or crushing, or chew the study intervention. If a patient vomits at any time after dosing, the dose should not be re-administered. Doses of encorafenib that are omitted for AEs or any other reason should not be made up during the day, or at the end of the dosing period. Additional information regarding encorafenib administration is provided in the IPM.

Encorafenib will begin on Cycle 1 Day 1 and will be self-administered continuously, except on study visit days (e.g., Day 1 of each cycle; see Table 3), and days when PK samples will be drawn (see Table 12 and Table 13), when the encorafenib dose will be administered at the study site under observation of the Investigator. Treatment may continue if the patient has not met any of the protocol-defined conditions for treatment withdrawal (see Section 6.7).

6.1.2. Binimetinib

Binimetinib will be self-administered orally without regard to food. Binimetinib should be taken 12 ± 2 hours apart in the morning and in the evening at approximately the same times every day. Patients should be directed to take binimetinib and encorafenib together as applicable. Patients will swallow the study intervention whole, and will not manipulate by, for example, opening or crushing, or chew the study intervention. If a patient vomits at any time after dosing, the dose should not be re-administered, and the patient should take the next scheduled dose. Doses of binimetinib that are omitted for AEs or any other reason should not be made up during the day, or at the end of the dosing period. Additional information regarding binimetinib administration is provided in the IPM.

Binimetinib will begin on Cycle 1 Day 1 and will be self-administered continuously, except on study visit days (e.g., Day 1 of each cycle; see Table 3), and days when PK samples will be drawn (see Table 12 and Table 13), when the morning binimetinib dose will be administered at the study site under observation of the Investigator. Treatment may continue if the patient has not met any of the protocol-defined conditions for treatment withdrawal (see Section 6.7).

Table 6. Study Treatments

Study Treatment Name	Encorafenib	Binimetinib
Type	Drug	Drug

Table 6. Study Treatments

Study Treatment Name	Encorafenib	Binimetinib
Dose Formulation	Capsule	Tablet
Unit Dose Strength	75 mg	15 mg
Dosage Levels	450 mg QD	45 mg BID
Route of Administration	Oral	Oral
Sourcing	Encorafenib will be provided centrally by the Sponsor or designee	Binimetinib will be provided centrally by the Sponsor or designee
Packaging and Labeling	Encorafenib will be provided in high-density polyethylene bottles. Each bottle will be labeled per local regulatory requirements.	Binimetinib will be provided in high-density polyethylene bottles. Each bottle will be labeled per local regulatory requirements.
Former Names or Aliases	LGX818 ONO-7702 W0090	ARRAY-438162 MEK162 ONO-7703 W0074

6.2. Preparation/Handling/Storage/Accountability

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 patients enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatment must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator (or designee), is responsible for study drug accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by applicable regulatory authorities. The Investigator or designee must maintain records that document:

- Delivery of study drugs to the site.
- Inventory of study drugs at the site.
- Patient use of study drugs including capsule/tablet counts from each supply dispensed.
- Return of study drugs to the Investigator or designee by the patient.

The study treatment must be used only in accordance with the protocol. The Investigator will also maintain records adequately documenting that the patient was provided with the specified study drugs. These records should include dates, quantities, and any available batch or serial numbers or unique code numbers assigned to the study drugs and study patients.

Completed accountability records will be archived by the site. The Investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study drugs until verified by the study monitor (unless otherwise agreed to by the Sponsor). At the conclusion of the study, the Investigator or designee will oversee shipment of any remaining study drug back to the Sponsor or designee, or destruction of study drug according to institutional standard operating procedures.

Detailed information on study drug preparation, handling, storage and accountability will be provided in the IPM.

6.3. Randomization and Blinding

6.3.1. Randomization and Blinding

No randomization or blinding mechanisms will be used in this open-label study; however, the study treatment will be dispensed using an IWRS. The site will contact the IWRS to enroll the patient and to obtain the study drugs. All subsequent cycles will follow this process. The IWRS will also be used to order study drug supplies and document when patients are discontinued from treatment. Full details will be provided in the Study Manual.

6.3.2. Patient Numbering

Each patient is identified in the study by a Patient Number (Patient No.), that is assigned when the patient enters the screening period and is retained as the primary identifier for the patient throughout his/her entire participation in the study. The Patient No. consists of the 4 digits Center Number (as assigned by the Sponsor or designee to the investigative site) with a sequential patient number suffixed to it (the last 4 digits of the Patient ID), so that each patient is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Patient No. available to each Investigator through IWRS. Once assigned, the Patient No. must not be reused for any other patient and the Patient No. for that individual must not be changed, even if the patient is rescreened. If the patient fails to be enrolled or start treatment for any reason, the reason will be entered into the eCRF. Refer to Section 5.4 for further information on data collected for screen failures. The IWRS must be notified within 2 days that a patient did not initiate study drug dosing.

6.4. Study Treatment Compliance

Patient compliance with study treatment will be assessed at each visit. Compliance with all study-related treatments should be emphasized to the patient by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Compliance will be assessed by an accounting of returned study drugs (tablet/capsule counts) and patient interviews. Patients will be instructed to bring all study drugs (used, partially used, unused drug and/or empty containers) with them to study site visits in order for site personnel to

assess study drug accountability. Deviation(s) from the prescribed dosage regimen should be recorded in source and in the eCRF.

6.5. Concomitant Therapy

All concomitant medications and treatments (including over-the-counter or prescription medicines, vitamins, vaccines and/or herbal supplements) must be recorded in the eCRF. Details regarding **all** prior anticancer treatments will also be recorded in the eCRF.

Any prior medication received up to 28 days before the first dose of study treatment and 30 days after the last dose of study treatment, or until the patient begins a new anticancer therapy, whichever occurs first will be recorded in the eCRF. Any addition, deletion or change in the dose of these medications will also be recorded. Unless specifically prohibited, concomitant medications can be administered at the Investigator's discretion to manage the patient's medical condition.

All concomitant treatments/procedures (including over-the-counter or prescription medications, vitamins and/or herbal supplements) that are required to manage a patient's medical condition during the study will be recorded in the eCRF including:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information (using generic drug names when possible), including dose and frequency.

COVID-19 vaccines approved under an EUA (or equivalent) are considered allowed concomitant medications and standard AE collection and reporting processes should be followed. The timing of vaccine dosing relative to the dosing of study medications is at the discretion of the investigator although administration should be avoided on the first day of study medication dosing.

The Sponsor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1. Permitted Concomitant Therapy Requiring Caution and/or Action

6.5.1.1. CYP and UGT Substrates and Inhibitors

Encorafenib is a reversible inhibitor of CYP2B6, CYP2C9, CYP3A4 and UGT1A1. It is also a time-dependent inhibitor of CYP3A4, and induced CYP2B6, CYP2C9 and CYP3A4 in human primary hepatocytes. Permitted medications to be used with caution in this study include those that are sensitive substrates of CYP2B6, CYP2C9, CYP3A4 and UGT1A1 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. Therefore, the use of at least 1 form

of non-hormonal contraception is required for females of childbearing potential during participation in this study.

Caution should be used in patients 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 to be metabolized by CYP3A4 and to a lesser extent by CYP2C19 in vitro. **Concomitant use of moderate CYP3A4 inhibitors should be avoided.** If use of a moderate CYP3A4 inhibitor is unavoidable, short-term use (≤ 30 days) following discussion with the Sponsor may be permitted with an accompanying dose reduction to one-half of the encorafenib dose prior to use of the moderate CYP3A4 inhibitor. After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume the encorafenib dose that was taken prior to initiating the CYP3A4 inhibitor.

In vitro, binimetinib has been identified to be primarily metabolized by glucuronidation. Strong inducers of UGT1A1 should be taken with caution when co-administered with binimetinib.

For tabulated CYP substrates, inhibitors and inducers to be used with caution or avoided, please consult with the FDA website: Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers.

6.5.1.2. Transporter Substrates and Inhibitors

In vitro data showed that encorafenib is a substrate of the transporter P-gp. Thus, drugs that are known to inhibit or induce P-gp should be used with caution. Encorafenib is also a potent inhibitor of the renal transporters, OAT1, OAT3 and OCT2, and the hepatic transporters OATP1B1 and OATP1B3. The co-administration of drugs that are known to be sensitive or narrow therapeutic index substrates of OAT1, OAT3, OCT2, OATP1B1 or OATP1B3 should be used with caution.

Binimetinib has also been shown to be a substrate of P-gp and BCRP. It is advised that inhibitors and inducers of P-gp and BCRP transporters should be taken with caution when co-administered with binimetinib.

For tabulated transporter substrates, inhibitors and inducers to be used with caution, please consult with the FDA website: Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers.

6.5.1.3. Drugs with a Conditional or Possible Risk to Prolong 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. Patients receiving such medications must be carefully monitored for potentiating of toxicity due to any individual concomitant medication and may require dose titration of the concomitant medication. See the CredibleMeds® website: Combined List of Drugs That Prolong QT and/or cause Torsades de Pointes (TDP).

6.5.2. Prohibited Concomitant Therapy

Medications specifically outlined below are not allowed during the study. If there is a clinical indication for one of these medications specifically prohibited during the study, discontinuation from the study treatment may be required. Patients may receive other medications that the Investigator deems to be medically necessary. The Investigator should discuss any questions regarding medications with the Sponsor. The final decision on any supportive therapy rests with the Investigator and/or the patient's primary physician. The decision to continue the patient in the study requires mutual agreement of the Investigator, the Sponsor and the patient.

The following therapies are prohibited during the Screening and Treatment Periods of this study (unless otherwise noted). There are no prohibited therapies during the post-treatment Follow-up Period.

- No additional anticancer agents such as cytotoxic chemotherapy, small-molecule targeted agents, biological agents, immune response modifiers or hormonal therapy are to be administered to patients while they are receiving study treatment.

- Investigational drugs and devices.

- Radiation therapy (not including palliative radiotherapy at focal sites that covers ≤ 10% of the bone marrow reserve).
  Note: The patient 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. ***Note:*** Administration of palliative radiation therapy will be considered clinical progression for the purposes of determining PFS.

- Concomitant strong systemic CYP3A4 inhibitors, which could significantly increase the exposure of encorafenib.

- Concomitant moderate or strong systemic CYP3A4 inducers, which could significantly decrease the exposure of encorafenib.

6.6. Dose Modification

6.6.1. Dose Interruptions

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

Individual decisions regarding dose interruptions and modifications should be made using appropriate clinical judgment, considering relatedness of the AE to the study treatment and the patient's underlying condition. Adverse events that have a clear alternative explanation, or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms may be exempt from dose-reduction rules. The treating Investigator

should refer to and follow the labeled guidance and/or institutional guidelines for the management of toxicities relating to encorafenib and binimetinib. Detailed guidelines can also be found in Appendix 2 and Appendix 3.

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). Patients should be placed back 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 patient's study record.

If a patient misses > 6 weeks (i.e., 42 consecutive days) of dosing with encorafenib, study treatment with encorafenib will be permanently discontinued. Due to the potential for limited efficacy of binimetinib alone in the study population, if a patient permanently discontinues treatment with encorafenib, they must also permanently discontinue treatment with binimetinib.

If a patient misses > 6 weeks (i.e., 42 consecutive days) of dosing with binimetinib, study treatment with binimetinib will be permanently discontinued. If a patient discontinues treatment with binimetinib, the patient may continue treatment with encorafenib. Due to the potential for increased toxicity when binimetinib is discontinued, doses of single-agent encorafenib may need to be decreased.

6.6.2. Dose Modifications

Doses of encorafenib and binimetinib may be independently reduced for toxicity management as outlined in Table 7 and Table 8, respectively. All dose modifications are based on the worst preceding toxicity. The treating Investigator should refer to and follow the labeled guidance and/or institutional guidelines for the management of toxicities relating to encorafenib and binimetinib. Detailed guidelines can also be found in Appendix 2 and Appendix 3.

When the AE that resulted in a dose reduction improves to and remains stable to the patient's baseline for a minimum of 14 days, the dose can be re-escalated to the next higher dose level at the discretion of the Investigator, provided there are no other concomitant toxicities that would prevent drug re-escalation. There is no limit to the number of times the patient can have their dose reduced or re escalated; however:

- No dose re-escalation of encorafenib is allowed after a dose reduction due to prolonged QTcF ≥ 501 msec
- No dose re-escalation of binimetinib is allowed after a dose reduction due to LVEF dysfunction
- No dose re-escalation of binimetinib or encorafenib is allowed after a dose reduction due to ocular toxicity ≥ Grade 2

Table 7. Dose Reductions for Encorafenib

Dose Level	Encorafenib
0 (starting dose)	450 mg QD
-1	300 mg QD
-2	225 mg[a] QD

NOTE: Dose reduction should be based on the highest AE grade.
a Dose reduction below 225 mg QD of encorafenib is not allowed.

Table 8. Dose Reductions for Binimetinib

Dose Level	Binimetinib
0 (starting dose)	45 mg BID
-1	30 mg[a] BID

NOTE: Dose reduction should be based on the highest AE grade.
a Dose reduction below 30 mg BID of binimetinib is not allowed.

6.7. Criteria for Permanent Discontinuation of Study Treatment

A patient may choose to withdraw from study treatment at any time or be withdrawn from study treatment by the Investigator or Sponsor, if the patient does not comply with study requirements. If a patient is withdrawn from any/all study treatment, reasonable efforts will be made to determine the reason for withdrawal, and this information will be recorded in the eCRF.

As of IRB/IEC approval of Amendment 3, patients who request to discontinue receipt of study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures (see Section 7.1.4.2 and Section 7.1.4.3). The only exception to this is when a patient specifically withdraws consent for any further contact with him or her or persons previously authorized by the patient to provide this information. Patients should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study treatment or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the patient is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Patients meeting any of the following criteria **must** discontinue all study treatment:

- Withdrawal of consent. Patients may choose to withdraw from the study at any time without penalty of jeopardizing their healthcare or loss of benefits to which the patient is otherwise entitled. Patients will have the option of withdrawing consent for study treatment but continue in the follow-up period of the study for safety/efficacy assessments.
  Note: Consent withdrawn **from study treatment** means that the patient may choose to discontinue study treatment but remain in the study to be followed for safety, progression, subsequent therapies and survival. In this case, follow-up data will continue to be collected for this patient.
  Note: Consent withdrawn for the **study** means that the patient has explicitly indicated that they do not want to be followed any longer; in this case no further data, except data in the public domain, may be solicited from or collected on the patient.

- Unacceptable AEs or failure to tolerate study treatment is defined as:

  - Grade 4 or life-threatening AE as outlined in Appendix 2 and Appendix 3, (except with approval from the Sponsor);

  - Toxicity requiring more than the allowed number of dose reductions for encorafenib and binimetinib as described in Table 7 and Table 8, respectively;

  - Occurrence of an AE that is related to study treatment and in the judgment of the Investigator compromises the patient's ability to continue study-specific procedures, or is considered to not be in the patient's best interest.

- Patient has missed > 6 weeks (i.e., 42 consecutive days) of dosing per Section 6.6.1.

- Disease progression per RECIST v1.1.

- Clinical progression, as determined by the Investigator in the absence of radiographic progression.

- Patient becomes pregnant or begins breastfeeding.

- Significant protocol deviation that, in the opinion of the Investigator and/or Sponsor, renders the patient unsuitable for further study treatment administration.

- Patient is noncompliant with study procedures or study treatment that in the judgment of the Investigator or Sponsor renders the patient unsuitable for further study participation.

- Patient is lost to follow-up.

- Death.

- Termination of the study by the Sponsor (described in Section 4.6 and Section 9.10).

If the decision is made to permanently discontinue study treatment the EOT visit should be conducted (see Section 7.1.3). Reasonable efforts should be made to have the patient return for all applicable follow-up visits (safety and efficacy), as outlined in the Table 3. The date of the last dose of study treatment will be recorded in the eCRF.

6.8. Criteria for Study Discontinuation

Patients will be considered as having discontinued the study if any of the following criteria are met:

- Patient completes all required follow-up visits.
- Patient dies, and the date of death is available or patient is known to have died; however, the date of death cannot be obtained.
  Note: Every effort must be made to obtain the date of death.
- Consent is withdrawn for any further contact related to the study.
  Note: Every reasonable effort should be made to determine the reason a patient withdraws prematurely, and this information should be documented in the eCRF.
- Patient is lost to follow-up.
- Termination of the study by the Sponsor (described in Section 4.6 and Section 9.10).
- Termination of the study by the local health authority, IRB or IEC.

6.9. Intervention after the End of the Study

At the end of the study, all patients who have otherwise not met the protocol-defined criteria for treatment withdrawal (see Section 6.7), will be offered access to study treatment in accordance with applicable regulations and requirements (i.e., including where required, separate health authority approval for continued access).

6.10. Enrollment of Additional Patients

Additional patients may be enrolled to ensure that there are at least 60 treatment-naïve patients and 37 previously treated patients whose tumors have locally confirmed *BRAF*^{V600E} mutation, and who have received at least one dose of study treatment. Up to 10 additional patients who have a *BRAF*^{V600} mutation other than *BRAF*^{V600E} (*BRAF*^{V600x}) can be enrolled and treated. It is not expected that more than 107 patients with any *BRAF*^{V600} mutation will be enrolled and treated.

6.11. Lost to Follow up

A patient 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 patient fails to return to the study site for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether the patient wishes to and/or should continue in the study.

- Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient. These contact attempts will be documented in the patient's medical record.

- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study and lost to follow-up.

7. STUDY VISITS AND ASSESSMENTS

The timing of study visits and assessments are summarized in the SoA (Table 3). Protocol waivers or exemptions are not allowed. Safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

7.1. Study Visits

7.1.1. Screening

Screening is the interval between signing the ICF up to the time at which the patient receives the first dose of study treatment (i.e., Cycle 1 Day 1). Screening may not exceed 28 days. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during the Screening process.

Procedures conducted as part of the patient's routine clinical management (e.g., blood count, imaging study) and obtained before signing of the ICF may be utilized for Screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Table 3). If baseline scans from an institution other than the investigational site are used, the site must obtain copies of the scans prior to enrollment of the patient, or the scans must be repeated at the investigational site and submitted for independent review (see Section 7.2.4).

All Screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable. Tests with results that fail eligibility requirements may be repeated once during screening if the Investigator believes the results to be in error. For screening assessments that are repeated, the most recent available results before first dose of study treatment will be used to determine eligibility.

See Section 5.4 and Section 6.10 for information regarding screen failures and enrollment of additional patients, respectively.

7.1.1.1. *BRAF*^{V600} Mutation Testing

Patients will be eligible for the study based on identification of a *BRAF*^{V600} mutation in the tumor tissue or blood (e.g., ctDNA genetic testing), as determined by a local laboratory assay. Patients must have written documentation from a previous local pathology report of *BRAF*^{V600} mutation in tumor tissue or by genetic blood test. Only PCR and NGS-based local assay results will be acceptable for tumor tissue or blood.

The Investigator must confirm prior to enrollment that the patient has adequate tumor tissue available for confirmation of *BRAF*^{V600} mutation status by the central laboratory. Results of central confirmation of *BRAF*^{V600} mutation status is not required prior to enrollment and will not be used for determining patient eligibility.

Archived tumor tissue or a newly obtained core or excisional biopsy sample from all patients are required to be submitted to the central testing laboratory. FNA is acceptable provided there is sufficient material (1 block or a minimum of 8 unstained slides [up to 15 unstained slides is preferred]) from the same sample used to obtain the local BRAF positive result available to send to the central laboratory.

For archival tumor tissue samples, whenever possible the sample sent for central testing should be from the same tumor block that was used for local *BRAF*^{V600} mutation testing. A minimum of 8 slides (up to 15 is preferred) should be submitted to the central laboratory to ensure adequate sample for testing. Tumor cells from pleural fluid are permitted provided the sample has been centrifuged to generate a formalin-fixed, paraffin-embedded block with sufficient tumor nuclei (i.e. >20% tumor nuclei). Liquid samples are not permitted. One block or a minimum of 8 unstained slides (up to 15 unstained slides is preferred) must be sent to the central laboratory. Further details regarding sample submission including instructions for sample preparation and shipping will be provided in the Laboratory Manual.

If a fresh biopsy is taken, the biopsy should be taken from a nontarget lesion when possible.

7.1.2. Treatment Period

The treatment period begins on the day the patient receives the first dose of study treatment (i.e., Cycle 1 Day 1) through the point which the patient permanently discontinues all study treatment. During the treatment period, patients will have regularly scheduled assessments as outlined in the SoA (Table 3).

7.1.3. End of Treatment and/or Early Termination

When the patient permanently discontinues all study treatment (see Section 6.7), whether the patient is terminating the study early or has completed the study (see Section 6.8), the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of the scheduled visit, and the data will be entered in the EOT visit in the eCRF.

If the patient is withdrawn from study treatment and/or study:

- The study monitor and Sponsor must be notified.
- The primary reason for withdrawal must be documented in the patient's medical record and in the eCRF.
  Note: The reason for withdrawal from treatment may be different from the reason for withdrawal from study. For example, patients can discontinue treatment for disease progression or toxicity, but remain in the study for safety and survival follow-up.
- The EOT and safety follow-up visits as outlined in the SoA (Table 3) should be performed.
- Patients should be followed for safety as outlined in Sections 7.1.4.1 and 7.5.1.1.
- Patients who discontinue study treatment for reasons other than disease progression will continue to be followed for disease status as outlined in Section 7.1.4.2.
- All patients who discontinue study treatment will continue to be followed for subsequent anticancer therapies and survival (see Section 7.1.4.3).
- If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a patient 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.

7.1.4. Post-treatment Follow-up

Cutaneous squamous cell carcinoma has been observed in patients treated with BRAF inhibitors including encorafenib. It is recommended that dermatologic screening for skin malignancies be performed every 8 weeks until 6 months after the last dose of encorafenib. Patients should be instructed to immediately inform the Investigator if new skin lesions develop.

7.1.4.1. 30-Day Safety Follow-up

The safety follow-up period is the interval between the EOT visit and the scheduled follow-up visit, which should occur 30 days (+ 7 days) after the EOT visit (or after the last dose of study treatment if the EOT was not performed). Adverse events and SAEs must be reported as outlined in Section 7.5.1.1 and Section 7.5.1.2. Information related to AEs (including concomitant medication taken for ongoing AEs) and new anticancer therapies will be collected. Reasonable efforts should be made to have the patient return for the safety follow-up visit and report any AEs that may occur during this period. If the patient is scheduled to start a new anticancer therapy before the end of the 30-day follow-up period, the safety follow-up visit should be performed before the new anticancer therapy is started.

7.1.4.2. Disease Follow-up

Patients who discontinue study treatment **for a reason other than disease progression** will move into the disease status follow-up and should be assessed every 8 weeks (±7 days) by radiological imaging to monitor disease status. If the patient discontinues for reasons other than disease progression after 12 months of treatment, then radiographic disease assessments will be performed every 12 weeks (±7 days). Every effort should be made to collect information regarding disease status until:

- Initiation of subsequent anticancer therapy
- Disease progression
- Death
- Withdrawal of consent
- Patient is lost to follow-up
- Defined end of study

7.1.4.3. Survival Follow-up

Once a patient has received the last dose of study treatment, has confirmed disease progression, or starts a new anticancer therapy, the patient moves into the survival follow-up period and should be contacted by telephone, email, or site visit by the patient or patient's caregiver at least every 12 weeks (±7 days), until withdrawal of consent, the patient is lost to follow-up, death or defined end of the study, whichever occurs first. The following information will be recorded at each follow-up assessment:

- Following the 30-day safety follow-up period, record new SAEs that are considered related to study treatment.
- Record all subsequent anticancer therapies.
- Determine survival status.

If patients withdraw consent for study treatment, they will be asked if they are willing to be contacted via telephone for survival status. If the patient refuses to be contacted, attempts to determine survival status should be made via access to public records/databases where permitted by local laws.

7.1.5. Unscheduled Visits

Unscheduled study visits may occur at any time if medically warranted. Any assessments performed at those visits should be recorded in the eCRF.

7.2. Efficacy Assessments

7.2.1. Radiological Tumor Evaluation

RECIST v1.1 (Eisenhauer et al, 2009) will be applied by the site as the primary measure of tumor assessment and response and as the basis for protocol guidelines related to disease status (e.g., discontinuation of study treatment).

Radiological scans of all suspected sites of disease will be performed utilizing the same method and technique throughout the study. Target lesions should demonstrate the patient's baseline tumor burden and will be selected based on size (i.e., lesions with the longest diameter), and suitability for accurate repeat assessment.

The following should be performed:

- Chest, abdomen, and pelvis CT scans (or MRI if CT is contraindicated) scans are required for all patients at Screening. An MRI of the brain is also required for all patients at Screening. A CT scan of the brain, preferably with IV contrast, may be performed if MRI is contraindicated. Additional imaging of anatomical sites (e.g., head and neck, etc.) should be performed as applicable based on location of disease sites.

- During the study chest, abdomen, and pelvis CT scans (or MRI if CT is contraindicated) are required for all patients. If additional imaging of anatomical sites (e.g., head and neck) were performed at baseline, they should be continued throughout the duration of the study. Additional imaging of anatomical sites (e.g., head and neck, etc.) should be performed as applicable based on location of disease sites. Subsequent MRIs of the brain will only be performed if there were lesions present at baseline.

- Skeletal lesions identified at Screening should continue to be imaged at subsequent scheduled visits using localized CT, MRI, or X-ray (using the same method used at Screening for all visits for any given lesion).

- 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. If off schedule imaging evaluations are performed in the absence of progression, every effort should be made to perform subsequent imaging evaluations in accordance with the original imaging schedule or discussed with the Sponsor as applicable.

Chest X-ray or ultrasound should not be used for tumor response assessments in this study.

While FDG-PET scans are not required for this study, sites may perform combined PET/CT scans per their local standard of care, provided the CT is of similar diagnostic quality as CT performed without PET, including the use of oral and IV contrast media. If acquired according to local standard of care, FDG-PET may be relied upon to document PD in accordance with RECIST.

7.2.2. Tumor Imaging During Screening

Initial tumor imaging must be performed within 28 days before the first dose of study treatment. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days before the first dose of study treatment.

The patient must have documentation of measurable disease per RECIST v1.1. Any lesions that have been subjected to loco-regional therapies (e.g., radiotherapy, ablation, etc.) should not be considered measurable, unless they have clearly progressed since the therapy. Previously treated lesions that have not progressed should be considered non-measurable and assessed as non-target lesions.

7.2.3. Tumor Imaging During Treatment

The first imaging assessment should be performed as follows:

- 8 weeks after the first dose of study treatment
- Every 8 weeks (56 days ± 7 days) for 12 months, and then every 12 weeks (± 7 days) thereafter until disease progression is determined or until any of the criteria in Section 7.1.4.2 are met.
- Imaging assessments may be performed more frequently if clinically indicated.

Imaging should follow calendar days and should not be delayed, irrespective of study treatment administration (i.e. delays in cycles or dose holds).

Per RECIST v1.1, responses (PR or CR) should be confirmed by a repeat radiographic assessment. The scan for confirmation of response may be performed no sooner than 4 weeks after the first documented response and no later than the next per-protocol scheduled scan, whichever is clinically indicated.

Radiographic disease assessments should be performed until disease progression per RECIST v1.1, withdrawal of consent, initiation of subsequent anticancer therapy, patient is lost to follow-up, death or defined end of study (see Section 4.5 and Section 6.8).

7.2.4. Independent Radiology Review

All radiographic images from screening and performed during the study are to be sent to a central imaging vendor to perform an independent radiographic imaging assessment of tumor status. Further details of the IRR are described in the Independent Radiology Review Charter. A detailed description of the procedures for the collection and storage of radiological scans is provided in the Study Manual. Of note, patient management decisions will be made by Investigator assessment and not by the independent central review. Results from IRR will not be provided to the Investigator.

7.2.5. Performance Status

Assessment of ECOG PS (Oken et al, 1982) will be conducted as shown in Table 9 and at the time points specified in the SoA (Table 3).

Table 9. Eastern Cooperative Group Performance Status Scoring

Grade	ECOG Performance Status
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 house work, 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

7.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 3).

7.3.1. Patient Demographics and Other Baseline Characteristics

Demographic data and general medical history will be collected at Screening by the Investigator or qualified designee and will include relevant medical and surgical history **within the last 10 years**, smoking history and current illnesses.

7.3.2. Disease Characteristics and Treatment History

A disease-targeted medical and treatment history will be collected at Screening. Details regarding the patient's malignancy under study, including date of diagnosis, initial and current cancer stage, tumor histology, relevant disease characteristics, and prior treatments including systemic, radiation, and surgical procedures, will be recorded.

7.3.3. Physical Examinations

Physical examinations will be performed by trained medical personnel at the time points specified in the SoA (Table 3).

At Screening, the physical examination should be comprehensive and include the examination of general appearance, skin, 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, breast and pelvic examinations will be performed. Body weight will be measured as part of the physical examination at each visit. Height will be measured only at Screening.

For subsequent visits (e.g., Day 1 of each cycle), the physical examinations should be targeted as clinically indicated. Investigators should pay special attention to clinical signs related to previous serious illnesses.

All physical examinations occurring on dosing days must be performed prior to study drug administration. Any treatment-emergent abnormal findings will be recorded as AEs.

7.3.4. Dermatological Examinations

Dermatologic evaluations will be performed at the site by the Investigator 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 et al, 2010; Kefford et al, 2010; Robert et al, 2011). This assessment may be performed predose or postdose at the time points specified in the SoA (Table 3).

In addition, dermatologic screening for skin malignancies will be performed every 8 weeks until 6 months after the last dose of encorafenib (see Section 7.1.4).

In case of occurrence of keratoacanthoma or squamous cell carcinoma, patients will undergo complete surgical excision of the skin lesion following institutional standards. Dermatologic evaluations will be performed by a dermatologist as clinically indicated.

7.3.5. Ophthalmic Examinations

Full ophthalmic examination will be performed by an ophthalmologist at Screening (Table 3), including best corrected visual acuity, slit lamp examination, intraocular pressure, dilated fundoscopy and optical coherence tomography. Examination of the retina is required (especially to identify findings associated with RPED, serous detachment of the retina and RVO). The ophthalmic evaluation should be repeated at any point during the treatment period as clinically indicated.

During the treatment period, visual acuity testing will be performed on Day 1 of each cycle.

7.3.5.1. Additional Ophthalmic Testing

Patients with clinical suspicion of retinal abnormalities of any grade (e.g., RPED, serous detachment of the retina, RVO, photopsia, metamorphopsia, impairment of visual acuity) **must** complete at least one of the following additional assessments:

- For non-vascular abnormalities: optical coherence tomography (spectral domain optical coherence tomography recommended)
- For vascular abnormalities: fluorescein angiography of the central 30 degrees.

Images/results of the ophthalmic examinations (at a minimum, optical coherence tomography and/or fluorescein angiography) must be sent to the investigational site and be maintained in the patient's source document file. These images/results must be made available upon Sponsor request.

7.3.6. Vital Signs

Vital sign measurements (should be taken before blood collection for laboratory tests or at least 30 minutes after blood collection for laboratory tests), will be measured per institutional standards as part of the physical examination at the time points specified in SoA (Table 3). Vital sign assessments include the following:

- Temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure will be assessed with the patient in a recumbent, semi recumbent, or sitting position. Manual techniques will be used only if an automated device is not available. Blood pressure and pulse measurements will be preceded by at least 5 minutes of rest.

All vital sign measurements occurring on dosing days must be performed prior to study drug administration. Abnormal vital sign results identified after the first dose of study treatment constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug/treatment.

7.3.7. Electrocardiograms

A triplicate ECG (3 serial ECGs conducted within approximately 5 to 10 minutes total time) will be performed at Screening to confirm patient eligibility and predose on Cycle 1 Day 1 to serve as a baseline measurement of cardiac function. A single ECG will be performed at all remaining time points specified in the SoA (Table 3). Timing for when ECGs should be performed is outlined in Table 10.

Prior to performing the 12-lead ECG, patients will rest in the supine position for at least 5 minutes. When an ECG is to be performed at the same time point as a blood collection, the ECG is to be performed first.

Interpretation of the tracing will be made by a qualified physician and documented in the eCRF. QT interval values will be corrected for heart rate using the Fridericia formula (QTcF). Clinically significant abnormalities present when the patient signed the informed consent/assent but prior to the first dose of study treatment should be recorded as medical history in the eCRF. New or worsened clinically significant findings occurring after the first dose of study treatment must be recorded as an AE in the eCRF.

An abnormal ECG (e.g., ECG 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.

Table 10. Timing of ECGs

Visit	Anytime	Before Morning Dose of Study Treatment	2 hours (± 15 min) After Morning Dose of Study Treatment
Triplicate ECGs			
Screening	X		
Cycle 1 Day 1		X	
Single ECGs			
Cycle 1 Day 1			X
Cycle 2 Day 1		X	X
Every 12 Weeks (Cycle X Day 1)		X	X
EOT	X		

7.3.8. Echocardiogram/Multi-gated Acquisition

Cardiac ejection fraction will be assessed by transthoracic ECHO or MUGA at the time points specified in SoA (Table 3). The same method should be used throughout the study. Patients who develop signs/symptoms of CHF at any point during the study are required to have an evaluation of LVEF measurements by ECHO or MUGA and should be monitored per institutional guidelines.

7.3.9. Clinical Laboratory Assessments

Blood and urine samples for the laboratory tests listed in Table 11 will be collected at the time points specified in the SoA (Table 3).

A central laboratory will perform all clinical laboratory assessments (i.e., blood chemistries, hematology, coagulation, serology, serum pregnancy and urinalysis), PK assessments (see Section 7.8) and biomarker assessments (see Section 7.10). Additional testing may be required by the Sponsor based on emerging safety data. Additional tests may also be performed if clinically indicated.

All protocol-required laboratory assessments outlined in Table 11 must be conducted in accordance with the Laboratory Manual. Information regarding collection, processing, and shipping of laboratory assessments is provided in the Laboratory Manual. The Investigator must review the laboratory report and document this review. The laboratory reports must be filed with the source documents.

Local site laboratories may be utilized, in addition to the central laboratory, if more rapid results are required for treatment decisions or for patient safety. Local site laboratory results obtained during the study will not be captured in the eCRF unless the Investigator determines they are needed to clarify why a treatment decision was made or an AE was recorded.

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in patient management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification), then the results of the specific laboratory assessment must be recorded in the eCRF.

Screening laboratory assessments for hematology and serum chemistry must be performed within 7 days of Cycle 1 Day 1. After Cycle 1, predose laboratory procedures can be conducted up to 72 hours (within a 3-day window) before study treatment administration, and results should be reviewed by the Investigator or qualified designee and found to be acceptable before a treatment is initiated.

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 patient's condition. All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator.

Table 11. Summary of Clinical Laboratory Tests

Hematology	Chemistry	Urinalysis	Coagulation	Others
Hemoglobin Hematocrit RBC Platelets WBC Neutrophils/ANC Lymphocytes Monocytes Eosinophils Basophils	Albumin Alkaline phosphatase ALT Amylase AST Bicarbonate or CO_2 Total bilirubin BUN or urea Calcium Chloride CK (If total CK ≥ 3 × ULN, then measure isoenzymes, serum creatinine and myoglobin in blood weekly) Creatinine Glucose LDH Lipase Magnesium Phosphate Potassium	Appearance Color Specific gravity pH Protein Glucose Ketones Blood Nitrite Leukocytes	PT INR PTT or aPTT	**At Screening only:** Hepatitis B surface antigen Hepatitis B surface antigen antibody Hepatitis B core antibody Hepatitis C antibody HIV, as applicable per local regulations **If applicable:** Only females of childbearing potential require pregnancy testing. Serum and urine pregnancy tests will be performed as per the SoA (Table 3). Pregnancy tests (serum or urine) should be repeated if required by local regulations or as clinically indicated.

Table 11. Summary of Clinical Laboratory Tests

Hematology	Chemistry	Urinalysis	Coagulation	Others
	Total protein Sodium Uric acid Direct bilirubin (if total bilirubin values are above ULN)			

7.3.9.1. Serology

Hepatitis screening assessments will be performed by the central laboratory at the Screening visit to rule out hepatitis infection; required analytes are shown in Table 11. Generally, hepatitis tests should be performed early in the screening process due to the length of time needed to obtain the results. HIV testing will only be done at sites where mandated locally. Additional tests may be performed if clinically indicated.

7.3.9.2. Pregnancy Testing

Pregnancy testing (serum and urine) as outlined in the SoA (Table 3) will only be required for women of childbearing potential as defined in Appendix 1. Serum pregnancy tests will be performed centrally, and urine pregnancy tests will be performed locally. Pregnancy testing (serum or urine) should be repeated as medically indicated (e.g., in case of loss of menstrual cycle, when pregnancy is suspected), or per country-specific requirement (note that country-required urine pregnancy testing will be outlined and communicated to the investigational sites under separate cover). All blood and urine collections for pregnancy tests occurring on dosing days (i.e., Day 1 of each cycle) must be performed with results available prior to study treatment administration.

If a urine pregnancy test is positive, the results will be confirmed with a serum pregnancy test. If the serum pregnancy test is negative after a urine test was positive, the Investigator will assess the potential benefit/risk to the patient and determine whether it is in the patient's best interest to resume study treatment and continue participation in the study. If pregnancy is confirmed by a serum pregnancy test, see Section 7.5.5 for reporting requirements.

Patients of nonchildbearing potential as defined in Appendix 1 do not require pregnancy tests.

7.4. Other Study Procedures

7.4.1. Distribution of Dosing Diary

Patients will be provided with a dosing diary at study visits as outlined in Table 3. The dosing diary will include the following information:

- Date and time of the next visit.

- Dosing instructions (see Section 6.1).
- Reminder that the patient should not take their morning dose of study treatment on study visit days (Day 1 of each cycle) and days when PK samples are collected (see Table 12 and Table 13).
- Date and time of each dose taken daily for both encorafenib and binimetinib.
- Information regarding missed/skipped doses.
- Instructions to bring all unused study drugs and/or empty containers to the site at each visit to assess patient compliance with study treatment (see Section 6.4).

7.5. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 4.

AEs will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the patient to discontinue the study treatment (see Section 6.7).

Each patient or legally authorized representative will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

7.5.1. Time Period and Frequency for Collecting AE and SAE Information

As of IRB/IEC approval of Amendment 3, the time period for actively eliciting and collecting AEs and SAEs (“active collection period”) for each patient begins from the time the patient provides informed consent, which is obtained before the patient’s participation in the study (ie, before undergoing any study-related procedure and/or receiving study treatment), through and including a minimum of 30 calendar days, except as indicated below, after the last administration of the study treatment. ***Note***: Prior to IRB/IEC approval of Amendment 3 only study procedure related AEs were required to be reported from the time the patient provided informed consent up to the first dose of study treatment.

During the long-term follow up period in this study for survival, only SAEs will be actively elicited and collected after completion of the active collection period described above. The SAEs identified during long-term follow-up will be reported to Pfizer Safety on the CT SAE Report Form only if considered reasonably related to the study treatment.

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For patients who are screen failures, the active collection period ends when screen failure status is determined.

If the patient withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a patient definitively discontinues or temporarily discontinues study treatment because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the patient has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a patient has completed the study, and he/she considers the event to be reasonably related to the study treatment, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

7.5.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a patient during the active collection period as described above in Section 7.5.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

If a patient begins a new anticancer therapy, SAEs occurring during the above-indicated active collection period must still be reported to Pfizer Safety irrespective of any intervening treatment. Note that a switch to a commercially available version of the study treatment is considered as a new anticancer therapy for the purposes of SAE reporting.

7.5.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a patient during the active collection period, which begins after obtaining informed consent as described in Section 7.5.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the patient.

If a patient begins a new anticancer therapy, the recording period for nonserious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above-indicated active collection period. Note that a switch to a commercially available version of the study treatment is considered as a new anticancer therapy for the purposes of SAE reporting.

7.5.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

7.5.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each patient at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 6.11).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 4.

7.5.4. Regulatory Reporting Requirements for SAEs

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

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator 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 SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator Brochures for the study and will notify the IRB/EC, if appropriate according to local requirements.

7.5.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study treatment under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

7.5.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female patient is found to be pregnant while receiving or after discontinuing study treatment.
- A male patient who is receiving or has discontinued study treatment exposes a female partner prior to or around the time of conception
- A female is found to be pregnant while being exposed or having been exposed to study treatment due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study treatment by ingestion.
    - A male family member or healthcare provider who has been exposed to the study treatment by ingestion then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a patient or a patient's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study treatment and until 6 months after the last dose.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the patient enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study treatment.

Additional information regarding the EDP may be requested by the sponsor. Further followup of birth outcomes will be handled on a case by case basis (eg, followup on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the patient with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the patient was given the Pregnant Partner Release of Information Form to provide to his partner.

7.5.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female patient is found to be breastfeeding while receiving or after discontinuing study treatment.
- A female is found to be breastfeeding while being exposed or having been exposed to study treatment (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study treatment by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the patient enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

7.5.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study treatment, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial patient's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the CT SAE Report Form. Since the information does not pertain to a patient enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

7.5.6. Cardiovascular and Death Events

Not applicable

7.5.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

7.5.8. Adverse Events of Special Interest

See Section 2.1.4 Clinical Safety of Combination Encorafenib and Binimetinib for descriptions of AESIs.

All AESIs must be reported as an AE or SAE following the procedures described in Section 7.5.1 through Section 7.5.1.2. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the CT SAE Report Form.

7.5.8.1. Lack of Efficacy

Lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

7.5.9. Medical Device Deficiencies

Not applicable.

7.5.10. Medication Errors

Medication errors may result from the administration or consumption of the study treatment by the wrong patient, or at the wrong time, or at the wrong dosage strength.

Exposures to the study treatment under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the AE CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	Only if associated with an AE or SAE	Only if associated with an SAE

Medication errors include:

- Medication errors involving patient exposure to the study treatment;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study patient.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

If applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE.**

7.6. Treatment of Overdose

There is no antidote known to over dosage either encorafenib or binimetinib. Supportive measures should be instituted.

In the event of an overdose, the investigator/treating physician should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the patient for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of study treatment (whichever is longer). Closely monitor the patient for any AEs/SAEs.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Sponsor Medical Monitor based on the clinical evaluation of the patient.

7.7. Product Complaints

The Sponsor collects product complaints on study treatments used in clinical studies in order to ensure the safety of study patients, monitor quality, and facilitate process and product improvements.

All product complaints associated with material packaged, labeled, and released by the Sponsor (or designee) will be reported to the Sponsor. All product complaints associated with other study material will be reported directly to the respective manufacturer.

The Investigator or his/her designee is responsible for reporting a complete description of the product complaint via email or other written communication to the Sponsor contact or respective manufacturer as noted in the packaging information. Any AE associated with a product complaint should be recorded as described in Section 7.5.1.1.

If the Investigator is asked to return the product for investigation, he/she will return a copy of the product complaint communication with the product.

7.8. Pharmacokinetics

For patients enrolled under Protocol Versions 0 through 3, serial blood samples (~4 mL each) for plasma PK analysis of encorafenib, its metabolite (LHY746), and binimetinib will be collected as shown in Table 12.

For patients enrolled under Protocol Version 4 or later, blood samples (~4 mL each)for plasma concentration of encorafenib, its metabolite (LHY746), and binimetinib will be collected as shown in Table 13.

Complete instructions for sample processing, handling and shipment will be provided in the Laboratory Manual.

Study visits for PK sampling should be scheduled in the morning so that proper predose and postdose PK blood samples can be collected. On the PK visit days, the morning doses of encorafenib and binimetinib will be taken at the study site under observation by the Investigator or designee at approximately the same time, only after collecting the predose PK sample. Predose sampling information will include the date and exact time of the most recent previous dose of binimetinib and encorafenib (except Cycle 1 Day 1), including the dose amount taken. Postdose sampling information, only needed for days with postdose PK sampling (i.e., Cycle 1 Day 1 and Cycle 1 Day 15), will include the date and exact time of the morning dose, including the dose amount taken. Except for the Cycle 1 Day 1 PK samples, which have to be obtained on the scheduled day, other PK samples may be obtained ± 1 day from the scheduled date.

If vomiting occurs within 4 hours following study treatment administration on the day of PK sampling, no additional study treatment will be taken in an effort to replace the material that has been vomited and it is recommended that no more PK samples be taken after the emesis occurs. Any vomiting that occurs will be noted in the PK eCRF. Further doses will be administered with premedication with antiemetic medications and PK sampling will be performed after premedication with antiemetics.

In addition, exploratory analyses on remaining plasma samples may be performed using a validated or non-validated, semi-quantitative or qualitative liquid chromatography tandem mass spectrometry method, if deemed appropriate.

Table 12. Serial Pharmacokinetic Blood Sample Timing in Patients Enrolled under Protocol Versions 0 through 3

Study Visit	Timing of Sample
Cycle 1 Day 1	• 0.5 hours (± 5 min) post dose • 1.5 hours (± 5 min) post dose • 3 hours (± 10 min) post dose • 6 hours (± 20 min) post dose
Cycle 1 Day 15	• Predose (within 30 minutes prior to dose) • 0.5 hours (± 5 min) post dose • 1.5 hours (± 5 min) post dose • 3 hours (± 10 min) post dose • 6 hours (± 20 min) post dose
Cycle 2 Day 1	• Predose (within 30 minutes prior to dose)

Table 13. Pharmacokinetic Blood Sample Timing in Patients Enrolled under Protocol Version 4 or later

Study Visit	Timing of Sample
Cycle 1 Day 1	• Predose (within 30 minutes prior to dose)
Cycle 2 Day 1	• Predose (within 30 minutes prior to dose)
Cycle 3 Day 1	• Predose (within 30 minutes prior to dose)
Cycle 4 Day 1	• Predose (within 30 minutes prior to dose)
Cycle 5 Day 1	• Predose (within30 minutes prior to dose)
Cycle 6 Day 1	• Predose (within 30 minutes prior to dose)

7.9. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

7.10. Biomarkers

Patients will be eligible for the study based on identification of a *BRAF*^{V600} mutation in the tumor or blood as determined by the local laboratory, and are required to also submit archival or fresh tissue to confirm *BRAF*^{V600} mutation status by a central laboratory (see

Section 7.1.1.1). Complete instructions for sample processing, handling and shipment will be provided in the Laboratory Manual.

If the patient consents, and in accordance with local laws, any tumor (archival or fresh) or blood samples remaining after determination of *BRAF*-mutation status may be stored for up to 5 years (or according to local regulations) after the completion of the study. Research will focus on biomarkers relevant to *BRAF* V600-mutant cancer. Potential future testing of DNA, RNA and protein from the biomarker samples, for example, may include somatic mutation molecular analyses (i.e., PCR) and IHC assays. No cell lines or model systems will be generated from the samples. All samples and data collected in connection with the study will be encoded by the study doctor and patient identity for all samples will remain unknown to others, including the study Sponsor. Raw data will not be shared and will not be uploaded to public databases. Summarized data may be shared as part of a collaborative research projects for publications. The decision to perform such exploratory biomarker research studies would be based on outcome data from this study or from new scientific findings related to the drug class or disease, as well as reagent and assay availability. The Sponsor will be the exclusive owner of any data and discoveries resulting from this study. Genetic testing results can be provided at the completion of the study upon request.

7.10.1. Circulating Tumor DNA Biomarker Analysis

In addition to the supplied tumor biopsy sample, blood samples will be collected as outlined in the SoA (see Table 3). The blood samples will be processed to plasma and purified ctDNA analyzed for potential genomic markers of encorafenib and/or binimetinib activity. The blood samples may be used for companion diagnostics or for exploratory research investigating genetic variants in ctDNA, such as $BRAF^{V600}$ mutations as well as additional tumor mutations.

The biomarker samples should be drawn prior to PK samples. Complete instructions for sample collection, processing, handling and shipment to a central laboratory will be provided in the Laboratory Manual.

Further exploratory biomarker research may be conducted on collected blood (including PK) samples. These additional investigations would be dependent upon clinical outcome, reagent and sample availability.

Samples may be stored for up to 5 years (or according to local regulations) following completion of the study to enable further analysis of biomarker responses to encorafenib and binimetinib.

7.10.2. Circulating Serum Biomarker Analysis

After IRB/IEC approval of Protocol Version 4 or later, peripheral blood samples (serum) will be collected as specified in the SoA (Table 3) for analysis of potential proteomic or metabolomic factors and signals.

7.11. Genetics

See Section 7.10.

7.12. Patient-Reported Outcomes

Patient-reported outcomes are not evaluated in this study.

7.13. Health Economics

Health Economics or Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

8. STATISTICAL CONSIDERATIONS

A detailed SAP will be prepared by the Sponsor or designee. This plan may modify the statistical methods outlined in the protocol; however, any major modifications of the primary endpoint definition or analysis will also be described in a protocol amendment.

8.1. Statistical Hypotheses

The primary endpoint of the study is ORR for treatment-naïve and previously treated patients as determined by IRR per RECIST v1.1. The study is designed to test the null hypothesis of ORR ≤ 39% for treatment- naïve patients with *BRAF*^{V600E} NSCLC, which is considered not sufficiently clinically meaningful to warrant further study in this indication where similar therapies are already available. The alternative hypothesis is ORR >39% with the assumption that the true ORR is at least 65%. Hypotheses are based on the results observed in the dabrafenib plus trametinib study in *BRAF*^{V600E}-mutant NSCLC patients, in which the ORR per Investigator assessment was 64% (95% CI: 46, 79) for treatment-naïve patients (Planchard et al, 2017) and the results observed in patients with NSCLC whose tumors expressed PD-L1 levels with a TPS ≥ 50% and received pembrolizumab as a single agent (Keynote-042) in which ORR per IRR was 39% (95% CI: 34, 45) (Mok et al, 2019).

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

8.2. Sample Size Determination

The sample size calculation is based on the primary endpoint of ORR as determined by IRR per RECIST v1.1. The hypotheses to be tested are described in Section 8.1. With 60 evaluable treatment-naïve patients with *BRAF*^{V600E} NSCLC, the power is greater than 95% to test the null hypothesis that the ORR is less than or equal to 39% versus the alternative hypothesis that it is greater than 39% assuming an alternative target rate of 65% with a one-sided $\alpha \leq 0.025$ based on a single-stage design using exact test. The null hypothesis will be rejected if ≥32 confirmed objective responses are observed. With 37 evaluable previously treated patients with *BRAF*^{V600E} NSCLC, there is at least 90% power to test the null hypothesis that the ORR is less than or equal to 20% versus the alternative hypothesis that it is greater than 20% assuming an alternative target rate of 45% with a one-sided $\alpha \leq 0.025$ based on a single stage design using exact test. The null hypothesis will be rejected if ≥13 confirmed objective responses are observed.

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

8.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Table 14. Populations for Analysis

Population	Description
Screened	All patients who sign the ICF.
Safety Set	The Safety Set (SS) includes all patients who receive at least 1 dose of study drug.
PK Set	The PK Set includes all patients in the SS who have at least 1 postdose PK blood collection after the first dose of study drug with associated bioanalytical results.

8.4. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the patient populations to be included in the analyses and procedures for accounting for missing, unused and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

All efficacy endpoints will be evaluated in treatment-naïve and previously treated patients with *BRAF*^{V600E} included in the SS. If sufficient number of patients (as described in the SAP) with other types of *BRAF*^{V600} mutations will be enrolled in the study, the endpoints may be evaluated in patients with all *BRAF*^{V600} mutations.

Primary analyses of all tumor related efficacy endpoints will be based on IRR review. Additional, sensitivity analyses will be based on Investigator assessment.

8.4.1. Primary Analyses

The primary endpoint is ORR in treatment-naïve and previously treated patients with *BRAF*^{V600E}. It is defined as the proportion of patients who have achieved a confirmed best overall response of CR or PR as determined by IRR per RECIST v1.1, relative to the SS.

The ORR will be calculated with an exact two-sided 95% CI.

8.4.2. Secondary Analyses

The secondary efficacy endpoints are listed in Table 5.

8.4.2.1. Duration of Response

DOR, based on IRR and investigator assessments is defined as the time from the date of the first documented response (CR or PR) that is subsequently confirmed (by IRR and by

Investigator, respectively) to the earliest date of disease progression, as determined by Investigator review of radiographic disease assessments and IRR per RECIST v1.1, or death due to any cause. If a patient with a CR or PR has neither progressed nor died at the time of the analysis cutoff or at the start of any new anticancer therapy, the patient will be censored at the date of last adequate tumor assessment. DOR will be calculated for patients who have achieved a confirmed overall response (i.e., CR or PR).

The survival distribution function for DOR will be estimated using the Kaplan-Meier method. In addition, descriptive statistics and frequency distribution will be provided.

8.4.2.2. Disease Control Rate

Disease control rate is defined as the proportion of patients who have achieved a confirmed overall response of CR, PR or SD, as determined by Investigator review of radiographic disease assessments and IRR per RECIST v1.1. Additional information regarding DCR will be specified in the SAP.

DCR will be calculated along with exact two-sided 95% CIs.

8.4.2.3. Progression-free Survival

Progression-free survival is defined as the time from the date of first dose of study drug to the earliest date of disease progression, as determined by IRR and Investigator review of radiographic disease assessments per RECIST v1.1, or death due to any cause. If a patient has not had a PFS event at the time of the analysis cutoff or at the start of any new anticancer therapy, PFS is censored at the date of last adequate tumor assessment.

The survival distribution function for PFS will be estimated using the Kaplan-Meier method.

8.4.2.4. Overall Survival

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

The survival distribution function for OS will be estimated using the Kaplan-Meier method.

8.4.2.5. Time to Response

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

TTR will be summarized using descriptive statistics.

8.4.3. Safety Analyses

Safety data will be presented, based on the SS, in tabular and/or graphical format and summarized descriptively, where appropriate. Adverse events will be coded using MedDRA®. The incidence of AEs will be summarized by system organ class and/or preferred term, maximum severity (based on CTCAE grades), type of AE and relation to study treatment.

Laboratory parameters will be presented in shift tables of baseline grade vs. maximum grade on study. For laboratory parameters that are not gradable by CTCAE, shift tables of normal-abnormal will be provided. Summaries of clinically notable measurements will also be provided. Definitions of clinically notable will be provided in the SAP.

Vital signs, body weight, ECOG PS, ECHO/MUGA and select ophthalmic examination data will be summarized.Clinically notable vital sign measurements will be summarized. Definitions of clinically notable will be provided 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.

8.4.4. Pharmacokinetic Analyses

Plasma concentrations of encorafenib and its metabolite (LHY746), and binimetinib will be determined using validated bioanalytical methods. Plasma concentration-time profiles for encorafenib, LHY746 and binimetinib will be generated for only patients enrolled under Protocol Versions 0 through 3. Descriptive summaries for encorafenib, LHY746 and binimetinib concentrations will be presented. Trough plasma concentration-visit of encorafenib and LHY746 and binimetinib will be reported and summarized for all patients treated in this study.

PK parameters will be determined for all PK-evaluable patients enrolled under Protocol Versions 0 through 3 using noncompartmental methods using Phoenix WinNonlin Version 8.0 or higher (Pharsight, Mountain View, CA). PK parameter estimates will be presented, summarized, and reported. Details of the analyses will be included in the SAP.

After IRB/IEC approval of Protocol Version 4, PK parameters of encorafenib and LHY746 and binimetinib will be estimated using a population model-based approach. Relationships between PK of encorafenib/binimetinib and biomarkers, clinical response and/or safety will be conducted using post hoc exposure estimates (eg, C_{max}, AUC or C_{min}) from population PK modeling, if possible and appropriate. Measures of efficacy may include but are not limited to ORR and DOR by IRR. Selection of safety measures will be based on frequency of observations or by selection of safety measures of interest. Analyses will be described in a separate stand-alone modeling plan and a separate report will be produced.

8.4.5. Other Analyses

Biomarker and exposure-response exploratory analyses, if appropriate, will be described in the SAP. The biomarker and exposure-response analyses may be presented separately from the main CSR.

8.5. Interim Analyses

The Sponsor may conduct 2 interim analyses for treatment-naïve patients, after about 90% [n=54] of the planned treatment-naïve patients [n=60] will be enrolled and after 6 months from the last treatment-naïve patient enrolled into the study. Results of the IA may be considered for discussion, based on criteria specified in the SAP, with regulatory authorities.

9. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

9.1. Regulatory, Ethical, and Study Oversight Considerations

The study will be performed in accordance with the requirements of the applicable regulatory authorities in each country where this study is conducted and will also meet all of the requirements of ICH GCP guidance. In addition to IRB/IEC and regulatory authority approval, all other required approvals (e.g., approval from the local research and development board or scientific committee) will be obtained prior to recruitment of patients into the study and shipment of study drug.

Amendments to the protocol will be submitted to all applicable regulatory authorities for approval prior to implementation. Only the Sponsor may modify the protocol. The only exception is when the Investigator considers that a patient's safety is compromised without immediate action. In these circumstances, immediate approval of the chairman of the IRB/IEC must be sought, and the Investigator will inform the Sponsor and the full IRB/IEC within 5 working days after the emergency occurred. All amendments that have an impact on patient's risk or the study objectives or require revision of the informed consent document must receive approval from the IRB/IEC prior to implementation.

9.2. Investigator Responsibilities

The Investigator is the person responsible for the conduct of the study at the investigational site. A sub-Investigator is any member of the clinical study team designated and supervised by the Investigator to perform critical study-related procedures and/or to make important study-related decisions.

The protocol, protocol amendments, ICF, IBs, 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 patients.

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 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Investigators must apply due diligence to avoid protocol deviations, (with the exception of medical emergencies); the Sponsor (or designee) will not pre-authorize deviations. If the Investigator believes a change to the protocol would improve the conduct of the study, this must be considered for implementation in a protocol amendment approved by the Sponsor and by the IRB/IEC. The Investigator is responsible for enrolling patients who have met the specified eligibility criteria. All protocol deviations will be recorded.

The Investigator must retain records in accordance with all local, national, and regulatory laws, but for the minimum period of at least 2 years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or if not approved, 2 years after the termination of the study drug for investigation to ensure the availability of study documentation should it become necessary for the Sponsor or a regulatory authority to review.

The Investigator must not destroy any records associated with the study without receiving written approval from the Sponsor. The Investigator must notify the Sponsor or designee in the event of accidental loss or destruction of any study records. If the Investigator leaves the institution where the study was conducted, the Sponsor or designee must be contacted to arrange alternative record storage options (if applicable).

All eCRF data entered by the site (including audit trial), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The Sponsor will retain the original eCRF data and audit trial.

9.3. Financial Disclosure

Before study initiation, all clinical Investigators participating in clinical studies patient to FDA Regulation Title 21 CRF Part 54- Financial Disclosure by Clinical Investigators (i.e., “covered studies”) and are required to submit a completed Clinical Investigator Financial Disclosure form that sufficiently details any financial interests and arrangements that apply. For the purpose of this regulation, this applies to the Investigator and any sub-Investigator who is directly involved in the treatment of or evaluation of research patients, including the spouse and each dependent child of the Investigator or sub-Investigator. These requirements apply to both US and foreign clinical Investigators conducting covered clinical studies. Any new clinical Investigators added to the covered clinical study during its conduct must also submit a completed Investigator Financial Disclosure Form.

During the clinical study, any changes to the financial information previously reported by the Investigator or sub-Investigator must be reported to the Sponsor or designee. At the conclusion of the clinical study, the Investigator and sub-Investigators will remain obligated to report to the Sponsor or designee any changes to the financial information previously reported, as well as any changes in their financial information for a period of 1 year after the completion of the clinical study.

9.4. Informed Consent Process

It is the Investigator's responsibility (or designee) to obtain written informed consent from each patient after adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study and before any study procedures are initiated. The Investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.

Informed consent must be obtained before any study-related procedures are conducted, unless otherwise specified by the protocol. Informed consent must be obtained using the IRB/IEC-approved version in a language that is native and understandable to the patient. A template will be provided by the Sponsor or designee. The Sponsor or designee must review and acknowledge the site-specific changes to the ICF template. The ICF must include a statement that the Sponsor or designee and regulatory authorities have direct access to patient records.

The ICF must contain all required elements and describe the nature, scope, and possible consequences of the study in a form understandable to the patient. The medical record must include a statement that written informed consent was obtained before the patient is enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

9.5. Data Protection

Patients will be assigned a unique identifier by the Sponsor. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only. Patient names or any information which would make the patient identifiable will not be transferred. If the patient's name appears on any record or document, it must be obliterated on the copy of the document to be supplied to the Sponsor or designee. Study finding stored on a computer will be stored in accordance with local data protection laws.

The Investigator will permit authorized representatives of the Sponsor, regulatory authorities and ethics committees to review the portion of the patient's medical record that is directly related to the study. The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

The patient 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 regulatory authorities.

The Investigator and the Sponsor or designee must adhere to applicable data privacy laws and regulations. The Investigator and the Sponsor or designee are responsible for ensuring that sensitive information is handled in accordance with local requirements (e.g., HIPAA). Appropriate consent and authorizations for use and disclosure and/or transfer (if applicable) of protected information must be obtained.

9.6. Committees

9.6.1. Safety Monitoring

Encorafenib and binimetinib are commercially available for the treatment of advanced *BRAF*$^{V600E/K}$-mutant melanoma in a number of jurisdictions including the US and EU (BRAFTOVI™ [encorafenib] prescribing information; MEKTOVI® [binimetinib] prescribing information). The dose and administration schedule of encorafenib 450 mg orally QD in combination with binimetinib 45 mg orally BID will be used in this study. Over 1,000 patients have been treated with the combination of encorafenib and binimetinib in completed and ongoing clinical trials. Cumulative safety data for these patients is included in the respective Investigator's Brochures for encorafenib and binimetinib, and the primary risks of the combination are well characterized (see Sections 2.1.4 and 2.1.5). As the patient population for this study is similar to the approved indication (i.e., adult patients with an advanced solid tumor), an independent DMC to monitor safety in this open-label study is not required to ensure safety. Safety and efficacy data will be monitored at regular intervals throughout the study by the Sponsor and a Steering Committee comprised of select study Investigators to ensure patient safety. In addition, ongoing global pharmacovigilance monitoring by the Sponsor for the marketed products will inform any changes in the safety profile of the combination, as well as any necessary changes in safety assessments. Details regarding routine safety reviews will be included in the Steering Committee Charter.

9.7. 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. By signing this protocol, the Investigator and his/her institution agree that the results of the study may be used by the Sponsor, for the purposes of national and/or international registration, publication, and information for medical and pharmaceutical professions. Information regarding this study and study results will be published in accordance with applicable local and national regulations. If necessary, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

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. The Investigator understands that he/she has an obligation to provide complete test results and all data obtained during this study to the Sponsor. Data analysis performed independently by an Investigator will be submitted to the Sponsor before publication or presentation.

9.7.1. Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bonafide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

9.8. Data Quality Assurance

- Data management will be performed in a validated EDC system. All patient data relating to the study will be recorded in an eCRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF. The Investigator will be provided with access to an EDC system so that the eCRF can be completed for each patient.

- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF. Following review and approval, the Investigator will electronically sign and date the pages. This signature certifies that the Investigator has thoroughly reviewed and confirmed all data on the eCRF.

- A PDF and/or electronic file of the eCRFs will be provided to the site after all data have been monitored and reconciled and will be archived at the site as required by any applicable local regulatory requirements.

- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

- 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 noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan and in accordance with the signed site agreement. Monitoring will include personal visits with the Investigator and study staff as well as appropriate communications by telephone, fax, mail, email or use of the EDC system, if applicable.

- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

- The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).

- Qualified study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients 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. Every effort will be made to maintain the anonymity and confidentiality of patients during this study.

- Qualified representatives of the Sponsor or designee may audit the clinical study site and study data to evaluate compliance with the protocol, applicable local clinical study regulations, and overall study conduct. The Investigator must allow the auditors to review original source documents and study documentation for all patients.

- Regulatory authorities may conduct and inspection of the study and the site at any time during the study. The Investigator and site staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study-related documents. The Investigator must immediately notify the Sponsor when contacted by any regulatory authority for the purposes of conducting an inspection.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for at least 2 years after study completion unless local regulations or institutional 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.

9.9. Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's 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. Also, current medical records must be available. Changes or corrections to eCRFs will be made by the Investigator or an authorized member of the study staff according to the policies and procedures at the site.

9.10. Study and Site Closure

The Sponsor or 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.

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 GCP guidelines

- Inadequate recruitment of patients by the Investigator

- Discontinuation of further study treatment development

9.11. Publication Policy

The conditions regulating dissemination of the information derived from this study are described in the Clinical Trial Agreement. The Sponsor will comply with the requirements for publication of study results. Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

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11. APPENDIX 1: CONTRACEPTIVE GUIDANCE

Female patients of childbearing potential must agree to take appropriate precautions to avoid pregnancy from Screening through 30 days after the last dose of study drug/treatment.

Male patients should use a condom during treatment and through 90 days after the end of systemic exposure to study treatment. If the male patient has a partner that is of child-bearing potential, the partner should also use contraception through 90 days after the end of systemic exposure to study treatment. In addition, male patients must refrain from donating sperm during the study through 90 days after the end of systemic exposure of study drug/treatment. Males who have had a vasectomy ≥ 90 days from the start of treatment qualify as having met the requirement for a highly effective birth control method.

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal 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 1 of the following:
    - Documented hysterectomy.
    - Documented bilateral salpingectomy.
    - Documented bilateral oophorectomy.

    For individuals 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 site personnel's: review of the patient'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.
        - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH 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.

Contraception Guidance:

NOTE: There is a potential for encorafenib to induce CYP3A4, which may reduce the effectiveness of hormonal contraception methods. Therefore, the use of at least 1 form of non-hormonal contraception is required for females of childbearing potential during participation in this study.

The contraception guidelines outlined below are adapted from the recommendations related to contraception and pregnancy testing in clinical trials guidance document (Clinical Trials Facilitation Group Guidelines 2014). Patients must agree to use highly effective methods of contraception if it is mandated locally or when, in the judgment of the Investigator, compliance with acceptable methods is likely to be suboptimal. Any of the contraceptive methods listed below are permitted on the study and should be communicated to patient and their understanding confirmed.

The following methods have been classified as being highly effective (i.e., failure rate < 1% per year when used consistently and correctly) in preventing a pregnancy:

- Complete abstinence from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient
- 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 (IUD).
- Intrauterine hormone-releasing system (IUS).

- Bilateral tubal occlusion.

- Vasectomised partner (considered highly effective provided the vasectomized male has received medical assessment of surgical success and that the male is a female patient's sole sexual partner).

Acceptable birth control methods characterized as having 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.

12. APPENDIX 2: RECOMMENDED DOSE MODIFICATIONS FOR ENCORAFENIB-RELATED* ADVERSE EVENTS

Severity of Adverse Event	Dose Modifications
New Primary Malignancies	
Non-cutaneous *RAS* mutation-positive malignancies	Permanently discontinue encorafenib and binimetinib.
Uveitis	
Grade 1-3	If Grade 1 or 2 does not respond to specific ocular therapy, or for Grade 3 uveitis, withhold encorafenib and binimetinib for up to 6 weeks. • If improved, resume at same or reduced dose. • If not improved, permanently discontinue.
Grade 4	Permanently discontinue encorafenib and binimetinib.
Other Eye Disorders (i.e., non-Uveitis Events)	
Grade 1–2	Maintain dose level of encorafenib and binimetinib and increase frequency of ophthalmic monitoring to at least every 14 days until stabilization or resolution.
Grade 3	Interrupt dosing of encorafenib and binimetinib and refer patient to ophthalmologist within 7 days. • If resolved to Grade ≤ 1 in ≤ 21 days, resume treatment at 1 reduced dose level of encorafenib and binimetinib. • If not resolved to Grade ≤ 1 in ≤ 21 days, permanently discontinue encorafenib and binimetinib and close follow-up with ophthalmic monitoring until stabilization or resolution.
Grade 4	Permanently discontinue encorafenib and binimetinib and immediate follow-up with ophthalmic monitoring until stabilization or resolution.
QTc Prolongation	
QTcF > 500 ms and ≤ 60 ms increase from baseline	1st occurrence: • Temporarily interrupt dosing of encorafenib until QTcF < 500 ms. Then resume treatment at 1 reduced dose level of encorafenib. 2nd occurrence:

Severity of Adverse Event	**Dose Modifications**
	• Temporarily interrupt dosing of encorafenib treatment until QTcF < 500 ms. Then resume treatment at 1 reduced dose level of encorafenib. 3rd occurrence: • Permanently discontinue encorafenib and binimetinib.
QTcF > 500 ms and > 60 ms increase from baseline	Permanently discontinue encorafenib and binimetinib.
Hepatotoxicity	
Grade 2 AST or ALT increased	Maintain encorafenib dose. • If no improvement within 4 weeks, withhold encorafenib until improved to Grade 0-1 or to pretreatment/baseline levels and then resume at the same dose.
Grade 3 or 4 AST or ALT increased	See Other Adverse Reactions
Dermatologic (Except Palmar-plantar Erythrodysesthesia Syndrome)	
Grade 2	If no improvement within 2 weeks, withhold until Grade 0-1. Resume at same dose if first occurrence or reduce dose if recurrent.
Grade 3	Withhold until Grade 0-1. Resume at same dose if first occurrence or reduce dose if recurrent.
Grade 4	Permanently discontinue encorafenib and binimetinib.
Hand-foot Skin Reaction (HFSR)/Palmar-plantar Erythrodysesthesia Syndrome (Dose Adjustment for Encorafenib ONLY)	
Grade 1	Maintain dose of encorafenib. Promptly institute supportive measures, such as topical therapy, for symptomatic relief. Give instruction on life-style 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 life-style 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 life-style modifications.

Severity of Adverse Event	Dose 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 life-style modifications. If interrupted dosing of encorafenib per Investigator's judgment, interrupt until resolved to Grade ≤ 1. Resume treatment with encorafenib at the same dose level or 1 reduced dose level based upon the Investigator's discretion.
Grade 3	1st or 2nd occurrence: • Interrupt dosing of encorafenib until resolved to Grade ≤ 1. Promptly initiate supportive measures, such as topical therapy, for symptomatic relief. Give instruction on life-style modifications. Reassess the patient weekly. Then resume treatment at one reduced dose level 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 or permanently discontinue encorafenib should be based upon the Investigator's discretion.
Nausea/Vomiting	
Grade 1-2	Maintain dose level of encorafenib and binimetinib. Promptly institute antiemetic measure.
Grade 3	Interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤ 1. Resume treatment at 1 reduced dose level of encorafenib. Resume treatment with binimetinib at the current dose if, in the judgment of the Investigator, the toxicity is considered to be unrelated to binimetinib, or at 1 reduced dose level. Note: Interrupt dosing of encorafenib and binimetinib for ≥ Grade 3 vomiting or Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetics (as per local practice).

Severity of Adverse Event	**Dose Modifications**
Grade 4	Permanently discontinue encorafenib and binimetinib.
Other Adverse Reactions (including renal, hemorrhage)	
Recurrent Grade 2 or First occurrence of any Grade 3	Withhold for up to 4 weeks. • If improves to Grade 0-1 or to pretreatment/baseline levels, resume at reduced dose. • If no improvement, permanently discontinue encorafenib and binimetinib.
First occurrence of any Grade 4	Permanently discontinue or withhold for up to 4 weeks. • If improves to Grade 0-1 or to pretreatment/baseline levels, then resume at a reduced dose. • If no improvement, permanently discontinue encorafenib and binimetinib.
Recurrent Grade 3	Consider permanently discontinuing encorafenib and binimetinib.
Recurrent Grade 4	Permanently discontinue encorafenib and binimetinib.

*For adverse events that may be related to both encorafenib and binimetinib, guidance is provided for the other agent also.

13. APPENDIX 3: RECOMMENDED DOSE MODIFICATIONS FOR BINIMETINIB-RELATED* ADVERSE EVENTS

Severity of Adverse Event	Dose Modifications
Cardiomyopathy	
Asymptomatic, absolute decrease in LVEF of > 10% from baseline that is also below the LLN	Withhold binimetinib for up to 4 weeks, evaluate LVEF every 2 weeks. Resume binimetinib at a reduced dose if the following are present: • LVEF is at or above the LLN and • Absolute decrease from baseline is 10% or less and • Patient is asymptomatic. If LVEF does not recover within 4 weeks permanently discontinue binimetinib.
Grade 3-4 (Symptomatic congestive heart failure or absolute decrease in LVEF of > 20% from baseline that is also below LLN)	Permanently discontinue binimetinib. Closely monitor LVEF until resolution or up to 16 weeks.
Venous Thromboembolism	
Uncomplicated DVT or PE	Withhold binimetinib. • If improves to Grade 0-1, resume at a reduced dose. • If no improvement, permanently discontinue binimetinib.
Life threatening PE	Permanently discontinue binimetinib.
Serous Retinopathy	
Symptomatic serous retinopathy/ Retinal pigment epithelial detachments	Withhold binimetinib for up to 10 days. • If improves and becomes asymptomatic, resume at the same dose. • If not improved, resume at a lower dose level or permanently discontinue binimetinib.
Retinal Vein Occlusion (RVO)	
Any Grade	Permanently discontinue binimetinib.
Uveitis	
Grade 1-3	If Grade 1 or 2 does not respond to specific ocular therapy, or for Grade 3 uveitis, withhold binimetinib and encorafenib for up to 6 weeks. • If improved, resume at same or reduced dose. • If not improved, permanently discontinue binimetinib.
Grade 4	Permanently discontinue binimetinib.

Severity of Adverse Event	Dose Modifications
Other Eye Disorders (i.e., Non-retinal Events, non-Uveitis Events	
Grade 1-2	Maintain dose level of encorafenib and binimetinib and increase frequency of ophthalmic monitoring to at least every 14 days until stabilization or resolution.
Grade 3	Interrupt dosing of encorafenib and binimetinib and refer patient to ophthalmologist within 7 days. • If resolved to Grade ≤ 1 in ≤ 21 days, resume treatment at 1 reduced dose level of encorafenib and binimetinib. • If not resolved to Grade ≤ 1 in ≤ 21 days, permanently discontinue encorafenib and binimetinib and close follow-up with ophthalmic monitoring until stabilization or resolution.
Grade 4	Permanently discontinue encorafenib and binimetinib and immediate follow-up with ophthalmic monitoring until stabilization or resolution.
Interstitial Lung Disease	
Grade 2	Withhold binimetinib for up to 4 weeks. • If improved to Grade 0-1, resume at a reduced dose. • If not resolved within 4 weeks, permanently discontinue.
Grade 3 or Grade 4	Permanently discontinue binimetinib.
Hepatotoxicity	
Grade 2 AST or ALT increased	Maintain binimetinib dose. • If no improvement within 2 weeks, withhold binimetinib until improved to Grade 0-1 or to pretreatment/baseline levels and then resume at the same dose.
Grade 3 or 4 AST or ALT increased	See Other Adverse Reactions.
Rhabdomyolysis or Creatine Phosphokinase (CPK) elevations	
Grade 4 asymptomatic CPK elevation or Any Grade CPK elevation with symptoms or with renal impairment	Withhold binimetinib dose for up to 4 weeks. • If improved to Grade 0-1 resume at a reduced dose. • If not resolved within 4 weeks, permanently discontinue binimetinib.

Severity of Adverse Event	Dose Modifications
Dermatologic	
Grade 2	If no improvement within 2 weeks, withhold until Grade 0-1. Resume at same dose if first occurrence or reduce dose if recurrent.
Grade 3	Withhold until Grade 0-1. Resume at same dose if first occurrence or reduce dose if recurrent.
Grade 4	Permanently discontinue binimetinib and encorafenib.
Nausea/Vomiting	
Grade 1-2	Maintain dose level of encorafenib and binimetinib. Promptly institute antiemetic measure.
Grade 3	Interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤ 1. Then resume treatment at 1 reduced dose level of encorafenib. Resume treatment with binimetinib at the current dose if, in the judgment of the Investigator, the toxicity is considered to be unrelated to binimetinib, or at 1 reduced dose level. Note: Interrupt dosing of encorafenib and binimetinib for ≥ Grade 3 vomiting or Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetics (as per local practice). If unresolved permanently discontinue binimetinib and encorafenib.
Grade 4	Permanently discontinue binimetinib and encorafenib.
Other Adverse Reactions	
Recurrent Grade 2 or First occurrence of any Grade 3	Withhold for up to 4 weeks. • If improves to Grade 0-1 or to pretreatment/baseline levels, resume at reduced dose. • If no improvement, permanently discontinue binimetinib and encorafenib.
First occurrence of any Grade 4	Permanently discontinue or withhold for up to 4 weeks. • If improves to Grade 0-1 or to pretreatment/baseline levels, then resume at a reduced dose. • If no improvement, permanently discontinue binimetinib and encorafenib.
Recurrent Grade 3	Consider permanently discontinuing binimetinib and encorafenib.

Severity of Adverse Event	**Dose Modifications**
Recurrent Grade 4	Permanently discontinue binimetinib and encorafenib.

*For adverse events that may be related to both binimetinib and encorafenib, guidance is provided for the other agent also.

14. APPENDIX 4: ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

14.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study patient, temporally associated with the use of study treatment, whether or not considered related to the study treatment.

- NOTE: An AE can therefore be any unfavorable 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 AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
  - Is associated with accompanying symptoms.
  - Requires additional diagnostic testing or medical/surgical intervention.
  - Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration 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. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE

Events Meeting the AE Definition
and meet the requirements as per Section 7.5. Also, "lack of efficacy" or "failure of expected pharmacological action" does not constitute an AE or SAE

Events NOT Meeting the AE 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 patient'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 patient's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen. • Worsening of signs and symptoms of the malignancy under study should be recorded as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

14.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the patient 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 AEs. If a complication prolongs

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

hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person'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, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect

Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately lifethreatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention 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.

- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the active collection period, then the event leading to death must be recorded as an AE on the CRF, and as an SAE with CTCAE Grade 5 (see the Assessment of Intensity section).

- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

14.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the CT SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study treatment under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study treatment under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the patient's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all patient identifiers, with the exception of

the patient number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- 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 AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories per CTCAE Version 4.03:

GRADE	Clinical Description of Severity
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/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 IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE 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 sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**

Assessment of Causality

- The investigator may change his/her opinion of causality in light of followup information and send an SAE followup report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study treatment caused the event, then the event will be handled as "related to study treatment" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

14.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety.
- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

15. APPENDIX 5: LIVER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some patients, transaminase elevations are a harbinger of a more serious potential outcome. These patients fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Patients who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the patient’s individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For patients with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy’s law case should be reviewed with the sponsor.

The patient should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

16. APPENDIX 6: ECG FINDINGS OF POTENTIAL CLINICAL CONCERN

ECG Findings That <u>May</u> Qualify as AEs

- Marked sinus bradycardia (rate <40 bpm) lasting minutes.
- New PR interval prolongation >280 msec.
- New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline.
- New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm.
- New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration.
- Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.

ECG Findings That <u>May</u> Qualify as SAEs

- QTcF prolongation >500 msec.
- New ST-T changes suggestive of myocardial ischemia.
- New-onset left bundle branch block (QRS >120 msec).
- New-onset right bundle branch block (QRS >120 msec).
- Symptomatic bradycardia.
- Asystole:
  - In awake, symptom-free patients in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;
  - In awake, symptom-free patients with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer;
  - Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
- Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (heart rate <40 bpm), accelerated idioventricular rhythm (HR 40 bpm to <100 bpm), and

monomorphic/polymorphic ventricular tachycardia (HR >100 bpm (such as torsades de pointes)).

- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The enumerated list of major events of potential clinical concern are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all inclusive of what to be reported as AEs/SAEs.

17. APPENDIX 7: SNELLEN EQUIVALENCE (VISUAL ACUITY CONVERSION CHART)

				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

Holladay J. Visual acuity measurements. J Cataract Refract Surg. 2004;30(2) 297-90.

18. APPENDIX 8: ALTERNATIVE MEASURES DURING PUBLIC EMERGENCIES

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 global pandemic and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories).

18.1. Eligibility

While SARS-CoV2 testing is not mandated for this study, local clinical practice standards for testing should be followed. A patient should be excluded if he/she has a positive test result for SARS-CoV2 infection, is known to have asymptomatic infection, or is suspected of having SARS-CoV2. Patients with active infections are excluded from study participation as per Section 5.2 Exclusion Criteria. Active infection requiring systemic therapy.

When the infection resolves, the patient may be considered for re-screening.

18.2. Telehealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study patients at scheduled visits per the Schedule of Activities or unscheduled visits. Telehealth visits may be used to continue to assess patient safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (e.g., audio, video, video-conferencing software) remotely, allowing the patient and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit:

- Review and record study treatment(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 7.5.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the patient is adhering to the contraception method(s) required in the protocol. Refer to Appendix 1 and Section 18.3.1 of this appendix regarding pregnancy tests.

Study patients must be reminded to promptly notify site staff about any change in their health status.

18.3. Alternative Facilities for Safety Assessments

18.3.1. Laboratory Testing

If a study patient is unable to visit the site for protocol-specified safety laboratory evaluations, testing may be conducted at a local laboratory if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital. The following safety laboratory evaluations may be performed at a local laboratory:

- Refer to Section 7.3.9 Clinical Safety Laboratory Assessments, Table 11 for the list of safety laboratory evaluations, including pregnancy testing required per protocol.

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/ accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the patientt's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

If a patient requiring pregnancy testing cannot visit a local laboratory for pregnancy testing, a home urine pregnancy testing kit with a sensitivity of at least 25 IU/mL may be used by the patient to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the patient's source documents/medical records and relevant data recorded on the CRF. Confirm that the patient is adhering to the contraception method(s) required in the protocol.

18.3.2. Imaging

If the patient is unable to visit the study site for safety imaging assessments (e.g., echocardiogram or MUGA), the patient may visit an alternative facility to have the safety imaging assessments performed. Qualified study site personnel must order, receive, and review results.

18.3.3. Electrocardiograms

If the patient is unable to visit the study site for ECGs, the patient may visit an alternative facility to have the ECGs performed. Qualified study site personnel must order, receive, and review results.

18.4. Study Treatment

If the safety of a trial patient is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that patient from study treatment must be considered.

Study drugs may be shipped by courier to study patients if permitted by local regulations and in accordance with storage and transportation requirements for the study drugs. Pfizer does not permit the shipment of study drugs by mail. The tracking record of shipments and the chain of custody of study drugs must be kept in the patient's source documents/medical records.

The following is recommended for the administration of study drugs for patients who have active [confirmed (positive by regulatory authority-approved test) or presumed (test pending/clinical suspicion)] SARS-CoV2 infection:

- For symptomatic patients with active SARS-CoV2 infection, study drugs should be delayed for at least 14 days from the start of symptoms. This delay is intended to allow the resolution of symptoms of SARS-CoV2 infection.

- Prior to restarting treatment, the patient should be afebrile for 72 hours, and SARS-CoV2-related symptoms should have recovered to ≤ Grade 1 for a minimum of 72 hours. Notify the study team when treatment is restarted.

- Continue to consider potential drug-drug interactions as described in protocol Section 6.5 for any concomitant medication administered for treatment of SARS-CoV2 infection.

18.5. Home Health Visits

A home health care service may be utilized to facilitate scheduled visits per the Schedule of Activities. Home health visits include a healthcare provider conducting an in-person study visit at the patient's location, rather than an in-person study visit at the site. The following may be performed during a home health visit:

- Physical exam including dermatological lesions and vital signs

- Review and record study treatment(s), including compliance and missed doses.

- Review and record any AEs and SAEs since the last contact. Refer to Section 7.5

- Review and record any new concomitant medications or changes in concomitant medications since the last contact.

- Review and record contraceptive method and results of pregnancy testing. Confirm that the patient is adhering to the contraception method(s) required in the protocol. Refer to Appendix 1 and Section 18.3.1 of this appendix regarding pregnancy tests.

18.6. Adverse Events and Serious Adverse Events

If a patient has COVID-19 during the study, this should be reported as an adverse event (AE) or serious adverse events (SAE) and appropriate medical treatment provided. Temporary discontinuation of the study treatment may be medically appropriate until the patient has recovered from COVID-19.

It is recommended that the investigator discuss temporary or permanent discontinuation of study treatment with the study medical monitor.

18.7. Efficacy Assessments

If the patient is unable to visit the study site for imaging assessments (e.g., CT, MRI, X-ray, FDG-PET), the patient may visit an alternative facility to have the imaging assessments performed. Qualified study site personnel must order, receive, and review results.

18.8. Steering Committee

There will be no impact on the Steering Committee Charter. The Steering Committee will continue to be consulted during public health emergencies.

19. APPENDIX 9: PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Version 5	24 September 2021
Version 4	16 February 2021
Version 3	25 August 2020
Version 2	03 October 2019
Version 1	04 March 2019
Original Version 0	27 November 2018

Version 5 (24 September 2021)

The primary purpose of this amendment is to provide clarification to the eligibility for the previously treated patients, and to update the Secondary Objectives and Interim Analysis sections to maintain consistency with the SAP. This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacts the scientific value of the study.

Section # and Name	Description of Change	Brief Rationale
List of Abbreviations and Definition of Terms	Added TTR	Added abbreviation for Time to Response as added in Objectives and Endpoints and Section 8.4.2.5
Section 1.1 Synopsis Table 1 Section 3 Objectives and Endpoints Table 5	Included TTR as a Secondary Objective and Endpoint, and update to DOR endpoint.	Protocol sections updated to maintain consistency with the SAP
Section 5.1 Inclusion Criteria, #6	Updated 2nd note to clarify the eligibility for previously treated patients	To ensure eligible patients are enrolled appropriately into each study population group
Section 8.4.2.1 Duration of Response	Updated to include DOR based on IRR and Investigator assessments	Protocol section updated to clarify DOR will be based on both IRR and Investigator assessments
Section 8.4.2.5 Time to Response	New section to describe the TTR endpoint and analysis	Protocol section added to maintain consistency with the SAP
Section 8.5 Interim Analyses	Updated to accommodate possible interim analyses for the study	Protocol section updated to maintain consistency with the SAP

Version 4 (16 February 2021)

The primary purpose of this amendment is to support a registrational status of this study by revision of the primary objective and corresponding endpoint into 2 subgroups (treatment-naïve and previously treated) and to update the sample size to describe the 2 subgroups. Corresponding statistical analyses sections have been updated to reflect these changes. This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union

because it significantly impacts the safety or physical integrity of patients and the scientific value of the study.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 2.1.2 Treatment of *BRAF*-mutant Non-small Cell Lung Cancer	Updated reference data within the rationale.	Data within referenced articles have been updated.
Section 1.1 Synopsis Table 1 Primary and Select Secondary Objectives and Endpoints Section 3 Objectives and Endpoints Table 4	Objectives and endpoints have been updated to distinguish between treatment naïve and previously treated patients, and to centralize assessments for the primary objective/endpoint.	Following consultation with the FDA, the design of the study has been revised to allow for registration of either or both a treatment naïve population and a previously treated population.
Section 1.1 Synopsis Table 2 Study Design Elements Section 6.10 Enrollment of Additional Patients	Updated number of patients to reflect new sample sizes for the 2 subgroups.	Following consultation with the FDA, the design of the study has been revised to allow for registration of either or both a treatment naïve population and a previously treated population.
Section 1.2 Study Schema Figure 1 Overall Study Design	Updated schema to reflect changes made within the protocol.	Due to change in sample size to distinguish between two treatment groups, schema has been updated.
Section 1.3 Schedule of Activities (SoA) Table 3	Revised PK assessments schedule; added schedule of assessments for proteomic/metabolic serum sample and circulating serum biomarker.	Revisions made to reflect updated PK and biomarker sample schedule.
Section 4.1 Overall Design	Added description of the 2 subgroups.	Following consultation with the FDA the design of the study has been revised to allow for registration of either or both a treatment naïve population and a previously treated population.
Section 5.2 Exclusion Criteria	Reworded Exclusion Criterion #13 to reflect criterion in original protocol.	Original criterion enhances patient safety. All patients enrolled in the study will follow the same eligibility criteria.
Section 5.2 Exclusion Criteria Section 6.5 Concomitant Therapy	Added clarifications to Exclusion Criterion #4b and Concomitant Therapy to clarify administration of COVID-19 vaccine.	COVID-19 vaccines approved under an EUA or equivalent are not considered investigational products.
Section 6.1.1 Encorafenib Section 6.1.2 Binimetinib	Added clarifier to indicate doses administered on PK days must be performed under observation by the Investigator or designee; additional instruction to not manipulate the study drug	Clarification has been added due to presence of protocol deviations related to the observation around these doses. Additional instructions added to maintain integrity of study medication.
Section 7.1.1.1 $BRAF^{V600}$ Mutation Testing	Additional text added to clarify requirement for samples to be sent to central lab.	To ensure the centralization of mutation status confirmation, text has been added.
Section 7.2.4 Independent Radiology Review	Updated section to indicate that the review of tumor scans will be	Central radiology review has been implemented as part of the

Section # and Name	Description of Change	Brief Rationale
	both by the Investigator and the central radiology review.	primary objective/endpoint of ORR to ensure consistency with registration.
Section 7.4.1 Distribution of Dosing Diary	Updated to reflect change from patient reminder card to dosing diary for patient completion.	To ensure complete and accurate drug accountability, the protocol requirements will include a dosing diary for each patient to complete to document their doses.
Section 7.8 Pharmacokinetics Section 7.8 Table 12 Serial Pharmacokinetic Blood Sample Timing in patients Enrolled under Protocol Versions 0 through 3 Section 7.8 Table 13 Pharmacokinetic Blood Sample Timing in patients enrolled under protocol version 4 or later	Updated PK collection schedule; clarified Table 12 and added Table 13 to reflect new schedules.	Approximately 50 patients enrolled under the Protocol Version 3 have provided serial PK samples, which are sufficient to characterize PK in this population. To reduce patient burden, only predose PK samples will be collected from future patients for exposure-response analysis. FDA agreed on the changes of PK collection.
Section 7.10.2 Circulating Serum Biomarker Analysis	Added section for additional samples collected.	To monitor proteomic correlates of response and resistance to therapy.
Section 8 Statistical Considerations	Revised to update changes to statistical analyses due to sample size updates and to support registrational status of study.	Following consultation with the FDA, the design of the study has been revised to allow for registration of either or both a treatment naïve population and a previously treated population
Section 8.1 Statistical Hypotheses	Updated to reflect new calculations for the 2 subgroups.	Following consultation with the FDA, the design of the study has been revised to allow for regulatory approval of either or both a treatment naïve population and a previously treated population.
Section 8.2 Sample Size Determination	Updated to reflect the sample size for each subgroup.	Following consultation with the FDA, the design of the study has been revised to allow for regulatory approval of either or both a treatment naïve population and a previously treated population.
Appendix 7 Snellen Equivalence (Visual Acuity Conversion Chart)	Included conversion chart of visual acuity reading.	To assist in the consistent conversion of values, the conversion chart has been included.

Version 3 (25 August 2020) The primary purpose of this amendment is to increase the sample size to support a potential registrational status of the study, and to provide clarification on acceptable methods for BRAF mutation status confirmation. Country specific changes per Korean Amendment 2.1 and 2.2 have been incorporated. This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive

2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacts the safety or physical integrity of patients and the scientific value of the study.

Section # and Name	Description of Change	Brief Rationale
Table 2, Study Design Elements Section 1.2, Study Schema Section 6.10, Enrollment of Additional Patients Section 8.2, Sample Size Determination	Revision of sample size from approximately 40 patients to at least 80 patients with a $BRAF^{V600E}$ mutation, but no more than 90 patients with any other $BRAF^{V600}$ mutation will be enrolled and treated	Current data from Planchard et al, 2017 have been updated. As such the hypothesis and sample size for this study has been adjusted based on the reported ORR of 64%.
Section 5.1, Inclusion Criteria Section 5.2, Exclusion Criteria Section 7.1.1.1 $BRAF^{V600}$ Mutation Testing	Updated to include changes per country specific Amendment 2.1 and 2.2; clarified FNA is acceptable for BRAF mutation testing.	Refer to country specific Amendments 2.1 and 2.2 for rationale. A FNA is an acceptable method for confirmation of BRAF mutation with the central lab as long as there is sufficient material from the same sample used to confirm BRAF mutation.
Section 6.7, Criteria for Permanent Discontinuation of Study Treatment Section 7.5 Appendix 4 Appendix 5 Appendix 6	Pfizer master template text included	Safety reporting and processes have migrated from the Array system and processes to the Pfizer system and processes.
Section 8.1, Statistical Hypotheses Section 8.2, Sample Size Determination	Changes made to the sample size; hypotheses, populations, and analyses to support change in sample size.	The hypothesis has been updated based on the results observed from Planchard et al, 2017 which showed an ORR per Investigator assessment of 64%.

This amendment incorporates all revisions to date, including changes made at the request of country health authorities.

Version 2 (03 October 2019) The primary purpose of this amendment is to revise patient eligibility criteria based on investigator feedback and changes in standard of care for identifying *BRAF* mutation status in this patient population. This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacts neither the safety or physical integrity of patients nor the scientific value of the study.

Section # and Name	Description of Change	Brief Rationale
1.1, Synopsis 4.1, Overall Design 5.1, Inclusion Criteria	Inclusion of NSCLC patients with other V600 Class 1 BRAF mutations (e.g., K or D)	Encorafenib binds to V600 K and D. Although these mutations are much less common, patients with these

Section # and Name	Description of Change	Brief Rationale
		mutations should respond similarly as patients with a V600E mutation.
5.1, Inclusion Criteria	Patients must have histologically confirmed NSCLC by AJCC 8th edition (M1a, M1b, or M1c)	Updated to the most recent version of AJCC.
5.1, Inclusion Criteria 7.1.1.1, *BRAF*^{V600} Mutation Testing 7.12, Biomarkers	Patients can qualify for the study with written documentation from a previous local pathology report of *BRAF*^{V600} mutation in tumor tissue or by a liquid biopsy (e.g., ctDNA genetic testing).	Liquid biopsy results are available much more quickly and current standard oncology practice is to first perform mutation analyses on peripheral blood samples and base targeted therapy on positive results. Tissue analyses are more often performed to corroborate negative results from a liquid biopsy. Liquid biopsy tests are as specific as tissue-based testing but not as sensitive, so tissue analyses serve to corroborate negative results from liquid biopsy testing. Patients can qualify for the study with a positive *BRAF*^{V600} result in a liquid biopsy and will be required to submit tissue for central confirmation.
4.1, Overall Design 5.1, Inclusion Criteria	Patients may qualify for the study if they have received prior PD-1/PD-L1 therapy in combination with immune therapies (e.g., ipilimumab) with or without platinum-based chemotherapy.	Emerging clinical data have demonstrated clinical benefit in patients with NSLC who have been treated with the combination of a PD-1/PD-L1 and other immune therapies (e.g., CTLA-4), either with and without platinum-based chemotherapy. Therefore, patients who have received these treatments in the 1L setting will be eligible for enrollment in the study.
5.1, Inclusion Criteria 7.1.1, Screening	If baseline scans from an institution other than the investigational site are used, the site must obtain copies of the scans prior to enrollment of the patient, or the scans must be repeated at the investigational site and submitted for potential future independent review.	To ensure that all baseline scans are available for central review.
5.1, Inclusion Criteria	Patients with documented Gilbert syndrome or hyperbilirubinemia due to non-hepatic cause (e.g., hemolysis, hematoma) may be enrolled following discussion and agreement with the Sponsor.	Patients with these conditions may have elevated bilirubin but still be suitable candidates for study treatment and therefore not excluded from enrollment.
5.2, Exclusion Criteria	Modifications to text regarding thromboembolic or cerebrovascular events.	To provide additional clarification regarding exclusion criteria for

Section # and Name	Description of Change	Brief Rationale
		thromboembolic or cerebrovascular events.
5.2, Exclusion Criteria	Removed exclusion of history of interstitial lung disease that required oral or intravenous glucocorticoid steroids for management.	Per investigator feedback, patients with NSCLC are likely to have had interstitial lung disease from prior treatments and excluding these patients would limit enrollment in the study.
5.2, Exclusion Criteria	Modifications to text regarding patients with previously treated brain metastases.	Modifications based on investigator feedback regarding standard of care treatment for patients with brain metastases.
5.2, Exclusion Criteria	Clarification provided for when exclusion criteria can be reviewed and discussed with the Sponsor.	To provide additional clarification regarding exclusion criteria.
6.6.2, Dose Modifications	Updated to allow for dose re-escalation of encorafenib and binimetinib after dose reduction and to adjust the lowest dose level of encorafenib and binimetinib.	Updated as per the current local prescribing instructions for encorafenib and binimetinib.
7.3.9, Clinical Laboratory Assessments	Updated to specify that screening laboratory assessments for hematology and serum chemistry must be performed within 7 days of Cycle 1 Day 1.	Clarification.
Table 10, Summary of Clinical Laboratory Tests	Removed urine testing if total CK ≥ 3 × ULN and to clarify that only hematology and serum chemistry need to be done within 7 days of Cycle 1 Day 1.	The central laboratory vendor does not perform urine testing.
7.12, Biomarkers	Clarification added regarding biomarker samples for future testing, storage, and reporting of results.	To provide additional clarification.
7.3.6 Vital Signs	Clarification added regarding timing for the collection of vital signs	To provide additional flexibility for sites regarding timing of vital sign collection.
8.4.4, Pharmacokinetic Analyses	Clarification added regarding PK analysis methods	Administrative update

Version 1 (04 March 2019)

This amendment regards the inclusion of patients with moderate hepatic impairment as per binimetinib labeling recommendations. This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it impacts the safety of patients.

Section # and Name	Description of Change	Brief Rationale

5.1 Inclusion Criteria	Inclusion criterion 10a was updated to only allow patients who have a total bilirubin ≤ 1.5 × ULN in the study.	Patients with moderate to severe hepatic impairment (i.e., total bilirubin > 1.5 × ULN with indirect bilirubin < 1.5 × ULN, with or without elevation of AST), will not be eligible to initiate treatment at the starting binimetinib dose in this protocol. Therefore, only patients with a total bilirubin ≤ 1.5 × ULN will be eligible for study inclusion.
Protocol Title Page	EudraCT Number is now available and has been added to the title page of the protocol.	To provide the EudraCT Number for the study.