CLINICAL STUDY ARRAY-818-201 / C4221006

Protocol Title:

A Phase 2, Open-Label, Randomized, Multicenter Trial of Encorafenib + Binimetinib Evaluating a Standard-dose and a High-dose Regimen in Patients With *BRAF*V600-Mutant Melanoma Brain Metastasis

Protocol Number:	ARRAY-818-201
Compound:	Encorafenib + Binimetinib in Combination
Study Phase:	Phase 2
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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ACR	albumin-to-creatinine ratio
AE	adverse event
AESI	adverse event of special interest
AJCC	American Joint Committee on Cancer
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the plasma concentration-time curve
AUC_{last}	area under the plasma concentration-time curve from time zero to T_{last}
AV	atrioventricular
BBB	blood-brain barrier
BCRP	breast cancer resistance protein
BICR	Blinded Independent Central Review
BID	twice daily
BMRR	brain metastasis response rate
BRAF	B-RAF proto-oncogene, serine/threonine kinase
*BRAF*V600E	B-RAF proto-oncogene, V600E mutant
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
C_{max}	maximum observed plasma concentration after drug administration
C_{min}	measured concentration at the end of a dosing interval at steady state (from predose PK sample)
COLUMBUS	Oncology Clinical Trial Protocol CMEK162B2301 COLUMBUS – Combined LGX818 Used with MEK162 in BRAF mutant Unresectable Skin cancer. A 2-part phase III randomized, open label, multicenter study of LGX818 plus MEK162 versus vemurafenib and LGX818 monotherapy in

Abbreviation or special term	Explanation
	patients with unresectable or metastatic BRAF V600 mutant melanoma. ClinicalTrials.gov Identifier: NCT 01909453
COVID-19	coronavirus disease 2019
CPK	creatine phosphokinase
CR	complete response
CRF	case report form
CSR	Clinical Study Report
CT	computed tomography; clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough concentration
CCI	[redacted]
CXDX	C = cycle, D = day and X = number of cycle or day number on a cycle
DCR	disease control rate
DILI	drug-induced liver injury
dL	deciliter(s)
DLT	dose-limiting toxicity
DOR	duration of response
DVT	deep vein thrombosis
EC	ethics committee (includes institutional review board, research ethics board and institutional ethics committee)
EC_{50}	half-maximal effective concentration
ECG	electrocardiogram
ECOG PS	Eastern Cooperation Oncology Group Performance Status
ECHO	echocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EDP	exposure during pregnancy
EOT	end of treatment
ERK	extracellular signal-regulated kinase
EU	European Union
FAS	Full Analysis Set
FDA	U.S. Food and Drug Administration
FDG-PET	fluorodeoxyglucose-positron emission tomography
FSH	follicle stimulating hormone

Abbreviation or special term	Explanation
g	gram(s)
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
H0	null hypothesis
HBV	hepatitis B virus
HCV	hepatitis C virus
HFSR	hand foot skin reaction
HIPAA	Health Information Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
IA	interim analysis
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
IRB	institutional review board
IRT	Interactive Response Technology
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
LH	luteinizing hormone
LLN	lower limit of normal
LV	left ventricular
LVEF	left ventricular ejection fraction
MAPK	mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
MEK	mitogen-activated protein kinase kinase
mg	milligram(s)

Abbreviation or special term	Explanation
mL	milliliter(s)
mm	millimeter
mRECIST v1.1	modified Response Evaluation Criteria in Solid Tumors version 1.1
MRI	magnetic resonance imaging
ms	millisecond(s)
MTD	maximum tolerated dose
MUGA	multi-gated acquisition
NA	not applicable
NCI	National Cancer Institute
NE	inevaluable or not evaluable
nM	nanomolar
OCT	optical coherence tomography
ORR	overall response rate
OS	overall survival
P-gp	P-glycoprotein
PD	progressive disease
PDF	portable document format
PE	pulmonary embolism
pERK	phosphorylated ERK
PET	positron emission tomography
PET-CT	positron emission tomography-computed tomography
PFS	progression-free survival
pH	hydrogen ion concentration
PK	pharmacokinetic(s)
PKS	Pharmacokinetics (PK) Set
pMEK	phosphorylated MEK
PO	oral
PPS	Per-protocol Set
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
PVC	premature ventricular contraction
Q8W	every 8 weeks
Q12W	every 12 weeks

Abbreviation or special term	Explanation
QD	once daily
QTcF	QT interval corrected for heart rate using Fridericia's formula.
RANO-BM	Response Assessment in Neuro-Oncology Brain Metastases
R_{AUC}	accumulation ratio calculated as $AUC_{last,ss}/AUC_{last}$
RBC	red blood cell(s)
RECIST v1.1	Response Evaluation Criteria in Solid Tumours version 1.1
RP2D	recommended Phase 2 dose
RPED	retinal pigment epithelial detachment
RVO	retinal vein occlusion
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	stable disease
SoA	schedule of activities
SOP	standard operating procedure
SRS	stereotactic radiosurgery
SRT	stereotactic radiotherapy
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$ TLF	terminal half-life tables, listings, and figures
TBili	total bilirubin
TDP	torsades de pointes
T_{last}	time of last PK sample
T_{max}	time to reach C_{max}
ULN	upper limit of normal
US	United States
vs.	versus
WBC	white blood cell(s)
WOCBP	woman of childbearing potential

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Phase 2, Open-Label, Randomized, Multicenter Trial of Encorafenib + Binimetinib Evaluating a Standard-dose and a High-dose Regimen in Patients With *BRAF*V600-mutant Melanoma Brain Metastasis

Protocol Number: ARRAY-818-201

Rationale:

Treatment with BRAF + MEK inhibitors has been shown to result in shrinkage of *BRAF*V600-mutant melanoma brain metastasis, albeit with a relatively short duration of response.

The pivotal COLUMBUS study demonstrated favorable efficacy and safety of combination encorafenib + binimetinib for patients with *BRAF*V600-mutant melanoma. Patients with asymptomatic brain metastasis have not been evaluated in a dedicated study with encorafenib + binimetinib. The aim of the present study is to evaluate the benefits of encorafenib and binimetinib specifically in a population of patients with *BRAF*V600-mutated melanoma brain metastasis. Moreover, the blood-brain barrier can limit concentrations of anti-cancer agents at the target for treatment of brain metastases; for this reason, a higher dose of combination therapy may potentially demonstrate greater efficacy without compromising safety for patients with *BRAF*V600 melanoma brain metastasis.

Objectives and Endpoints:

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

Table 1. Primary and Select Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
Safety Lead-in • Evaluate the safety of a high-dose regimen of encorafenib + binimetinib combination therapy in patients with *BRAF*V600-mutant melanoma who have asymptomatic brain metastasis	**Safety Lead-in** • Incidence of DLTs • Incidence and severity of AEs graded according to the NCI CTCAE version 4.03 and changes in clinical laboratory parameters, vital signs and ECGs • Incidence of dose interruptions, dose modifications and discontinuations due to AEs

Table 1. Primary and Select Secondary Objectives and Endpoints

Objectives	Endpoints

Phase 2
If the high-dose regimen is determined to be safe based on the results of the Safety Lead-in phase, then
• Evaluate the antitumor activity in brain metastases of the standard and high-dose regimens of encorafenib + binimetinib combination therapy in patients with *BRAF*V600-mutant melanoma who have asymptomatic brain metastasis
If the high-dose regimen is determined not to be safe based on the results of the Safety Lead-in phase, then
• Evaluate the antitumor activity in brain metastases of the standard dosing regimen of encorafenib + binimetinib combination in patients with *BRAF*V600-mutant melanoma who have asymptomatic brain metastasis
	Phase 2
	• BMRR per mRECIST v1.1

Secondary	
• Further evaluate the antitumor activity of encorafenib + binimetinib combination therapy in patients with *BRAF*V600-mutant melanoma who have asymptomatic brain metastasis	• Extracranial response rate per RECIST v1.1 • Global response rate (brain metastasis response per mRECIST v1.1 and extracranial response per RECIST v1.1) • DCR o for brain metastasis response per mRECIST v1.1 criteria o for extracranial response per RECIST v1.1 o for global response (brain metastasis per mRECIST v1.1

Table 1. Primary and Select Secondary Objectives and Endpoints

Objectives	Endpoints
	and extracranial per RECIST v1.1) • DOR o for brain metastasis response per mRECIST v1.1 criteria o for extracranial response per RECIST v1.1 o for global response (brain metastasis per mRECIST v1.1 and extracranial per RECIST v1.1) • PFS o for brain metastasis per mRECIST v1.1 o for global assessment (brain metastasis per mRECIST v1.1 and extracranial disease per RECIST v1.1) • BMRR per mRECIST v1.1 for Safety Lead-in only
• Evaluate the efficacy of encorafenib + binimetinib combination therapy as measured by OS in patients with *BRAF*V600-mutant melanoma who have asymptomatic brain metastasis	• OS
• Further evaluate the safety profile of encorafenib + binimetinib combination therapy in patients with BRAFV600-mutant melanoma who have asymptomatic brain metastasis	• Incidence and severity of AEs graded according to the NCI CTCAE version 4.03 and changes in clinical laboratory parameters, vital signs and ECGs
• Characterize the PK of encorafenib and its metabolite LHY746, and binimetinib and its metabolite AR00426032	• Plasma concentration-time profiles and PK parameter estimates for encorafenib its metabolite LHY746, and binimetinib and its metabolite AR00426032

Overall Design:

Table 2 presents the key study design elements.

Table 2. Key Study Design Elements

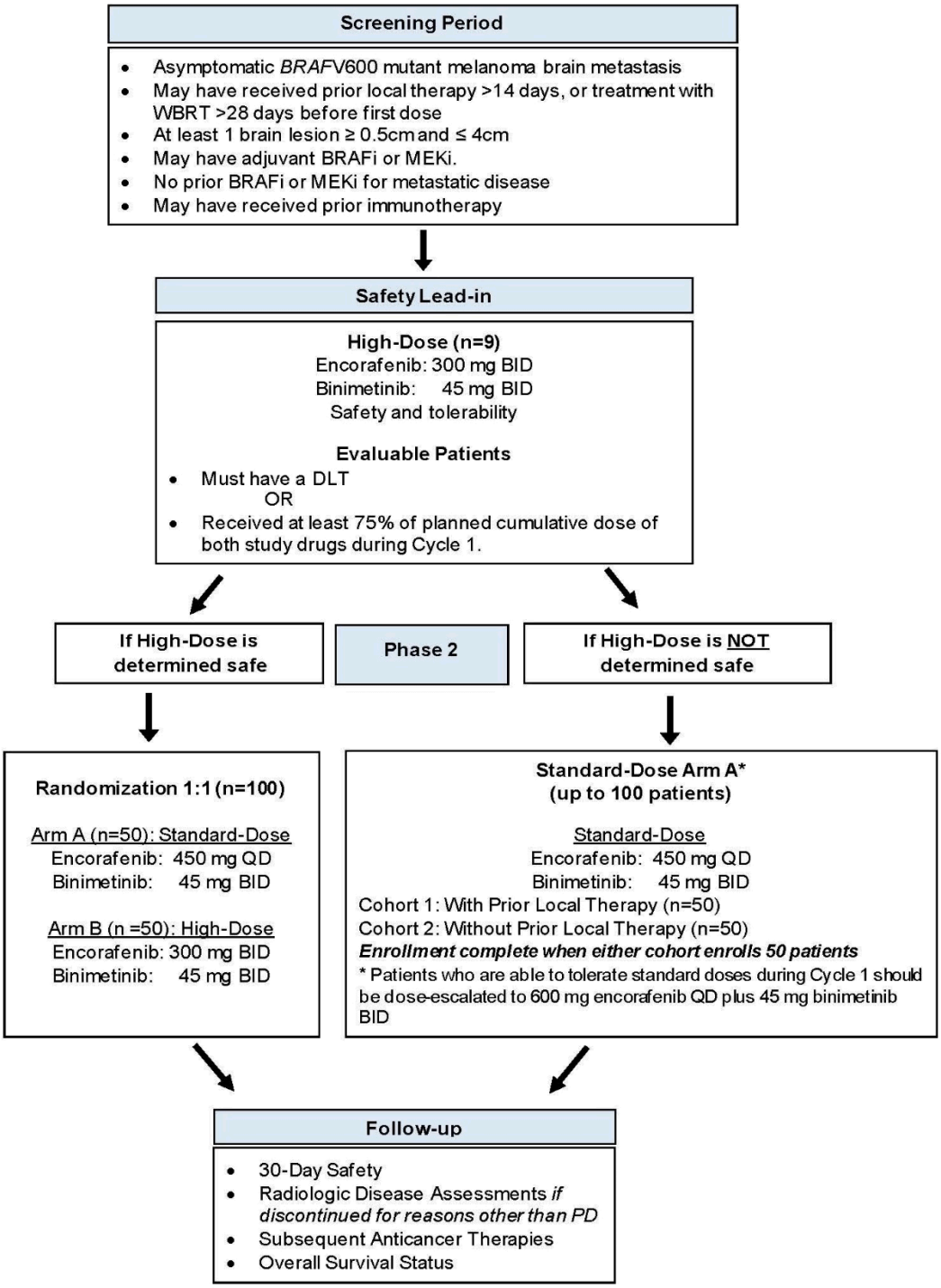
Study Phase	2
Type of Design	This is a multicenter, randomized, open-label Phase 2 study to assess the safety, efficacy and PK of 2 different dosing regimens of encorafenib + binimetinib combination therapy in patients with *BRAF*V600-mutant melanoma with asymptomatic brain metastasis. The first 9 evaluable patients in the high-dose treatment will constitute the high-dose Safety Lead-in cohort. Evaluable patients for the Safety Lead-in cohort must have either: • experienced a DLT or • received at least 75% of planned cumulative dose of both study drugs during Cycle 1. If the high-dose treatment is determined to be safe, approximately 100 eligible patients will be randomized 1:1 (50 in each arm) to receive either the standard-dose (Arm A) or the high-dose (Arm B) encorafenib + binimetinib combination. Randomization will be stratified by baseline tumor burden in the brain (1 to 2 brain lesions vs. ≥ 3 brain lesions at baseline assessment) and by prior local therapy [e.g., stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT), (yes vs. no)]. If the high-dose treatment is determined not to be safe in the Safety Lead-in, no patients will be enrolled into Arm B and up to 100 eligible patients will be enrolled into 2 cohorts in the standard-dose Arm A. **Cohort 1:** Up to 50 patients with *BRAF*V600 cutaneous melanoma with metastases to the brain confirmed by MRI, asymptomatic, and **with** prior local therapy (e.g., SRS or SRT). **Cohort 2:** Up to 50 patients with *BRAF*V600 cutaneous melanoma with metastases to the brain confirmed by MRI, asymptomatic, **without** prior local therapy (e.g., SRS or SRT). Phase 2 enrollment will close when either Cohort 1 or 2 reaches 50 patients. The Sponsor, in consultation with the Steering Committee, will perform a comprehensive evaluation of safety, efficacy and PK data in the Safety Lead-in, as well as periodic safety evaluations during the conduct of the study.
Primary Purpose	Combination treatment with encorafenib + binimetinib using either a standard- or high-dose regimen is being evaluated for use in patients with *BRAF*V600-mutant melanoma brain metastasis.
Intervention Model	Parallel: Patients are randomized to standard- or high-dose treatment arms unless the high-dose treatment arm is found intolerable during the Safety Lead-in.
Clinical Indication	Patients with *BRAF*V600-mutant melanoma brain metastasis.

Table 2. Key Study Design Elements

Population	Adult patients ≥ 18 years with asymptomatic *BRAF*V600-mutant melanoma brain metastasis. Patients must have at least 1 contrast-enhancing metastatic brain lesion ≥ 0.5 cm and ≤ 4 cm, defined by MRI. Patients may have received prior immunotherapy and may have received BRAF or MEK inhibitors in the adjuvant setting provided that the treatment ended ≥ 6 months prior to enrollment. Patients treated with BRAF or MEK inhibitors in the metastatic setting are excluded. Patients must have presence of a *BRAF*V600 mutation in tumor tissue previously determined by a local PCR or NGS-based laboratory assay at any time prior to Screening or by a central laboratory during Screening. Patients are required to submit archival or fresh tissue and a blood sample prior to enrollment. Tissue samples will be used to confirm *BRAF*V600-mutation status by central laboratory within 30 days of enrollment.
Number of Patients	Approximately 110.
Study Centers	Up to 75 centers in the US, Europe, Australia, New Zealand and other regions.
Treatment Regimens	Patients in the standard-dose treatment arm will receive encorafenib 450 mg orally QD and binimetinib 45 mg orally BID in 28-day cycles. Patients who are able to tolerate the standard dose during the first 4 weeks of treatment (Cycle 1) should be dose-escalated to 600 mg encorafenib QD plus 45 mg binimetinib BID provided they meet protocol-defined criteria. Patients in the Safety Lead-in and the high-dose treatment arm will receive encorafenib 300 mg orally BID and binimetinib 45 mg orally BID in 28-day cycles.
Estimated Duration of Study Participation	Up to 28 days for screening; continuous treatment in consecutive 28-day cycles provided the patient is receiving benefit and has not met criteria for treatment withdrawal; and follow-up for safety, disease assessments and survival. End of study will be defined as 2 years after treatment initiation of the last enrolled patient or the time when all patients have died, withdrawn consent or have been lost to follow up, whichever occurs first.

1.2. Schema

Figure 1. Study Schema



1.3. Schedule of Activities (SoA)

Table 3. Schedule of Activities

Procedure/Assessment (± 3-day window for all Treatment Period visits except for C1D1 [no window])	Screening	Treatment Period					Post-treatment Period			Notes/Protocol Section
		Cycle 1		Cycle 2	Subsequent Cycles		EOT	30-Day Follow up	Survival Follow up	
Evaluation/Window	**Day -28 to -1**	**Day 1**	**Day 15**	**Day 1**	**Day 1**	**Day 15**	**± 7D**	**± 7D**	**Q12W ± 7D**	
Informed consent	X									See Sections 7.1 and 9.4
Inclusion/exclusion criteria	X	X								See Section 5.1 and 5.2
Demography and baseline characteristics	X									See Section 7.3.1
Tumor sample (archival or fresh biopsy)	X									Central laboratory testing to confirm *BRAF*V600 status. See Section 7.2.6 and Section 7.9
Tumor sample (optional)							X			See Section 7.9.1
CCI [redacted]	[redacted]			[redacted]	[redacted]		[redacted]			[redacted]
[redacted]	[redacted]			[redacted]	[redacted]		[redacted]			[redacted]
Medical history, cancer diagnosis, extent of cancer (including AJCC stage)	X									See Section 7.3.2
Prior systemic cancer therapies, radiation and surgeries	X									See Section 7.3.2
Contact IWRS	X	X		X	X		X			See Section 6.3

Table 3. Schedule of Activities

Procedure/Assessment (± 3-day window for all Treatment Period visits except for C1D1 [no window])	Screening	Treatment Period					Post-treatment Period			Notes/Protocol Section
		Cycle 1		Cycle 2	Subsequent Cycles		EOT	30-Day Follow up	Survival Follow up	
Evaluation/Window	**Day -28 to -1**	**Day 1**	**Day 15**	**Day 1**	**Day 1**	**Day 15**	**± 7D**	**± 7D**	**Q12W ± 7D**	
HBV and HCV serology testing and HIV where applicable	X									See Section 7.3.10 and Table 11
LH, FSH and/or estradiol	X									See Appendix 1
Dermatologic examination	X	X			X		X	X		Performed Q8W after C3D1. See Section 7.3.4
Physical exam	X	X		X	X			X		Height to be measured at Screening only; see Section 7.3.3
Vital signs	X	X	X	X	X		X	X		See Section 7.3.5
ECOG / Karnofsky status	X	X		X	X			X		See Section 7.2.5
Full ophthalmic examination	X	Only if clinically indicated								See Section 7.3.12
Triplicate 12-Lead ECG	X	X								Triplicate 12-lead ECGs performed predose on C1D1. See Section 7.3.6 and Table 10 for timing of ECG collection.
Single 12-Lead ECG		X		X	X		X			See Section 7.3.6 and Table 10 for timing of ECG collection
ECHO/MUGA	X			X	Every 12 weeks		X	X		ECHO/MUGA scans will be performed on C2D1, then every 12 weeks. ECHO/MUGA scans should be every 24 weeks (or more frequently if clinical indicated) for patients who have been on treatment for ≥ 24 months without decreases of > 10% in LVEF compared

Table 3. Schedule of Activities

Procedure/Assessment (± 3-day window for all Treatment Period visits except for C1D1 [no window])	Screening	Treatment Period					Post-treatment Period			Notes/Protocol Section
		Cycle 1		Cycle 2	Subsequent Cycles		EOT	30-Day Follow up	Survival Follow up	
Evaluation/Window	**Day -28 to -1**	**Day 1**	**Day 15**	**Day 1**	**Day 1**	**Day 15**	**± 7D**	**± 7D**	**Q12W ± 7D**	
										to baseline and LVEF < LLN at any time while on study. See Section 7.3.11
MRI of brain (and spinal cord at Screening only). Contrast-enhanced CT or MRI of chest, abdomen and pelvis Brain metastasis target and non-target lesion assessment	X			X	At Cycle 2 Day 1, Cycle 3 Day 1 and then every 8 weeks through Cycle 11. After Cycle 11, scans occur every 12 weeks, unless response confirmation. Complete response/partial response confirmation assessments must take place at least 4 weeks after the initial response.					EOT scan NOT required if scan was done within 8 weeks of treatment discontinuation and progressive disease has been documented. See Section 7.2.1
Extracranial target and non-target lesion assessment	X			X	At Cycle 2 Day 1, Cycle 3 Day 1 and then every 8 weeks through Cycle 11. After Cycle 11, scans occur every 12 weeks, unless response confirmation. Complete response/partial response confirmation assessments must take place at least 4 weeks after the initial response.					EOT scan NOT required if scan was done within 8 weeks of treatment discontinuation and progressive disease has been documented. See Section 7.2.1
Dispense encorafenib + binimetinib (with dosing diary)		X		X	X					See Section 6.1 and 6.2
Administer encorafenib + binimetinib		X								Administer daily in 28-day cycles. See Section 6.1
Review dosing diary. Assess encorafenib			X	X	X	X	X			See Section 6.4

Table 3. Schedule of Activities

Procedure/Assessment (± 3-day window for all Treatment Period visits except for C1D1 [no window])	Screening	Treatment Period					Post-treatment Period			Notes/Protocol Section
		Cycle 1		Cycle 2	Subsequent Cycles		EOT	30-Day Follow up	Survival Follow up	
Evaluation/Window	**Day -28 to -1**	**Day 1**	**Day 15**	**Day 1**	**Day 1**	**Day 15**	**± 7D**	**± 7D**	**Q12W ± 7D**	
and binimetinib compliance										
Prior/concomitant medication	X	Assess continuously								See Section 6.5
Adverse event assessment	X	Assess continuously								See Section 7.4
Document subsequent anticancer therapies								X	X	See Section 7.2.4.2 and 7.2.4.3
Survival status								X	X	See Section 7.2.4.3
Hematology	X	X	X	X	X		X	X		See Section 7.3.7 and Table 11
Chemistry including troponin	X	X	X	X	X		X	X		See Section 7.3.7 and Table 11
Coagulation	X	Patients on anticoagulation treatment should have parameters monitored throughout the study as clinically indicated								See Section 7.3.7 and Table 11
Serum pregnancy test	X						X			Serum pregnancy test within 24 hours prior to Day 1. See Section 7.3.8
Urine pregnancy test		X		X	X					See Section 7.3.8
Renal functioning monitoring	X	X	X	X	X		X			See Section 7.3.9
Urinalysis	X	Only if clinically indicated					X			See Section 7.3.7 and Table 11
PK blood sample		X	X	X	X					PK blood samples will be collected through Cycle 3 only. See Section 7.7.1, Table 12 and Table 13

2. INTRODUCTION

2.1. Background

2.1.1. Overview of Melanoma Brain Metastasis

Metastatic melanoma has a high risk of spreading to the central nervous system (Cohen et al, 2016, Sampson et al, 1998). The development of brain metastases in patients with melanoma has an observed incidence of up to 43% and 75% in clinical and autopsy studies, respectively (Long and Margolin 2013, Sampson et al. 1998). Intracranial melanoma accounts for up to 54% of deaths in patients with melanoma (Budman et al, 1978, Davies et al, 2011). Multiple brain metastases are more common than oligometastasis. Contrast-enhanced MRI is the standard diagnostic modality, as CT imaging is less specific. Therefore, CT imaging requires MRI confirmation, particularly for a single metastasis (Usuki et al, 2016).

The most frequent genetic alteration in melanoma is the *BRAF*V600 mutation, which occurs in up to 50% of cases. *BRAF* mutations drive constitutive MAPK pathway activation and in turn proliferation with enhanced cellular survival. It is known that *BRAF*-mutated melanoma can be inhibited clinically by BRAF and MEK inhibitors (Dummer et al, 2018a).

2.1.2. Local Treatment for *BRAF*-mutant Melanoma Brain Metastasis

Treatment options for patients with melanoma brain metastasis are evolving, with adoption recently of targeted and immunotherapies for metastatic melanoma including *BRAF*-mutant disease. In past decades surgery, whole brain radiation therapy and stereotactic radiosurgery were the accepted standard of care for the management of melanoma brain metastasis.

Currently stereotactic radiosurgery is an accepted alternative to resection followed by radiation therapy for a limited number of brain metastases, up to 3 lesions and 4 cm or less in size (Andrews et al. 2004, Kondziolka et al, 1999, Kondziolka et al, 2005, Sanghavi et al, 2001, Shaw et al, 2000, Sneed et al, 2002). Local therapy modalities offer control of a limited number of melanoma brain lesions, but do not control spread of metastatic brain lesions beyond the locally controlled lesions or extracranial disease (Tawbi et al. 2018a, Yamamoto et al,2017). Chao et al, (2008) showed that new tumors developed in 45% of patients at 6 months after whole brain radiotherapy, the local modality considered to control the progression of micrometastatic brain tumors. In a multi-institutional pooled analysis of 569 patients with brain metastasis treated with stereotactic radiosurgery alone compared to stereotactic radiosurgery with whole brain radiotherapy, Sneed et al (2002) reported that 37% of the patients with brain metastases treated with stereotactic radiosurgery alone underwent salvage therapy at a median 5.7 months after treatment compared to 7% after a median 8 months following whole brain radiation therapy. Research and debate continue regarding the optimal number of lesions appropriate for stereotactic radiotherapy, fractionation schedules and feasibility of retreatment with stereotactic radiotherapy (Grob et al, 2018).

Surgery and radiotherapy continue to have a role in the management of symptomatic and large melanoma brain metastasis. Current prospective clinical research evaluating targeted therapies and checkpoint inhibitors has demonstrated clinical activity that supports clinical investigation to optimize systemic treatment of melanoma patients with brain metastasis (Davies et al, 2017, Goyal et al, 2015, Tawbi et al, 2018b).

2.1.3. Systemic Treatment for *BRAF*-mutant Melanoma Brain Metastasis

Early clinical results suggested a role for targeted agents in *BRAF*-mutated melanoma brain metastasis. In a Phase 1 dose-finding study, Falchook et al, (2012a) described outcomes when the BRAF inhibitor dabrafenib was administered to patients with previously untreated melanoma brain metastasis. Nine of 10 patients with treatment-naïve melanoma brain metastasis experienced a reduction in brain lesion size. In a Phase 1 dose-finding study of the MEK inhibitor trametinib, Falchook et al, (2012b) identified 1 CR and 6 PRs among 16 *BRAF*-mutant patients with previous and locally treated brain metastases who had not received prior BRAF inhibitor treatment. In patients with *BRAF*V600E-mutant melanoma brain metastases having had no prior local therapy, patients receiving dabrafenib monotherapy had ORR of 39.2%, median PFS of 16.1 weeks, median OS of 33.1 weeks and 6-month OS rate of 61% (Long et al, 2012).

In a retrospective chart review of patients from 3 institutions, 75.8% of 161 patients with unresectable stage IIIC or IV *BRAF*-mutant melanoma received the BRAF inhibitor vemurafenib (Gummadi et al, 2015). The incidence rate ratio of brain metastasis between patients treated with vemurafenib before the development of brain metastasis and those not treated with vemurafenib before the development of brain metastases was 0.51 (95% CI 0.30, 0.86, p = 0.009). While there was no difference in OS among patients with brain metastases and *BRAF*-mutated melanoma regardless of treatment with vemurafenib, the authors suggest a modest protective effect of vemurafenib from development of brain metastases in patients with melanoma. McArthur et al, (2017) evaluated vemurafenib monotherapy in patients with melanoma brain metastasis. Median PFS in the brain was relatively short, 3.7 months for patients with no prior brain metastasis treatment and 4.0 months for patients with previously treated brain metastasis. Combination BRAF and MEK inhibition therapy was suggested as another option for evaluation in patients with melanoma brain metastasis.

In the COMBI-MB study (Davies et al, 2017), the combination of dabrafenib plus trametinib resulted in a 58% intracranial response rate in 76 patients with *BRAF*V60*0E*-mutant melanoma brain metastases naïve to prior local therapy. The median duration of response was 6.5 months with a response rate at 6 months of 63%. The most common SAEs were pyrexia and decreased ejection fraction. Grade 3 AEs were reported in 39%, Grade 4 AEs in 5% and Grade 5 AEs in 1% of patients. Grade 3 pyrexia was reported in 3% of patients. The 6.5-month duration of response fell short of that observed in patients with melanoma without brain metastasis. Extracranial responses observed in 55% in the same cohort lasted a median of 10.2 months. In the Phase 3 COMBI-d trial, patients with asymptomatic and untreated extracranial melanoma treated with dabrafenib plus trametinib demonstrated a 12-month duration of response (Long et al, 2017).

Recent clinical studies continue to report responses to treatment with BRAF, MEK and checkpoint (i.e., anti-CTLA-4, anti-PD-1, alone or combined) inhibitors in patients with melanoma brain metastasis (Ascierto et al. 2016, Davies et al. 2017, Larkin et al. 2015, Long et al. 2015, Robert et al. 2015a, Robert et al. 2015b). Long et al, (2018a) reported on a randomized Phase 2 study of nivolumab and ipilimumab or nivolumab alone in patients with asymptomatic brain metastases with no previous local brain therapy or immunotherapy. In patients who received nivolumab and ipilimumab, 46% (16 of 35 patients) had an intracranial

response at or after Week 12. The landmark intracranial 6-month PFS was 53%. Grade 3 to 4 AEs were reported in 54% of patients.

Pembrolizumab was investigated in a Phase 2 single-institution study of intracranial response in patients with untreated or progressive melanoma brain metastasis (Goldberg et al, 2016). Goldberg et al. found that 22% of patients had a confirmed PR (4 of 18 patients) after pembrolizumab monotherapy. None of the 4 responders had *BRAF*-mutant melanoma.

The CheckMate 204 study evaluated nivolumab and ipilimumab in asymptomatic metastatic melanoma patients with at least 1 brain metastasis. In this single-arm Phase 2 study, 94 patients with a minimum follow up of 6 months and a median follow up of 14.0 months demonstrated an intracranial clinical benefit (SD+PR+CR) of 57% (95% CI 47%, 68%) (Tawbi et al, 2018b). Thirty percent of patients had a PR and 26% had a CR. The intracranial clinical benefit for *BRAF*-mutated patients totaled 59.3% (95% CI 45.0, 72.4) (32 of 54 patients with *BRAF* mutation). The 12-month landmark global PFS (intracranial and extracranial*)* was 56.6%. Safety results in CheckMate 204 were consistent with the safety profile of nivolumab and ipilimumab in patients without melanoma brain metastasis. Grade 3 to 4 AEs were reported in 60% of patients; 27% of patients discontinued treatment because of a treatment-related AE.

Despite recent clinical improvements for patients with *BRAF*-mutant melanoma brain metastasis, the brain continues as a prominent organ for metastatic progression after targeted or checkpoint therapy. Current melanoma treatments show efficacy for metastatic disease to the brain, but short durations of response and suboptimal safety profiles necessitate evaluation of a new regimen for *BRAF*V600 melanoma brain metastasis.

Encorafenib and binimetinib have received marketing approval in the US, EU and several other regions. Regulatory approval of encorafenib and binimetinib in combination was based on the Phase 3 COLUMBUS study (randomized, 2-part, open-label, multicenter, international clinical study) (Dummer et al, 2018a, Dummer et al, 2018b). COLUMBUS demonstrated that combination encorafenib + binimetinib has favorable efficacy and safety in patients with *BRAF*-mutant metastatic melanoma. The aim of the present study is to evaluate through a dedicated melanoma brain metastasis trial the combination of encorafenib and binimetinib at the standard and high-dose regimens for patients with *BRAF*V600-mutated disease. The high-dose treatment arm investigates whether a high-dose regimen may overcome potential limitations in brain penetration for patients with melanoma brain metastasis. A detailed justification for evaluating a higher dose is provided in Section 4.3.

2.2. Overview of Encorafenib and Binimetinib

2.2.1. Encorafenib

Encorafenib is a potent and selective ATP-competitive inhibitor of *BRAF*V600-mutant kinase. Encorafenib 450 mg orally QD in combination with binimetinib 45 mg orally BID have been approved by the US FDA, the EMA and by other health authorities for the treatment of patients with unresectable or metastatic melanoma with a *BRAF*V600E or V600K mutation as detected by an FDA-approved test. Encorafenib is known to induce CYP3A4. Therefore, hormonal birth control agents are permissible only when combined with

other highly effective or acceptable methods (see Section 6.5.1.1, Section 5.3 and Appendix 1.

Detailed information regarding nonclinical studies and clinical pharmacokinetics of encorafenib are presented in the Investigator's Brochure.

2.2.2. Binimetinib

Binimetinib is a potent and selective allosteric, ATP-uncompetitive inhibitor of MEK1/2. Binimetinib 45 mg orally QD in combination with encorafenib 450 mg orally QD have been approved by the US FDA, the EMA and by other health authorities for the treatment of patients with unresectable or metastatic melanoma with a *BRAF*V600E or V600K mutation as detected by an FDA-approved test. Detailed information regarding nonclinical studies and clinical pharmacokinetics of binimetinib are presented in the Investigator's Brochure.

2.2.3. Clinical Safety of Combination Encorafenib and Binimetinib

The COLUMBUS trial is a two-part, randomized Phase 3 trial evaluating the efficacy and safety of the combination of encorafenib and binimetinib compared to vemurafenib and encorafenib monotherapy in patients with locally advanced, unresectable or metastatic melanoma with *BRAF*V600 mutation. 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 MEK inhibitor and a BRAF inhibitor results in improved tolerability compared with either agent alone (Flaherty et al, 2012, Long et al, 2014, Robert et al, 2015a, Larkin et al, 2014, Ascierto et al, 2016).

Among patients receiving encorafenib and binimetinib combination therapy in the COLUMBUS study, the most common adverse reactions (≥ 20%, 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%), 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%) 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. Uveitis, including iritis and iridocyclitis, has been reported in patients treated with encorafenib in combination with binimetinib. In the COLUMBUS study, the incidence of uveitis among patients treated with encorafenib 450 mg QD in combination with binimetinib 45 mg BID was 4.4%.
- **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 alanine aminotransferase (ALT), 2.6% for aspartate aminotransferase (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.

2.2.4. Clinical Safety of Encorafenib as a Single Agent in the COLUMBUS Study

The maximum well-tolerated dose of encorafenib when given as a single agent is 300 mg daily. Encorafenib 300 mg daily 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%).

Detailed information regarding clinical safety of encorafenib is presented in the encorafenib Investigator's Brochure.

2.2.5. Clinical Safety of Encorafenib 600 mg QD in the CMEK162X2110 Study

Clinical Study CMEK162X2110 was a Phase 1b/2 multicenter, open-label, dose-finding, dose-escalation study. In Phase 1b, the primary objective was to estimate the MTD(s) and/or RP2D(s) of encorafenib + binimetinib (dual combination) and of encorafenib + binimetinib + ribociclib (triple combination) in patients with *BRAF* V600-dependent advanced solid tumors. In Phase 2, the primary objective of the study was to assess the clinical efficacy of the dual combination and the triple combination at each MTD/RP2D in the selective Phase 2 populations.

A total of 47 patients treated with dual combination therapy were enrolled in the Phase 1b study, with only 1 patient (2.3%) across all cohorts investigated experiencing a DLT occurring in a patient receiving 800 mg encorafenib and 45 mg binimetinib (nonserious AE of Grade 3 arthritis). The most frequently reported AEs for the 600 mg QD encorafenib plus 45 mg binimetinib Phase 1b patients (n=8) were nausea in 5 patients (62.5%), diarrhea in 7 patients (87.5%) fatigue, constipation, and abdominal pain in 3 patients (37.5%). The proportion of patients reporting each of these events was generally comparable across all Phase 1b dose cohorts, with a higher incidence of nausea and diarrhea reported in the higher encorafenib dose cohorts.

At the completion of the Phase 1b, dose escalation portion of the CMEK162X2110 study, 2 separate RP2Ds, encorafenib 600 mg QD (n=8) and 450 mg QD (n= 13), both in combination with binimetinib 45 mg BID, were identified.

A total of 79 patients were treated in Phase 2 with 64 patients receiving 600 mg QD as the starting encorafenib dose and 15 patients received 450 mg QD as the starting encorafenib dose. Early-onset renal insufficiency (Grade 3 creatinine increase) was observed in 3 melanoma patients (2 with pre-existing conditions that could be associated with renal insufficiency) at the higher encorafenib dose level (600 mg QD), leading to a decision to no longer treat patients at this dose. All subsequent Phase 2 patients were started at 450 mg QD, and all ongoing patients on the higher encorafenib dose were given the option to reduce the dose to 450 mg QD in combination with their current binimetinib dose. Further evaluation of

renal failure/acute renal injury have been evaluated during ongoing aggregate safety reviews across clinical trials with encorafenib. Most cases of renal impairment/insufficiency/failure or chronic kidney injury were associated with pre-renal causes, such as dehydration with vomiting or diarrhea, and other pre-existing conditions or risk factors, such as diabetes and hypertension. Furthermore, the Sponsor had an expert nephrologist consultant review renal biopsy reports, which concluded that these events were likely not intrinsic drug-induced toxicity.

All 79 Phase 2 patients experienced at least 1 adverse event of any grade. The most frequently reported adverse events (≥ 25% of patients) regardless of grade were diarrhea in 41 patients (51.9%), nausea in 37 (46.8%), vomiting in 29 patients (36.7%), pyrexia in 26 patients (32.9%), arthralgia in 24 patients (30.4%), fatigue in 24 patients, constipation in 20 patients (25.3%), and AST increased in 20 patients (25.3%). Most of the AESIs were reported with a severity of Grade 1 or 2.

Detailed information regarding clinical safety of encorafenib 600 mg QD in combination with binimetinib 45 mg BID is presented in the encorafenib Investigator's Brochure.

2.3. Study Rationale

Results from the COLUMBUS Phase 3 trial provide the clinical support and rationale to conduct a study in a subpopulation of *BRAF*V600 melanoma patients with asymptomatic brain metastases. The Phase 3 COLUMBUS study (randomized, 2-part, open-label, multicenter, international clinical study) demonstrated clinically meaningful results of encorafenib + binimetinib treatment in patients with metastatic *BRAF*V600-mutant melanoma. Median PFS was 14.9 months (95% CI 11,0, 20.2) with encorafenib + binimetinib and 7.3 months (95% CI 5.6, 8.2) with vemurafenib (hazard ratio 0.54 [95% CI 0.41, 0.71]; two-sided p <0.0001) (Dummer et al, 2018a). The hazard ratio for PFS in the encorafenib + binimetinib group compared to the encorafenib monotherapy group was 0.77 (95% CI 0.59, 1.00, 2-sided p = 0.050) (Dummer et al, 2018b), thus confirming that combined BRAF and MEK inhibition provides a superior response compared to BRAF-inhibitor monotherapy. Median OS was 33.6 months (95% CI 24.4, 39.2) with encorafenib + binimetinib and 16.9 months (95% CI 14.0, 24.5) with vemurafenib (hazard ratio 0.61 [95% CI 0.47, 0.79]; two-sided p < 0.0001).

A dedicated trial comparing high- and standard-dose regimens of encorafenib and binimetinib will provide additional clinical evidence in the subset of advanced melanoma patients with metastasis to the brain. In addition, the study will evaluate whether a high-dose regimen may overcome potential limitations in brain penetration compared to the standard-dose regimen.

2.4. Benefit/Risk Assessment

The primary risks of encorafenib + binimetinib treatment are well characterized and include known class effects of BRAF and MEK inhibitors. These include skin toxicities; eye toxicities including RVO, serous retinopathy and uveitis; hypertension; hepatic toxicity; LV dysfunction; hemorrhage; thromboembolism; and rhabdomyolysis. The combination of encorafenib + binimetinib has a lower frequency and severity of pyrexia and photosensitivity

reactions than dabrafenib + trametinib and vemurafenib + cobimetinib combinations, respectively. Observed toxicities of encorafenib + binimetinib combination are generally manageable by dose modification, temporary interruption of treatment or discontinuation in conjunction with established medical management.

Investigators selected to participate in this study are experienced in managing toxicities associated with combination BRAF and MEK inhibitor therapy. This, together with regular monitoring of LVEF, liver function, CK, renal function (Section 7.3.9) and appropriate patient counseling regarding potential toxicities, minimizes the potential risks associated with treatment with encorafenib + binimetinib. The level of risk compared to the potential benefit to metastatic melanoma patients is acceptable. The relatively low rate of treatment discontinuation for adverse reactions, 6% in the COLUMBUS study (Dummer et al, 2018a) and dose intensity achieved for both encorafenib and binimetinib demonstrate that the combination is well tolerated.

There is a risk that the high-dose regimen will not be tolerable. However, the study design, including a Safety Lead-in will mitigate that risk. Results may demonstrate an effective treatment alternative for patients with melanoma brain metastasis after first-line checkpoint inhibitor therapy.

3. OBJECTIVES AND ENDPOINTS

Table 4. Objectives and Endpoints

Primary Objective	Primary Endpoint
Safety Lead-in • Evaluate the safety of a high-dose regimen of encorafenib + binimetinib combination therapy in patients with *BRAF*V600-mutant melanoma who have asymptomatic brain metastasis	**Safety Lead-in** • Incidence of DLTs • Incidence and severity of AEs graded according to the NCI CTCAE version 4.03 and changes in clinical laboratory parameters, vital signs and ECGs • Incidence of dose interruptions, dose modifications and discontinuations due to AEs
Phase 2 If the high-dose regimen is determined to be safe based on the results of the Safety Lead-in phase, then • Evaluate the antitumor activity in brain metastases of the standard and high dose regimens of encorafenib + binimetinib combination therapy in patients with *BRAF*V600-mutant	**Phase 2** • BMRR per mRECIST v1.1

Table 4. Objectives and Endpoints

melanoma who have asymptomatic brain metastasis If the high-dose regimen is determined **not** to be safe based on the results of the Safety Lead-in phase, then • Evaluate the antitumor activity in brain metastases of the standard dosing regimen of encorafenib + binimetinib combination in patients with *BRAF*V600-mutant melanoma who have asymptomatic brain metastasis	
Secondary Objectives	**Secondary Endpoints**
• Further evaluate the antitumor activity of encorafenib + binimetinib combination therapy in patients with *BRAF*V600-mutant melanoma who have asymptomatic brain metastasis	• Extracranial response rate per RECIST v1.1 • Global response rate (brain metastasis response per mRECIST v1.1 and extracranial response per RECIST v1.1) • DCR o for brain metastasis response per mRECIST v1.1 o for extracranial response per RECIST v1.1 o for global response (brain metastasis per mRECIST v1.1 and extracranial per RECIST v1.1) • DOR o for brain metastasis response per mRECIST v1.1 o for extracranial response per RECIST v1.1 o for global response (brain metastasis per mRECIST v1.1 and extracranial per RECIST v1.1) • PFS o for brain metastasis per mRECIST v1.1 o for global assessment (brain metastasis per mRECIST v1.1

Table 4. Objectives and Endpoints

	and extracranial disease per RECIST v1.1) • BMRR per mRECIST v1.1 for Safety Lead-in only
• Evaluate the efficacy of encorafenib + binimetinib combination therapy as measured by OS in patients with *BRAF*V600-mutant melanoma who have asymptomatic brain metastasis	• OS
• Further evaluate the safety profile of encorafenib + binimetinib combination therapy in patients with *BRAF*V600-mutant melanoma who have asymptomatic brain metastasis	• Incidence and severity of AEs graded according to the NCI CTCAE version 4.03 and changes in clinical laboratory parameters, vital signs and ECGs
• Characterize the PK of encorafenib and its metabolite LHY746, and binimetinib and its metabolite AR00426032	• Plasma concentration-time profiles and PK parameter estimates for encorafenib and its metabolite LHY746, and binimetinib and its metabolite AR00426032
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, randomized open-label Phase 2 study to assess the safety, efficacy and PK of 2 dosing regimens of encorafenib + binimetinib combination therapy in patients with *BRAF*V600-mutant melanoma with asymptomatic brain metastasis. Approximately 110 eligible patients will be enrolled, including 9 patients in a single-arm Safety Lead-in. After a Screening Period, treatment will be administered in 28-day cycles and will continue until disease progression, unacceptable toxicity, withdrawal of consent, start of subsequent anticancer therapy, death. Once the patient discontinues study treatment, the Treatment Period will end, and the patient will enter the Follow-up Period. The 2 doses of encorafenib + binimetinib combination treatment to be evaluated are summarized in Table 5.

The first 9 evaluable patients in the high-dose treatment will constitute the high-dose Safety Lead-in cohort. Evaluable patients for the Safety Lead-in cohort must have experienced:

- either a DLT (Table 7) or
- received at least 75% of the planned cumulative dose of both study drugs during Cycle 1.

If the high-dose treatment is found safe during the Safety Lead-in, based on predefined evaluation criteria (Section 6.6), eligible patients will be randomized (1:1; approximately 50 patients in each treatment arm) to the standard-dose (Arm A) or high-dose (Arm B) treatment arm stratified by:

- baseline number of brain metastases (1 to 2 brain lesions vs. ≥ 3 brain lesions at baseline assessment) and
- history of prior local therapy [e.g., SRS or SRT (yes vs. no)].

Table 5. Planned Treatment Arms

Treatment Arm	Encorafenib Dose	Binimetinib Dose
A (standard-dose)[1]	450 mg QD	45 mg BID
B (high-dose)	300 mg BID	45 mg BID

1. The standard dose arm (Arm A) includes patients who have intra-patient dose escalation (see Section 6.7.2).

If the high-dose treatment is determined not to be safe in the Safety Lead-in, no patients will be enrolled into Arm B, and up to 100 patients will be enrolled into 2 cohorts in the standard-dose Arm A:

- **Cohort 1:** Up to 50 patients with *BRAF*V600 cutaneous melanoma with metastases to the brain confirmed by MRI, asymptomatic, and with prior local therapy (e.g., SRS or SRT).

- **Cohort 2:** Up to 50 patients with *BRAF*V600 cutaneous melanoma with metastases to the brain confirmed by MRI, asymptomatic, without prior local therapy (e.g., SRS or SRT). Phase 2 enrollment will close when either Cohort 1 or 2 reaches approximately 50 patients.

Patients who are able to tolerate the standard dose of encorafenib (450 mg QD) plus binimetinib (45 mg BID) during the first 4 weeks of treatment (Cycle 1) should be dose-escalated to 600 mg encorafenib QD plus 45 mg binimetinib BID provided they meet protocol-defined criteria (see Section 6.7.2).

As described in Section 6.10, patients who remain on treatment at the end of the study and who may, in the opinion of the Investigator, derive benefit from continued treatment with encorafenib + binimetinib may be provided the opportunity to continue treatment in accordance with local regulations.

4.2. Discussion of Study Design

This Phase 2 trial uses accepted tumor assessment endpoints with a primary endpoint of response, BMRR. Predefined, standardized and generally accepted criteria for this patient population are used to ascertain responses, specifically RECIST v1.1 and mRECIST v1.1. Response rate is deemed a direct measure of drug antitumor activity that can be evaluated in a single-arm trial (US Department of Health and Human Services 2007).

The study design incorporates a Safety Lead-in to ensure an appropriate safety evaluation of a previously untested dosing regimen. If the high-dose regimen is determined to be safe based on the Safety Lead-in results, the stratified randomized study design provides an unbiased approach to evaluate the efficacy and safety of 2 dosing regimens. If the high-dose regimen is determined not to be safe based on the Safety Lead-in results, the 2 cohorts in the standard-dose treatment arm will allow the evaluation of the efficacy of standard-dose regimen in those patients with prior local therapy and those without prior local therapy in order to better understand the impact, if any, of prior local therapy on objective response to subsequent systemic therapy with encorafenib and binimetinib.

Patients who are able to tolerate the standard dose of encorafenib (450 mg QD) plus binimetinib (45 mg BID) during the first 4 weeks of treatment (Cycle 1) should be dose-escalated to 600 mg encorafenib QD plus 45 mg binimetinib BID provided they meet protocol-defined criteria (see Section 6.7.2). This update in protocol amendment version 3.0 provides additional data to evaluate the safety, tolerability and efficacy of encorafenib + binimetinib combination therapy with dose-escalation to encorafenib 600 mg QD.

4.3. Justification for Dose

This study evaluates the combination of encorafenib and binimetinib using 2 regimens:

- A standard-dose treatment arm (encorafenib 450 mg QD + binimetinib 45 mg BID)
- A high-dose treatment arm (encorafenib 300 mg BID + binimetinib 45 mg BID)

The standard-dose treatment employs a regimen for binimetinib and encorafenib identical to that used in the COLUMBUS study, which demonstrated clinically meaningful antineoplastic efficacy in patients with *BRAF*-mutant metastatic melanoma. Patients who tolerate the first cycle (4 weeks) of standard-dose treatment (see Section 6.7.2), should be dose escalated to receive encorafenib 600 mg QD, a dose that was previously shown to be safe and efficacious in Clinical Study CMEK162X2110 (see Section 2.2.5).

Encorafenib is a P-gp substrate and an inhibitor of BCRP, while binimetinib is a P-gp and BCRP substrate. Due to the function of the blood-brain barrier, the penetration of a drug into the brain depends on its intrinsic membrane permeability and its susceptibility to active efflux (Di et al. 2013). Although encorafenib and binimetinib have high intrinsic membrane permeability, efflux transporters may result in reduced brain concentrations for both. Animal models have limited utility in predicting the effect of efflux transporter proteins on human brain concentrations (Di et al, 2013, Syvanen et al, 2009, Chu et al, 2013).

The BBB may be compromised in patients with brain metastases (Cohen et al, 2016). The compromised blood brain barrier may at least in part explain the activity of other drugs in melanoma brain metastases. For example, dabrafenib and trametinib are efflux transporter substrates thought to have limited brain penetration based on nonclinical data (Mittapalli et al, 2013, Vaidhyanathan et al, 2014). Yet the combination had clinical activity in the COMBI-MB study (Davies et al, 2017). The role of the potentially compromised BBB in treating patients with brain metastases is not well understood, and thus evaluating a high-dose regimen when feasible is seen as a potentially useful strategy in these patients.

The high-dose treatment arm investigates whether an alternate regimen may overcome potential limitations in brain penetration for patients with melanoma brain metastasis compared to the standard-dose treatment. The following sections describe the rationale for the high-dose regimen.

4.3.1. Binimetinib Regimen

Binimetinib monotherapy has been evaluated at 45 mg BID and 60 mg BID (clinical studies ARRAY-162-111 and CMEK162X2201). An observed incidence of reversible retinal events during dose expansion at 60 mg BID led to binimetinib dose reduction to 45 mg BID. A BID dosing regimen of 45 mg was used in the Phase 3 COLUMBUS study in *BRAF*V600-mutant melanoma (Dummer et al, 2018a, Dummer et al, 2018b). Options for increasing binimetinib dose are limited by transient ocular findings; therefore, the high-dose regimen for the current study explores only high-dose encorafenib in combination with the standard dose of binimetinib.

4.3.2. High-dose Encorafenib

The goals of including a high-dose regimen of encorafenib is this study are 2-fold: (1) to increase the total daily dose to offset the potential decrease in exposure in the brain due to the BBB and (2) to increase continuous target coverage throughout each day by increasing the dosing frequency.

Compared to 450 mg QD, encorafenib at 300 mg BID is expected to increase the daily AUC by 33% and the trough concentration by 700%. The C_{max} is expected to decrease by 32%. Higher daily encorafenib doses will increase exposure (i.e., AUC) and, in turn, result in higher brain exposure. The EC_{50} values for suppression of pMEK and pERK in A375 human melanoma cells expressing *BRAF*V600 are 2 nM and 3 nM, respectively. At a 450 mg QD encorafenib dose, the unbound steady-state C_{max} is approximately 850 nM, which is ~280- to 430-fold higher than these EC_{50} values. At a 300 mg BID encorafenib dose, the unbound steady-state C_{max} is approximately ~190- to 290-fold higher than these EC_{50} values. Therefore, it is likely that a 32% reduction in C_{max} will not be detrimental and may be offset by increases in AUC and trough concentrations.

Encorafenib BID regimen may have additional advantages for *BRAF*V600 coverage. The in vitro rate of dissociation of encorafenib from the target protein kinase, *BRAF*V600, has been observed to be slower than that of the *BRAF*V600 inhibitors dabrafenib and vemurafenib (Delord et al, 2017). The relationship between the in vitro and in vivo kinetics and target inhibition in tumors has not been established. Once daily dosing is efficacious in peripheral *BRAF*V600 mutant melanomas (Dummer et al 2018a, Dummer et al 2018b). However, encorafenib concentrations in the brain may not provide adequate target inhibition during an entire 24-hour dosing cycle. With a 300 mg BID encorafenib regimen, an increased AUC and trough concentration may increase target inhibition in the brain.

There is limited clinical experience with higher dose BID encorafenib regimen. Dose-ranging Study CMEK162X2110 evaluated regimens up to encorafenib 800 mg QD + binimetinib 45 mg BID (see Section 2.2.5).

Due to the potential for increased toxicity associated with the high-dose BID regimen, the study design includes a Safety Lead-in to assess tolerability based on predefined evaluation criteria (Section 6.6). Specific guidance related to renal safety monitoring is provided in Section 6.7.3.

4.4. End of Study Definition

End of study will be defined as 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 are continuing to benefit from study treatment (see Section 6.10).

4.5. Study Termination

The Investigator retains the right to terminate conduct of the study at any time, according to the terms specified in the clinical trial agreement. The Investigator is required 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 Sponsor's 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

Patients must fulfill all eligibility criteria to be eligible for enrollment in the study. Questions regarding patient eligibility should be addressed to the Sponsor prior to enrollment.

Protocol deviations to recruitment and enrollment criteria 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 the following criteria to be eligible for enrollment in the study:

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

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

3. Histologically confirmed diagnosis of cutaneous melanoma with metastases to the brain.

4. Presence of *BRAF*V600 mutation in tumor tissue previously determined by a local PCR or NGS-based assay at any time prior to Screening or by a central laboratory during Screening.

5. Patients are required to submit archival or fresh tumor tissue and a blood sample prior to enrollment. Tissue samples will be used to determine *BRAF*V600-mutation status by central laboratory.

6. Must have at least 1 parenchymal brain lesion ≥ 0.5 cm and ≤ 4 cm, defined as an MRI contrast-enhancing lesion that may be accurately measured in at least 1 dimension.
   ***Note*:** Measurable intracranial lesions that have been previously irradiated and have not been shown to be progressing following irradiation should not be considered as target lesions.

7. Patients may have received the following prior therapies:

    a. **Safety Lead-in, Phase 2 Randomized , Phase 2 Arm A Cohort 1**: May have received prior local therapy for brain metastases including but not restricted to brain surgery, whole brain radiotherapy (WBRT), stereotactic radiotherapy or stereotactic radiosurgery (e.g. gamma knife, linear-accelerated-based radiosurgery, charged particles, and CyberKnife). Multiple local (brain) therapies or combinations of local therapies are allowed. For patients receiving local therapy to all brain lesions (including WBRT), progression of pre-existing lesions based on RECIST 1.1 (> 20% increase in longest diameter on baseline scan) or new measurable lesions are required. For patients receiving local therapy for some but not all lesions, disease progression based on RECIST 1.1 is not required as long as there are remaining brain lesions that are measurable and not previously treated.

    b. **Phase 2 Arm A Cohort 2:** Received no prior local therapy (e.g., brain surgery, craniotomy, SRS or SRT) for brain metastases.

    c. **All patients (Safety Lead-In and Phase 2):** May have received prior immunotherapy.

    d. **All patients (Safety Lead-In and Phase 2**): If receiving concomitant corticosteroids must be on a stable or decreasing dose (up to a total daily dose of 4 mg of dexamethasone or equivalent) for at least 2 weeks prior to first dose of study treatment.

8. An ECOG PS of 0 or 1 and Karnofsky score ≥ 80 (see Section 7.2.5).

9. Adequate bone marrow, organ function and laboratory parameters:

    a. ANC ≥ 1.5×10^9/L;

    b. Hemoglobin ≥ 9 g/dL with or without transfusions;

    c. Platelets ≥ 100×10^9/L;

    d. AST and ALT ≤ 2.5 × ULN; in patients with liver metastases ≤ 5 × ULN;

    e. Total bilirubin ≤ 1.5 × 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 Medical Monitor.

f. Serum creatinine ≤ 1.5 × ULN; OR calculated creatinine clearance > 50 mL/min by Cockcroft-Gault formula; OR estimated glomerular filtration rate > 50 mL/min/1.73m^2.

10. Female patients of childbearing potential, as described in Appendix 1, must have a negative serum β-HCG test result.

11. Female patients of childbearing potential must agree to protocol-approved methods of contraception, as described in Appendix 1, and to not donate ova from Screening until 30 days after the last dose of study drug.

12. 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.

13. The patient is deemed by the Investigator to have the initiative and means to comply with scheduled visits, treatment plan and study procedures.

5.2. Exclusion Criteria

Patients meeting any of the following criteria are not eligible for enrollment in the study.

1. Patients with symptomatic brain metastasis (e.g., have neurologic symptoms related to brain metastases).

2. Prophylactic or preventive anti-epileptic therapy.
   ***Note*:** Anti-epileptic therapy indicated in order to prevent neurologic symptoms caused by a preexisting condition and not related to brain metastasis is allowed.

3. Known hypersensitivity or contraindication to any component of study treatment or their excipients.

4. Inability to swallow and retain study treatment.

5. Uveal or mucosal melanoma.

6. History of or current leptomeningeal metastases.

7. Treatment with SRS or craniotomy within 14 days prior to start of study treatment, or treatment with whole-brain radiation within 28 days prior to study treatment. Patients who received local therapy should have complete recovery with no neurological sequelae.

8. Either of the following:

    a. Radiation therapy to non-brain visceral metastasis within 2 weeks prior to start of study treatment;

    b. Continuous or intermittent small-molecule therapeutics or investigational agents within 5 half-lives of the agent (or within 4 weeks prior to start of study treatment, when half-life is unknown).

9. Patients treated in the adjuvant setting with BRAF or MEK inhibitor(s) < 6 months prior to enrollment. Patients who received BRAF or MEK inhibitors in the metastatic setting are excluded.

10. Is currently participating in a study and receiving an investigational agent; has received an investigational agent or used an investigational device within 14 days prior to start of study treatment.

11. Patients who have undergone major surgery (e.g., inpatient procedure with regional or general anesthesia) ≤ 6 weeks prior to start of study treatment. For minor surgical procedures ≤ 6 weeks prior to start of study treatment, consult the Sponsor Medical Monitor.

12. Patient has not recovered to ≤ Grade 1 from toxic effects of prior therapy before starting study treatment.
    ***Note*:** Stable chronic conditions (≤ Grade 2) that are not expected to resolve (such as neuropathy, myalgia, alopecia, prior therapy-related endocrinopathies) are exceptions and patients with these may enroll.

13. Impaired cardiovascular function or clinically significant cardiovascular disease including, but not limited to, the following:

    a. History of acute coronary syndromes (including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty or stenting) < 6 months prior to Screening;

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

    c. An 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 current therapy;

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

f. Triplicate average baseline QTcF interval ≥ 480 msec.

14. Impairment of gastrointestinal function or disease which may significantly alter the absorption of study treatment (e.g., active ulcerative disease; uncontrolled nausea, vomiting or diarrhea; malabsorption syndrome; small bowel resection).

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

16. Known history of acute or chronic pancreatitis.

17. 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.

18. Use of herbal supplements, medications or foods that are moderate or strong inhibitors or inducers of cytochrome P450 (CYP) 3A4/5 ≤ 1 week prior to the start of study treatment.

19. History of a thromboembolic event < 12 weeks prior to starting study treatment. Examples of thromboembolic events include transient ischemia attack, cerebrovascular accident, deep vein thrombosis or pulmonary embolism. Catheter-related venous thrombosis is not considered a thromboembolic event for this trial even if < 12 weeks prior to starting study treatment.

20. 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 ≤ 6 Gleason prostate cancer. Patients with a history of other curatively treated cancers must be reviewed by the Sponsor prior to entering the study.

21. Active infection requiring systemic therapy.

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

23. 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.

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

25. Other severe, acute or chronic medical or psychiatric condition 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.

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, preferably 7 days before first dose of study drugs, due to potential CYP3A4 interaction with encorafenib. Orange juice is allowed.

5.3.2. Activity

Strenuous physical activities, such as competitive sports, may result in significant increases in CK levels while on binimetinib treatment. Patients should be cautioned to avoid new strenuous exercise 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 or randomized into the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients 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 SAE.

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 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 is defined as any investigational drugs intended to be administered to a study patient according to the protocol.

6.1. Study Treatments Administered

In patients who receive the standard dose, encorafenib 450 mg will be administered PO QD in continuous 28-day cycles. Patients receiving the standard dose of encorafenib will be instructed to take encorafenib daily in the morning at approximately the same time every day. In patients who receive the high dose, encorafenib 300 mg will be administered PO BID in continuous 28-day cycles. Patients receiving the high dose of encorafenib will be instructed to take encorafenib 12 ± 2 hours apart in the morning and in the evening at approximately the same times every day. On clinic visit days, dosing times may need to be adjusted to accommodate predose study assessments.

Binimetinib 45 mg will be administered PO BID in continuous 28-day cycles. Patients will be instructed to take binimetinib 12 ± 2 hours apart in the morning and in the evening at approximately the same times every day. On clinic visit days, dosing times may need to be adjusted to accommodate predose study assessments.

Encorafenib and binimetinib should be taken together, if applicable, and without regard to food. Patients will be instructed to swallow the capsules/tablets whole with a large glass of water and not to chew or crush them. Detailed information regarding the study treatment can be found in Table 6.

- Encorafenib QD Dosing: Patients will be instructed to take encorafenib capsules daily with a large glass of water in the morning at approximately the same time every day. Doses of encorafenib that are omitted for AEs or any other reason can be taken up to 12 hours prior to the next dose.
- Encorafenib BID Dosing (high-dose arm): Patients will be instructed to take encorafenib capsules 12 ± 2 hours apart with a large glass of water in the morning and in the evening at approximately the same times every day. Doses of encorafenib that are omitted for AEs or any other reason should not be made up later in the day, or at the end of the dosing period.
- Binimetinib BID Dosing (standard-dose and high-dose arms): Patients will be instructed to take binimetinib tablets 12 ± 2 hours apart with a large glass of water in the morning and in the evening at approximately the same times every day. Doses of binimetinib that are omitted for AEs or any other reason should not be made up later in the day, or at the end of the dosing period.

Both study drugs (encorafenib and binimetinib) will be taken together in the morning. In the standard-dose treatment arm, only the BID administered drug (binimetinib) will be taken in the evening. In the high-dose treatment arm, encorafenib and binimetinib will be taken together in the evening. Dosing on days when PK blood draws are performed is described in Section 7.7.1.

If a patient vomits at any time after dosing, the dose of study drug should not be re-administered.

Patients will receive a diary to document self-administered dosing of encorafenib and binimetinib in each cycle to include the dose of study drug taken, the date of dosing, if any doses were missed and the reason for the missed dose. Patients will be instructed to return unused encorafenib and binimetinib and the patient diary to the site at the end of each cycle. Drug accountability must be performed on a regular basis.

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

Table 6. Study Treatments

Study Treatment Name	Encorafenib	Binimetinib
Type	Drug	Drug
Dose Formulation	Capsule	Tablet
Unit Dose Strength	75 mg	15 mg
Dosage Levels	450 mg QD (standard-dose arm) or 300 mg BID (high-dose arm)	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	ARRAY-438162 MEK162 ONO-7703

6.2. Preparation/Handling/Storage/Accountability

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received and any discrepancies are reported and resolved before use of the study drug.

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 drug. These records should include dates, quantities and any available batch or serial numbers or unique code numbers assigned to the study drug 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 drug 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 its designee, or for the 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 Pharmacy Manual.

6.3. Randomization

This is an open-label study; however, the study treatment to be taken by a patient will be assigned using an IWRS. The site will contact the IWRS to enroll a patient and receive study drug assignment. The site will also contact the IWRS to order additional study drug supplies and discontinue patients from study treatment. The site will record the treatment assignment on the applicable eCRF, if required. Full details will be provided in the IWRS or Study Manual.

If the high-dose treatment is determined to be safe in the Safety Lead-in, a patient randomization list will be produced by the IWRS provider using a validated system that automates the random assignment of patient numbers. A 1:1 randomization into both treatment arms will be initiated and will be stratified by baseline tumor burden and history of prior local therapy (Section 4.1).

If the high-dose treatment is determined not to be safe in the Safety Lead-in, no patients will be enrolled into the high-dose (Arm B), and patients will be enrolled at the standard-dose (Arm A) in 2 cohorts; patients who have received prior local therapy (e.g., SRS, SRT) for brain metastasis (Cohort 1) and patients who had no prior local therapy for brain metastasis (Cohort 2).

6.3.1. Patient Numbering

Each patient is identified in the study by a Patient Number (Patient No.) that is assigned when the patient is first enrolled for screening 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 screening informed consent form, the patient is assigned to the next sequential Patient No. available to the 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 re-screened. If the patient fails to be randomized 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. IWRS must be notified within 2 days that the patient was not randomized.

6.4. Study Treatment Compliance

Compliance with all study-related treatments will be emphasized to the patient by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Patient compliance with study treatment will be assessed at each visit. Compliance will be assessed by an accounting of returned study drug, patient interviews and a review of patient diary entries. Patients will be instructed to bring all study drugs with them to the study visits in order for site personnel to assess study drug accountability. Deviation(s) from the prescribed dosage regimen will be recorded in the eCRF.

In the case of overdosage of encorafenib or binimetinib, see Section 7.6. There is no known antidote for overdosage of encorafenib or binimetinib. Supportive care should be instituted.

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 treatment will also be recorded in the eCRF.

Any medication received within 28 days before the first dose of study treatment and within 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. Details of prior antineoplastic treatments including number of prior metastatic regimens will also be recorded. Unless specifically prohibited, concomitant medications may be administered at the Investigator's discretion to manage the patient's medical condition and to conform to standard practice during the Treatment Period.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the patient is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use.
- Dates of administration including start and end dates.

- Dosage information (using generic drug names when possible), including dose and frequency.

The Sponsor Medical Monitor 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 as being 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 (i.e., for the standard-dose treatment arm, 225 mg encorafenib QD, and for the high-dose treatment arm, 150 mg encorafenib BID). 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 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 the FDA website: Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers.

6.5.1.3. Drugs with a Known 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 specified 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).

- 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*:* Palliative radiation therapy to target lesions is prohibited. 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.

No therapies are prohibited during the post-treatment Follow-up Period.

6.6. High-dose Safety Assessment

After 9 evaluable patients in the Safety Lead-in have completed one 28-day cycle of treatment, safety assessments will be conducted. All toxicities will be assessed for severity by the Investigator using CTCAE v4.03. Evaluable patients for the Safety Lead-in cohort must have either:

- experienced a DLT (Table 7) or
- received at least 75% of the planned cumulative dose of both study drugs during Cycle 1.

The Sponsor and participating Investigators will perform ongoing reviews of patient safety data through regular teleconferences approximately weekly during the Safety Lead-in. Once 9 evaluable patients are available for assessment, the Sponsor will convene a joint teleconference with participating Investigators. If the high-dose treatment is found safe based on 9 evaluable patients, subsequent patients will be randomized 1:1 to receive either the standard or high-dose treatment. If the high-dose treatment is determined not to be safe, enrollment will proceed with the standard-dose treatment as outlined in Section 4.1. The high-dose treatment will be considered safe if the rate of DLTs (Table 7) observed in the first cycle of treatment in the Safety Lead-in is < 33%.

Table 7. Criteria for Defining Dose-limiting Toxicities

DLT Definition
A DLT is defined as any AE or laboratory abnormality that is not explained by underlying disease, disease progression, intercurrent illness, or concomitant therapies that either meets the criteria described below or results in the inability to tolerate at least 75% of the planned dose of binimetinib or encorafenib during Cycle 1.
Specific DLT Criteria
Cardiac disorders • Absolute decrease of LVEF > 10% compared to baseline and the LVEF is below the institution's LLN • LV systolic dysfunction Grade ≥ 3 • Other cardiac disorders Grade ≥ 3
Vascular disorders • Grade 3 hypertension for > 14 consecutive days • Grade 4 hypertension
Skin and subcutaneous tissue disorders[a] • Rash, hand foot skin reaction (HFSR) or photosensitivity CTCAE Grade 3 for > 14 consecutive days despite maximal skin toxicity treatment (as per local practice) • Rash, HFSR or photosensitivity CTCAE Grade 4
Gastrointestinal disorders[a] • Diarrhea Grade 3 for ≥ 48 hours despite optimal use of antidiarrheal therapy • Diarrhea Grade 4 • Nausea/vomiting Grade 3 for > 48 hours despite optimal use of antiemetic therapy
Investigations • Total bilirubin Grade ≥ 3 • AST or ALT Grade ≥ 3 in conjunction with total bilirubin Grade ≥ 2 of any duration • AST or ALT Grade 3 for > 7 consecutive days • AST or ALT Grade 4 • Serum creatinine Grade ≥ 3 • CK elevation ≥ Grade 3 associated with an increase in creatinine ≥ 1.5 × the patient's baseline screening creatinine • ANC Grade 4 for > 7 consecutive days • Platelet count Grade 3 with signs of clinically significant bleeding • Platelet count Grade 4 • ECG QTcF prolonged ≥ Grade 3[b]
Eye disorders – Retinal • Retinopathy or retinal detachment Grade ≥ 3, confirmed by ophthalmic examination • Retinal vascular disorder including RVO, confirmed by ophthalmic examination
Eye disorders – Visual disturbances without ocular (retinal) changes • Blurred vision, flashing lights, floaters: Grade ≥ 3
Eye disorders – Other (specify) • Grade ≥ 3 for > 21 consecutive days • Grade 4 confirmed by ophthalmic examination
Other hematologic and nonhematologic toxicities[c] • Any other Grade ≥ 3 AE except: a. Lymphocyte count decreased (lymphopenia) Grade ≥ 3 unless clinically significant
Renal dysfunction • Calculated GFR decrease of 50% from baseline • Proteinuria 24-hour urine protein > 2 g/24 hours

a. Prophylactic treatment for nausea/vomiting or skin AEs is not required with binimetinib. However, antiemetics and treatments for skin AEs should be used at the discretion of the Investigator if the patient experiences nausea/vomiting and/or skin AEs Grade ≥ 1.

b. QTcF must be prolonged on 2 separate ECGs.

c. Isolated laboratory changes (e.g., alkaline phosphatase, cholesterol, lipase, serum amylase) or those due to sampling or laboratory errors without associated clinical signs or symptoms may be determined to not be reviewable toxicities upon review and agreement by the Investigator and Sponsor Medical Monitor.

6.6.1. Management and Follow up of Reviewable Toxicities

Patients who experience a reviewable toxicity will receive appropriate treatment and supportive care as necessary and will be monitored closely until resolution of the toxicity to baseline or the event appears to have stabilized for a minimum of 2 weeks (14 days). During follow up, patients should be seen as often as medically indicated to assure safety.

6.6.2. Procedure for High-dose Safety Review

The Sponsor and Investigators will perform a safety review of the high-dose treatment arm after there are 9 evaluable patients in the Safety Lead-in. An evaluable patient is defined in Section 6.6. The Sponsor and participating Investigators will also perform an ongoing weekly review of safety data to assess tolerability and safety during the Safety Lead-in. A Steering Committee will be consulted throughout the study on topics including ongoing individual toxicities and AEs (Section 9.6.1).

Routine safety monitoring is described from Section 7.3 through Section 7.6.

6.7. Dose Modification

6.7.1. General Procedures for Dose Modification

Treatment with encorafenib and binimetinib may be delayed, allowing for 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. Patients should resume study treatment within 2 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The Investigator should contact the Sponsor Medical Monitor to discuss the case of any patient whose treatment has been delayed for more than 2 weeks (14 days) before restarting study treatment.

Instructions for dose modifications and interruptions are outlined in Appendix 2 (encorafenib) and Appendix 3 (binimetinib). Individual decisions regarding dose interruptions and modifications should be made using appropriate clinical judgment in consultation with the Sponsor Medical Monitor, 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 as clinically appropriate. Dose interruptions are permitted in the case of medical or surgical events or logistical reasons not related to study treatment (e.g., elective surgery, unrelated medical events, patient vacation, holidays). The reason for interruption will be documented in the patient's study record. All dose modifications are based on the worst preceding toxicity.

Doses of encorafenib and binimetinib may be independently delayed and reduced for toxicity management as outlined in Table 8. The Investigator should refer to and follow the labeled guidance (if applicable) 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 up to the starting dose level (450 mg encorafenib QD plus 45 mg binimetinib BID) 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.

- Patients who are receiving 600 mg encorafenib QD plus 45 mg binimetinib BID who require a dose reduction are not permitted to re-escalate (see Section 6.7.2).

Table 8. Dose Reductions for Encorafenib and Binimetinib

Level	Dose
Dose Reduction for Encorafenib in the High-dose Combination Arm	
0 (starting dose)	300 mg BID
-1	225 mg BID
-2	150 mg BID
-3	75 mg BID[a]
Dose Reduction for Encorafenib in the Standard-dose Combination Arm	
0 (starting dose)	450 mg QD
-1	300 mg QD
-2	225 mg QD[b]
Dose Reduction for Single-agent Encorafenib[c]	
-1	300 mg QD
-2	225 mg QD[b]
Dose Reduction for Binimetinib (both arms)	
0	45 mg BID
-1	30 mg BID[d]

Table 8. Dose Reductions for Encorafenib and Binimetinib

Level	Dose

NOTE: Dose reduction is based on the highest AE grade.

a. Dose reduction below 75 mg BID is not allowed.
b. Dose reduction below 225 QD is not allowed.
c. Single-agent encorafenib dose reduction applies to patients who have permanently discontinued binimetinib.
d. Dose reduction below 30 mg BID is not allowed.

If a patient misses > 28 consecutive days of dosing with combination treatment (both encorafenib and binimetinib), study treatment will be discontinued unless, in the opinion of the Investigator, the patient will derive clinical benefit from continued treatment. The Investigator will discuss this decision with the Sponsor Medical Monitor. If a patient permanently discontinues binimetinib (i.e., no dose for > 28 days), the patient may continue single-agent encorafenib if, in the opinion of the Investigator, the patient is deriving clinical benefit. Doses of single-agent encorafenib are decreased to a maximum of 300 mg QD when binimetinib is permanently discontinued.

If a patient permanently discontinues treatment with encorafenib, he or she must discontinue treatment with binimetinib.

6.7.2. Intra-Patient Dose Escalation of Encorafenib

During the Phase 2 part of the study, all patients will begin treatment with standard doses of encorafenib (450 mg QD) plus binimetinib (45 mg BID). Patients who are able to tolerate the standard dose of encorafenib (450 mg QD) plus binimetinib (45 mg BID) during the first 4 weeks of treatment (Cycle 1) should be dose-escalated to 600 mg encorafenib QD plus 45 mg binimetinib BID provided the following criteria are met:

- Must not have experienced a clinically meaningful treatment-related adverse event of CTCAE ≥ Grade 2 that based on investigator assessment prohibits escalation.
- Requires no dose reductions during the first 4 weeks (Cycle 1; guidelines for dose reductions are detailed in Appendix 2 for encorafenib and Appendix 3 for binimetinib). However, a single dose interruption of up to 4 days is permitted during Cycle 1. To ensure steady state exposures of encorafenib + binimetinib in patients undergoing intra-patient dose escalation, 7 days of consecutive dosing at the starting doses (450 mg QD encorafenib + 45 mg BID binimetinib) are required prior to the intra-patient escalation (600 mg QD encorafenib + 45 mg BID binimetinib). Therefore, intra-patient dose escalation should occur on Cycle 2 Day 1 (+ 7 days).

Investigators must confirm patients meet all criteria to qualify for dose escalation. Patients who cannot tolerate 600 mg QD encorafenib plus 45 mg BID binimetinib will be dose reduced to 450 mg QD encorafenib plus 45 mg BID binimetinib. Re-escalation up to 600 mg QD will not be permitted. Additional dose delays or reductions will be permitted for toxicity management as outlined in Table 8.

6.7.3. Renal Changes in Dose Modification

Encorafenib dose reduction will be considered when either of the following criteria are met:

- ACR increase from baseline > 50%.
- Baseline absolute serum creatinine value increases by ≥ 2 grades on more than 1 occasion. If this occurs, obtain a second serum creatinine measurement within 1 week.

If either of the above criteria are met, a 24-hour urine collection will be assessed for protein and creatinine and serum creatinine will be repeated.

All dosing with study treatment will pause if any of the following criteria are met:

- Calculated GFR decrease of ≥ 50% from baseline.
- Creatinine clearance decrease of ≥ 50% from baseline.
- 24-hour urine protein of > 2 g/24 hours.

If any of the criteria for pausing study treatment are met, the site is directed to obtain a renal consult and to discuss whether the patients should continue study treatment with the Sponsor Medical Monitor.

6.8. Criteria for Permanent Discontinuation of Study Treatment

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

Patients meeting any of the following criteria should discontinue study treatment:

- Withdrawal of consent/assent (no further participation and thus no further protected health information may be collected).
  Note: Patients may choose to discontinue study treatment and remain in the study to be followed for progression and survival. Patients who indicate they wish to withdraw consent should be carefully assessed regarding their intention with respect to further follow-up assessments on study. Consent withdrawn means that the patient has explicitly indicated that he or she no longer wants to be followed; 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 as defined as:
  - Grade 4 or life-threatening AE;
  - Toxicity requiring more than the allowed number of dose reductions for encorafenib and binimetinib as described in Table 8;

  - 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;
- Missing > 28 consecutive days of dosing with treatment, unless, in the opinion of the Investigator and in consultation with the Sponsor Medical Monitor, the patient will derive clinical benefit from continued treatment.
- Clinical progression, as determined by the Investigator in the absence of radiographic progression as defined by RECIST v1.1.
- Disease progression per both mRECIST v1.1 for brain metastasis and RECIST v1.1 for extracranial disease. If there is progression in either brain metastasis or extracranial disease (not both compartments), the patient may continue treatment if, in the opinion of the Investigator, the patient is deriving clinical benefit.
- Patient becomes pregnant or begins breastfeeding.
- Significant protocol deviation that, in the opinion of the Investigator or Sponsor, renders the patient unsuitable for further study treatment administration.
- Patient noncompliance with study procedures that, in the judgment of the Investigator or Sponsor, renders the patient unsuitable for further study participation.
- Lost to follow up.
- Death.
- Termination of the study by the Sponsor (described in Section 9.10).

Note that patients who discontinue study treatment may participate in treatment discontinuation assessments at the EOT visit, if applicable, as outlined in the SoA (Table 3). The date of the last dose of study treatment will be recorded in the eCRF. See the SoA for data to be collected at the time of treatment discontinuation and follow up.

Patients will have the option to stop receiving study treatment and continue in the Follow-up Period of the study for safety/efficacy assessments. If the patient discontinues study treatment and actively withdraws consent for collection of follow-up data (safety follow up and disease assessments), no additional data collection will occur.

6.9. Patient Discontinuation/Withdrawal from the Study

- A patient may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance or administrative reasons. This is expected to be uncommon.
- See the SoA (Table 3) for data to be collected at the time of study discontinuation and follow up and for any further evaluations that need to be completed.
- 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.

6.10. Intervention After the End of the Study

At the end of the study, access to study treatment will be provided, in accordance with applicable regulations and requirements, to all patients who are continuing to benefit from study treatment. Where required by local regulations, this protocol may be amended to allow patients to continue treatment, and reconsent of ongoing patients will be required.

The Sponsor will notify all applicable regulatory agencies in accordance with local requirements when the study has ended. In such cases, appropriate safety information will continue to be captured per protocol and submitted to the Sponsor. The information to be collected includes treatment-related AEs and SAEs, laboratory results of special interest, study treatment administration, patient status and date and reason(s) for study withdrawal.

6.11. Replacement of Patients

Patients may be replaced for any of the following reasons:

- During the Safety Lead-in, any patient who receives < 75% of the planned cumulative dose of either encorafenib or binimetinib during Cycle 1 for any reason other than a DLT (e.g., not evaluable for a DLT [Table 7]) may be replaced to ensure a minimum number of evaluable patients.
- Patients who do not meet the eligibility requirements of the study may be replaced.
- Patients for whom the *BRAF*V600 mutation status is not confirmed by central laboratory may be replaced. This includes either an Indeterminate or a No Mutation *BRAF*V600 Detected result.

6.12. 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 clinic 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 or not 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 be unreachable, he/she will be considered to have withdrawn from the study and lost to follow up.

6.13. Withdrawal Consent

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. 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.

7. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Table 3). Protocol waivers or exemptions are not allowed. Safety concerns should be discussed with the Sponsor Medical Monitor 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. Screening Procedures

Screening is the interval between signing the ICF and the day the patient is enrolled in the study (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 used 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 radiographic scans prior to enrollment of the patient, or the scans must be repeated at the investigational site and submitted.

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 enrollment will be used to determine eligibility.

See Section 5.4 and Section 6.11 for information regarding screen failures and replacement of patients, respectively.

7.1.1. Baseline Documentation of Intracranial Target and non-Target Lesions

All baseline lesion assessments must be performed 28 days prior to the first dose of study treatment. Refer to Appendix 5.

Note:

- Cystic lesions thought to represent cystic metastases should not be selected as target lesions when other suitable target lesions are available.
- **Measurable intracranial lesions that have been previously irradiated and have not been shown to be progressing following irradiation should not be considered as target lesions.**
- Prior excision of a single melanoma brain metastasis is allowed and may be selected as a target lesion provided there is regrowth in the cavity.

All other intracranial lesions should be identified as non-target and should also be recorded at baseline. Measurements of non-target lesions are not required, but the presence or absence of each should be noted throughout follow-up.

7.1.2. Baseline Documentation of Extracranial Target and non-Target Lesions

All baseline lesion assessments must be performed 28 days prior to the first dose of study treatment. Refer to Appendix 4.

Note: **Measurable extracranial lesions that have been previously irradiated and have not been shown to be progressing following irradiation should not be considered as target lesions.**

All other lesions (or sites of disease, excluding the brain) should be identified as non-target and should also be recorded at baseline. Non-target lesions will be grouped by organ. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

7.2. Efficacy Assessments

All data acquired for efficacy purposes (e.g., CT, MRI, X-ray, FDG-PET, pathology reports, caliper measurements and measurements of tumor markers) obtained at Screening and while on study, including off-schedule imaging studies, will be made available if requested by the Sponsor.

7.2.1. Radiological Tumor Evaluation

Appropriate radiological scans of all suspected sites of disease are performed until disease progression using the same method and technique throughout the study. Target lesions should demonstrate the patient's baseline tumor burden and should be selected based on their size (i.e., lesions with the longest diameter) and their suitability for accurate repeat assessment. See the SoA (Table 3) for the schedule of brain and extracranial assessments.

When possible, each center will have a designated radiologist responsible for the interpretation of scans and response evaluations for study patients. A single radiologist should perform all evaluations for an individual patient.

Assessments will be performed until disease progression, withdrawal of consent, initiation of subsequent anticancer therapy, patient is lost to follow up, death or defined end of study (Section 4.4).

The following will be performed:

- Screening and on treatment gadolinium-enhanced MRI of the brain.
- Screening and on treatment chest, abdomen and pelvis CT (or MRI) scans.
- An MRI of spine is required at screening only.
- Skeletal lesions identified at baseline will continue to be imaged at subsequent scheduled visits using localized CT, MRI or X-ray (using the same method used at baseline for all visits for any given lesion). After baseline, whole-body bone scans need not be repeated unless clinically indicated.
- Additional imaging evaluations may be performed at any time if there is symptomatic evidence suggesting the possibility of disease progression based on clinical symptoms or physical examination.

If off-schedule imaging evaluations are performed or if progression is suspected, every effort should be made to perform subsequent imaging evaluations in accordance with the original imaging schedule.

Extracranial lesions will be assessed using RECIST v1.1 (Eisenhauer et al, 2009, Appendix 4); brain metastasis will be assessed per mRECIST v1.1 (Appendix 5) and per RANO-BM in an exploratory analysis (Lin et al, 2015). All CT scans will be performed with IV contrast. If a patient is known to have a medical contraindication to the contrast agent or develops a contraindication during the study, a CT scan without IV contrast of the chest and MRI with IV contrast, if possible, of the abdomen and pelvis may be performed. Chest X-ray or ultrasound will not be used for tumor response assessments in this study.

Any extracranial lesions that have been subjected to loco-regional therapies (e.g., radiotherapy, ablation, etc.) will not be considered measurable unless they have clearly progressed since the therapy. Previously treated lesions that have not progressed will be considered non-measurable and assessed as non-target lesions.

While FDG-PET scans are not required for this study, sites may perform extracranial imaging by PET-CT 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 standards, FDG-PET may be used to document PD in accordance with RECIST v1.1.

The initial Screening imaging should be performed within 28 days of the first dose of study treatment. Post-Screening assessments will be performed as described in the SoA (Table 3) (± 7 days). **Imaging will not be delayed for delays in cycle start.** Every effort must be made to assess each lesion that is measured at Screening by the same method throughout the study to enable consistent comparison.

Confirmation of brain, extracranial and global CR and PR is required. Confirmation assessments must be performed no less than 4 weeks after the criteria for response have initially been met and may be performed at the next scheduled assessment. If a confirmation assessment is performed prior to the next scheduled assessment, the next scheduled evaluation is still required (i.e., regularly scheduled study visit evaluations must occur at each scheduled time point regardless of unscheduled assessments). Partial response can be confirmed at an assessment later than the next assessment after the initial documentation of PR. If the criteria for a CR or PR are not confirmed, then SD can be considered the best response if it has been demonstrated for a minimum of 6 weeks.

7.2.2. Imaging Assessments for RECIST v1.1 and mRECIST v1.1

Details of response assessments are described in Appendix 4, Appendix 5 and Appendix 6.

Brain lesions will be assessed by mRECIST v1.1 criteria. Modification of RECIST v1.1 allows up to 5 intracranial target lesions of 5 to 40 mm in diameter and includes target lesions measuring 5 to 10 mm in their longest diameter. Brain lesions will be measured only by gadolinium-enhanced MRI, with a scan-slice thickness of 1 mm for metastases with a longest diameter of 5 to 10 mm.

7.2.3. Blinded Independent Central Review

All radiological assessments obtained for patients will be centrally collected by an imaging vendor designated by the Sponsor and may be assessed centrally by a BICR in addition to the local (Investigator) assessment if deemed necessary.

7.2.4. Post-treatment Follow up

All AEs suspected to be related to study treatment should be followed up weekly, or as clinically indicated, until resolution or stabilization. In addition, dermatologic screening for skin malignancies should be performed every 2 months until 6 months after the last dose of encorafenib.

7.2.4.1. 30-Day Safety Follow Up

All patients will return for a 30-Day Safety Follow-up Visit 30 ± 7 days after the last dose of study drug, or prior to starting subsequent anticancer therapy, whichever occurs first. Information related to AEs (including concomitant medication taken for ongoing AEs) and ongoing antineoplastic treatments will be collected for 30 days after the last dose of study drug.

7.2.4.2. 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. Every effort should be made to collect information regarding disease status until:

- The start of new anticancer therapy.
- Disease progression.
- Death.
- The end of study.

7.2.4.3. 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 to undergo the following assessments 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:

- Record new SAEs that are considered related to study drug.
- Record all subsequent anticancer therapies.
- Determine survival status.

7.2.5. Performance Status

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

Table 9. Performance Status Scoring

Karnofsky Status	Karnofsky Grade	ECOG Grade	ECOG Performance Status
Normal, no complaints	100	0	Fully active, able to carry on all pre-disease performance without restriction
Able to carry on normal activities. Minor signs or symptoms of disease	90	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
Normal activity with effort	80	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
Care for self. Unable to carry on normal activity or to do active work	70	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
Requires occasional assistance, but able to care for most of his needs.	60	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

Table 9. Performance Status Scoring

Karnofsky Status	Karnofsky Grade	ECOG Grade	ECOG Performance Status
Requires considerable assistance and frequent medical care	50	3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
Disabled. Requires special care and assistance	40	3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
Severely disabled. Hospitalization indicated though death non-imminent	30	4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
Very sick. Hospitalization necessary. Active supportive treatment necessary	20	4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
Moribund	10	4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
Dead	0	5	Dead

7.2.6. *BRAF* Testing

Patients will be eligible for the study based on identification of a *BRAF*V600 mutation in tumor tissue as determined by a local laboratory PCR or NGS-based assay. Patients must have written documentation from a previous local laboratory pathology report of a *BRAF*V600 mutation.

The investigator must confirm prior to enrollment that the patient has adequate tumor tissue available to determine *BRAF*V600 mutation status by a central laboratory. All patients are required to submit either an archived tumor tissue sample or a newly obtained core or excisional biopsy (fine needle aspiration is not adequate for either archival or new tissue samples).

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 testing. A minimum of 8-15 unstained slides or 1 block of tissue should be submitted to the central laboratory. Further details regarding sample submission including instructions for sample processing and shipping will be provided in the Laboratory Manual. If a biopsy is taken, the biopsy should be taken from a non-target lesion. If the patient is enrolled based on local assay results, the *BRAF* mutation status must be evaluated by a central laboratory no later than 30 days from first dose of study treatment.

In cases where there is discordance between the local assay and central laboratory results, or if a central laboratory is not able to confirm presence of a *BRAF*V600 due to inadequate or poor sample condition within 30 days of initiating study therapy, patients may only continue treatment if there is no clinical indication of deterioration or disease progression and the Investigator determines that the patient is deriving clinical benefit. In such instances, patients

must be informed that the *BRAF* mutation status is unconfirmed and must sign a separate ICF. Patients with discordant local and central results will be replaced.

Central laboratory *BRAF* mutation tests with a definitive result (positive or negative) may not be repeated to resolve a discordant result unless a biopsy sample from a different tumor lesion can be provided. Patients whose sample is determined inadequate or who have an indeterminate result on central testing may have samples resubmitted for testing.

7.3. Safety Assessments

The Sponsor Medical Monitor, or designee, and the Sponsor's Drug Safety and Pharmacovigilance Department will be responsible for the ongoing review and evaluation of safety data, including AEs, laboratory data and any other safety evaluations, throughout the duration of the study.

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, medical, surgical and social history will be collected at Screening.

7.3.2. Disease Characteristics and Treatment History

A history of present illness (disease-specific medical history) will be collected at Screening. Details regarding the patient's malignancy under study, including date of diagnosis, cancer stage at diagnosis, tumor histology and prior treatments 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 will 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 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, the physical examinations will 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 Table 3. In addition, dermatologic screening for skin malignancies will be performed every 8 weeks until 6 months after the last dose of encorafenib.

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 should be performed by a dermatologist as clinically indicated.

7.3.5. Vital Signs

Vital sign measurements (to be taken before 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 and pulse measurements will be assessed with a completely automated device. 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 for the patient in a quiet setting without distractions (e.g., television, cell phones).

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 treatment.

7.3.6. Electrocardiograms

A triplicate ECG (3 serial ECGs conducted within approximately 5 to 10 minutes total time) will be performed at Screening to determine eligibility and predose on Cycle 1 Day 1 to serve as baseline. A single ECG will be performed at all remaining time points specified in the SoA (Table 3). A detailed description of the timing of ECGs is provided 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. The ECG measurement at any time point will be used for AE grading and recommended dose modifications.

Interpretation of the tracing will be made by a qualified physician and documented in the eCRF. QT interval values will be corrected using the QTcF formula. Clinically significant abnormalities present when the patient signed the screening informed consent/assent will be reported in the eCRF. New or worsened clinically significant findings occurring after the screening informed consent/assent must be recorded 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 for central assessment by an independent reviewer.

Table 10. Timing of ECGs

Visit	Any Time	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
Subsequent Cycles Day 1		X	X
EOT	X		

7.3.7. Clinical Safety 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 certified laboratory local to the investigative site will be used for all clinical laboratory assessments for safety (i.e., blood chemistries, hematology, coagulation, serology, renal function, urinalysis), in accordance with the SoA (Table 3). The investigative site will enter the laboratory results into the eCRF. PK CCI [redacted] assessments will be sent to a central laboratory in accordance with the SoA and 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. Additional testing may be required by the Sponsor based on emerging safety data. Additional tests may also be performed if clinically indicated.

Screening laboratory assessments must be performed within 28 days of Cycle 1 Day 1. If performed more than 28 days before Cycle 1 Day 1, then the tests must be repeated, and eligibility confirmed, before study treatment administration on Cycle 1 Day 1. Laboratory assessments collected on Cycle 1 Day 1 must be performed before study treatment administration. After Cycle 1, predose laboratory procedures can be conducted up to 72 hours before study treatment administration (within a 3-day study window), and results will be reviewed by the Investigator or qualified designee and found to be acceptable before study treatment is administered.

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 significantly abnormal during participation in the study or within 30 days after the last dose of study intervention

should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator.

Electrolyte abnormalities including magnesium should be corrected and cardiac risk factors for QT prolongation (e.g., congestive heart failure, bradyarrhythmias) should be controlled.

Table 11. Summary of Clinical Laboratory Tests

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

7.3.8. Pregnancy Testing

A serum pregnancy test will be required for all women of childbearing potential (see Appendix 1) as outlined in the SoA (Table 3). Urine pregnancy tests will be performed locally as outlined in the SoA, 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 investigational sites

under separate cover). All blood and urine collections for pregnancy tests occurring on dosing days must be performed prior to study drug administration, with a negative test result required prior to administration of study treatment.

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. Any female patient who becomes pregnant while participating in the study will be instructed to immediately discontinue study treatment. If pregnancy is confirmed by a serum pregnancy test, see Section 7.4.5.1 for reporting requirements.

Patients of nonchildbearing potential (see Appendix 1) do not require pregnancy tests.

7.3.9. Renal Function Monitoring

Renal function monitoring will be conducted to assess for renal dysfunction at the time points specified in SoA (Table 3).

See Section 6.7.3 for renal-function-related criteria for modifying or pausing dosing.

7.3.10. Serology

Hepatitis screening assessments will be performed at a local laboratory at the Screening visit to rule out hepatitis infection; required analytes are shown in Table 11. Generally, hepatitis tests will be performed early in the screening process due to the length of time needed to obtain the results. Additional tests may be performed if clinically indicated.

7.3.11. 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 congestive heart failure at any point during the study are required to have an evaluation of LVEF measurements by ECHO or MUGA.

7.3.12. Ophthalmic Examination

7.3.12.1. Testing at Screening and During the Treatment Period

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 OCT. Examination of the retina is required (especially to identify findings associated with RPED, serous detachment of the retina and RVO). Ophthalmic evaluation may be performed again during the treatment period as clinically indicated.

7.3.12.2. Additional 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: OCT (spectral domain OCT recommended)
- For vascular abnormalities: fluorescein angiography of the central 30 degrees

Images/results of the ophthalmic examinations (at a minimum, OCT 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.

7.4. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 7.

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.

The patient 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.

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

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.

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.

7.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a patient during the active collection period as described in Section 7.4.1. 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 7.4. 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.

7.4.1.2. 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 9.4, 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.

7.4.2. Methods 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 7.

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.

7.4.3. 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.

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 7.3.

7.4.4. 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 (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator Brochure for the study and will notify the IRB/EC, if appropriate according to local requirements.

7.4.5. 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.

7.4.5.1. 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 30 days after 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 [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), 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 follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up 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.

7.4.5.2. 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 (e.g., 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.

7.4.5.3. 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.

7.4.6. Cardiovascular and Death Events

All cardiovascular events will be managed per the dose modification guidelines in Appendix 2 and Appendix 3. Additionally, cardiovascular events will be reported per AE and SAE reporting guidelines and ECG criteria, as detailed in Section 7.4 and Section 7.3.6, respectively. AEs and SAEs that result in death will be reported per the reporting guidelines as outlined in Section 7.4.

7.4.7. Disease-Related event and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable

7.4.8. Adverse Events of Special Interest

See Section 2.2.3 Clinical Safety of Combination Encorafenib and Binimetinib for descriptions of AESIs.

7.4.8.1. Lack of Efficacy

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

7.4.9. Medical Device Deficiencies

Not applicable

7.4.10. 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.**

7.5. Product Complaints

The Sponsor collects product complaints on study drugs/treatments used in clinical studies 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 within 1 business day of discovery. Any AE associated with a product complaint should be recorded as described in Section 7.4.4 and Section 7.4.5.

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.

7.6. 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. Pharmacokinetic Assessments

7.7.1. Blood Sample Collection

Blood samples (~4 mL each) for plasma PK analysis of encorafenib, its metabolite (LHY746), binimetinib and the active metabolite of binimetinib (AR00426032) will be collected from all patients enrolled in the Safety Lead-in portion of the study as shown in Table 12. If the high-dose regimen is determined to be safe and patients are randomized to the high-dose and standard-dose treatments in the Phase 2 portion of the study, PK samples will also be collected from all Phase 2 patients as shown in Table 12. However, if the high-dose regimen is determined not to be safe in the Safety Lead-in, PK samples will be collected from all Phase 2 patients as shown in Table 13 using a reduced sampling schedule.

In addition to PK samples stated above, blood samples for PK may be requested for patients experiencing unexpected or serious adverse events; with evidence of disease progression; or with other events where PK sampling is considered useful (upon agreement between investigator and Sponsor). More than 1 PK sample per patient may be collected throughout the study; however, the total blood volume of additional PK samples collected per patient should not exceed 20 mL (ie, no more than 5, 4 mL samples).

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 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 encorafenib and binimetinib (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 drug administration on the day of PK sampling, no additional study treatment will be taken to replace the material that has been vomited and it is recommended that no more PK samples be taken after the emesis occurs. Vomiting that occurs on Cycle 1 Day 1 and Day 15 will be noted in the PK eCRF. Further

doses should be administered with premedication with antiemetic medications. Cycle 1 Day 15 PK sampling that was compromised due to emesis will be repeated on Cycle 2 Day 1 after premedication with antiemetics.

Blood will be collected in accordance with institutional guidelines. Any sampling problems will be noted in the eCRF and on appropriate source documentation. Complete instructions for sample processing, handling and shipment will be provided in the Laboratory Manual.

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Table 12. Pharmacokinetic Blood Sample Timing in the Safety Lead-in Portion and in the Phase 2 Portion When the High Dose Regimen is Tested

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

Table 13. Pharmacokinetic Blood Sample Timing in the Phase 2 Portion When Only the Standard Dose Regimen is Tested

Study Visit	Timing of Sample
Cycle 1 Day 1	• 1.5 hours (± 15 min) postdose
Cycle 2 Day 1[1]	• Predose (within 30 minutes of dose) • 1.5 hours (± 15 min) postdose
Cycle 3 Day 1	• Predose (within 30 minutes of dose) • 1.5 hours (± 15 min) postdose

1 Seven days of consecutive dosing at the starting doses (450 mg QD encorafenib + 45 mg BID binimetinib) are required prior to the intra-patient escalation (600 mg QD encorafenib + 45 mg BID binimetinib) and the escalation must start within 7 days of Cycle 2 Day 1 (see Section 6.7.2.). If the escalation occurs after Cycle 2 Day 1 the Cycle 2 Day 1 PK samples must be taken on the same day as the patient dose escalates.

7.8. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

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7.10. Patient-reported Outcomes

Patient-reported outcomes are not evaluated in this study.

7.11. Unscheduled Visits

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

7.12. End of Treatment and/or Early Termination

When the patient permanently discontinues study treatment, whether the patient is terminating the study early or the patient has completed the study, the EOT evaluations must 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. The patient should be encouraged to return for the 30-Day Follow-up Visit.

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 BMRR per mRECIST v1.1. The study is designed to test the null hypothesis of BMRR $\leq$ 30%, which is considered not clinically meaningful and insufficient to warrant further study. The alternative hypothesis is the true BMRR for this patient population is at least 50%. This hypothesis applies to both the high-dose treatment arm and the standard dose treatment arm and will be tested using an exact binomial test at a one-sided 5% significance level.

8.2. Sample Size Determination

Safety Lead-in

During the Safety Lead-in, the first 9 evaluable patients will be enrolled to receive the high-dose encorafenib + binimetinib combination therapy. The high-dose treatment will be considered tolerable if the observed Cycle 1 DLT rate is < 33% (i.e., < 3 patients with DLTs out of 9 patients). Table 14 provides a comparison of the characteristics for this dose-escalation rule with 9 patients and the traditional 3 + 3 rules.

Table 14. Characteristics of Safety Lead-in Criteria for Cycle 1 Dose-limiting Toxicity Rate

True Cycle 1 DLT Rate	Probability of Dose Declared Toxic Using 3 + 3 Rules	Probability of Observed Cycle 1 DLT Rate ≥ 33% in 9 Patients
10%	0.094	0.053
20%	0.291	0.262
30%	0.506	0.537
40%	0.691	0.768
50%	0.828	0.910

If the Sponsor and Investigators determine that the high-dose treatment is safe in the 9 evaluable patients, randomization will start for the Phase 2 portion of the study. Otherwise, no patients will be enrolled into the high-dose treatment Arm in Phase 2.

Phase 2

The sample size calculation of Phase 2 portion of the study is based on the primary endpoint of BMRR per mRECIST v1.1. The hypothesis to be tested and details of testing strategy are described in Section 8.1.

If the high-dose treatment is determined to be safe in the Safety Lead-in phase, approximately 100 eligible patients will be randomized in a 1:1 ratio, stratified by baseline tumor burden in the brain (1 to 2 brain lesions vs. ≥ 3 brain lesions at baseline assessment) and by prior local therapy (yes vs. no) to the standard-dose and the high-dose treatment arm (i.e., approximately 50 patients per treatment arm). No formal statistical comparison will be performed between the 2 treatment arms and the statistical analysis will be performed separately by treatment arm.

If the high-dose treatment is determined not to be safe in the Safety Lead-in phase, no patients will be enrolled into the high-dose treatment arm. Up to 100 eligible patients will be enrolled into 2 cohorts in the standard-dose treatment arm. Phase 2 enrollment will close when either Cohort 1 or 2 reaches the enrollment of 50 patients.

- **Cohort 1:** Patients with locally confirmed *BRAF*V600 cutaneous melanoma with metastases to the brain confirmed by MRI, asymptomatic, and *with* prior local therapy (e.g., SRS or SRT).
- **Cohort 2:** Patients with locally confirmed *BRAF*V600 cutaneous melanoma with metastases to the brain confirmed by MRI, asymptomatic, *without* prior local therapy (e.g., SRS or SRT).

No formal statistical comparison will be conducted between the 2 cohorts.

Assuming a true BMRR ≥ 50%, the null hypothesis of BMRR ≤ 30% will be rejected if at least 21 brain metastasis responses per mRECIST v1.1 are observed in a cohort of 50 patients. With approximately 50 eligible patients, the study will provide approximately 90% power at a one-sided 5% significance level.

8.3. Analyses Sets

For purposes of analysis, the following analysis sets are defined in Table 15:

Table 15. Populations for Analysis

Population	Description
Screened	All patients who sign the ICF.
Dose-determining Set	The Dose-determining Set includes all patients enrolled in the high-dose treatment arm in the Safety Lead-in portion of the study who complete one 28-day cycle of treatment and receive at least 75% of the planned cumulative dose of both study drugs or discontinue treatment because of DLT.
Full Analysis Set	If the high-dose treatment is determined to be safe in the Safety Lead-in: The FAS includes all patients randomized during the Phase 2 portion of the study. According to the intention-to-treat principle, patients will be analyzed according to the treatment they have been assigned during randomization. If the high-dose treatment is determined not to be safe in the Safety Lead-in: The FAS includes all patients who receive at least 1 dose of any study drug in the Phase 2 portion of the study.
Efficacy Set	The Efficacy Set includes all FAS patients who receive at least 1 dose of any study drug in the Phase 2 portion of the study and have their *BRAFV*600 mutation status confirmed by central laboratory. Unless otherwise specified, the Efficacy Set will be the default analysis set used for all efficacy analyses.
Safety Set	The Safety Set includes all patients who receive at least 1 dose of any study drug. Unless otherwise specified, the Safety Set will be the default analysis set used for all safety analyses.
PK Set	The PKS includes all patients who receive at least 1 dose of any study drug and have at least 1 PK blood collection after the first dose of study drug with associated bioanalytical results. The PKS will be used for summaries and listings of PK data.
CCI [redacted]	[redacted]

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.

For Phase 2 portion of the study, separate summaries will be generated for Cohort 1 and Cohort 2. Patients in a cohort escalating to 600 mg encorafenib QD may also be summarized separately.

8.4.1. Primary Analyses

Safety Lead-in

The number and proportion of patients in the Dose-determining Set experiencing DLTs during the first treatment cycle in the Safety Lead-in will be summarized. Safety and exposure data will be summarized as described in the SAP.

Phase 2

The primary endpoint in the Phase 2 portion of the study is BMRR per mRECIST v1.1. It is defined as the proportion of patients who have achieved a best overall brain metastasis response of CR or PR according to mRECIST v1.1 per Investigator assessment. Details of best overall brain metastasis response are specified in Appendix 5.

Both confirmed and unconfirmed BMRR will be summarized, but the primary analysis will be based on confirmed responses.

The primary analysis will take place after all patients in the Efficacy Set have had the opportunity for at least 2 post-baseline tumor assessments, and after all patients with an initial response have had an opportunity to be followed up for at least 6 months.

The BMRR will be calculated with an exact two-sided 90% CI. In addition, the exact two-sided 95% CI of BMRR will also be calculated.

8.4.2. Secondary Analyses

The secondary efficacy endpoints are listed in Table 4.

8.4.2.1. Extracranial Response Rate

Extracranial response rate is defined as the proportion of patients with a best overall extracranial response of CR or PR according to RECIST v1.1 per Investigator assessment.

Extracranial response rate will be calculated with an exact two-sided 95% CI.

8.4.2.2. Global Response Rate

Global response rate is defined as the proportion of patients with a best overall response of CR or PR per Investigator assessment for brain metastasis and extracranial lesions according to mRECIST v1.1 and RECIST v1.1, respectively. Details of best overall response are specified in Appendix 6.

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

8.4.2.3. Disease Control Rate

Disease control rate is defined as the proportion of patients with a best overall response of CR, PR or SD per Investigator assessment.

DCR will be calculated for brain metastasis, extracranial and global response along with exact two-sided 95% CIs, respectively.

8.4.2.4. Duration of Response

Duration of response is defined as the time from the date of the first documented response to the first documented disease progression or death due to any cause, whichever occurs first. 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 is censored at the date of last adequate tumor assessment. DOR will be calculated for patients who achieve a confirmed response (i.e., CR or PR) for brain metastasis, extracranial and global response, respectively.

The survival distribution function for DOR will be estimated using the Kaplan-Meier method. In addition, the proportion of patients with a confirmed response for a duration of at least 6 months among all patients in the Efficacy Set will also be summarized.

8.4.2.5. Progression-free Survival

Progression-free survival is defined as the time from the date of first dose of study drug to the time of the first documented progression or death, whichever occurs first. 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.

8.4.2.6. 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.

8.4.2.7. Brain Metastasis Response Rate for Safety Lead-in

Brain metastasis response rate per mRECIST v1.1 will also be calculated for Dose-determining Set patients in the Safety Lead-in portion of the study. An exact two-sided 95% CI of BMRR will be reported.

8.4.3. Safety Analyses

Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate. Adverse events will be coded using the MedDRA®. Incidence tables will be presented for all AEs by maximum severity, SAEs, AEs assessed as related to study drug and AEs resulting in discontinuation of study drug. Listings of all safety data by treatment arm, patient and assessment date will be provided.

Clinical laboratory data will be analyzed using summary statistics. In addition, distributions of key laboratory parameters may be plotted over time; these values will also be classified into CTCAE toxicity grades and tabulated.

Summaries of clinically notable vital sign measurements will be provided. Definitions of “clinically notable” will be provided in the SAP.

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

8.4.4. Pharmacokinetic Analysis

Plasma concentrations of encorafenib and its metabolite (LHY746) and binimetinib and its metabolite (AR00426032) will be determined using validated bioanalytical methods. Plasma concentration-time profiles for binimetinib, AR00426032, encorafenib and LHY746 will be generated as appropriate. Descriptive summaries for encorafenib, LHY746, binimetinib and AR00426032 concentrations will be presented by dose and treatment arm, as appropriate.

PK parameters will be determined for all PK-evaluable patients using noncompartmental method(s). The PK parameters including, but not limited to the following will be estimated and reported, when feasible and appropriate.

- C_{max}
- C_{min}
- C_{trough}
- T_{last}
- T_{max}
- AUC_{last}
- R_{AUC}

Dose-normalized parameters will also be calculated as appropriate for C_{max}, C_{trough}, and AUC_{last}. Dose-normalized AUC_{last} values as well as R_{AUC} values for the standard- and high-dose treatment arms may be compared if data permit. A separate population PK analysis with exposure-response analyses, if appropriate, will be conducted. The analysis may include the pooled data from other clinical studies with encorafenib and/or binimetinib. Details of the analyses will be included in a PK analysis plan and results will be reported separately from the main CSR.

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8.5. Interim Analyses

No formal interim analysis is planned for this study.

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, Investigator Brochure and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated. Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study 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) and the Sponsor (and designee[s]) 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 its 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 its designee must be contacted to arrange alternative record storage options (if applicable).

All eCRF data entered by the site (including audit trail), 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 trail.

9.3. Financial Disclosure

Before study initiation, all clinical Investigators are required to abide by FDA Regulation Title 21 CFR 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 its designee. The Sponsor or its designee must review and acknowledge the site-specific changes to the ICF template. The ICF must include a statement that the Sponsor or its 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 was 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. 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 will be obliterated on the copy of the document to be supplied to the Sponsor or its designee. Study findings 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 its designee must adhere to applicable data privacy laws and regulations. The Investigator and the Sponsor or its 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. Steering Committee

A Steering Committee comprised of study Investigators and Sponsor representatives will be created. The Sponsor will consult with the Steering Committee about study design, eligibility criteria, quality, ongoing individual toxicities and AEs and writing study publications.

Section 7.3 describes ongoing safety monitoring for this study. No Data Monitoring Committee will be formed, as this study evaluates 2 agents with a well characterized safety

profile in combination. (Section 2.2.3 describes 2 recommended Phase 2 doses of encorafenib, one of which is 600 mg QD.) The study does not recruit vulnerable patients such as children, pregnant women or the incarcerated. It is an open-label study that will undergo continuous data review and on-site monitoring.

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 the 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. To allow the use of the information derived from this clinical study, the Investigator understands that he/she has an obligation to provide complete test results and all data obtained during this study to the Sponsor. 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 its 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 an 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 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 intervention development.

9.11. Publication Policy

The conditions regulating dissemination of the information derived from this study are described in the Clinical Trial Agreement.

10. REFERENCES

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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 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 treatment. Males who have had a vasectomy 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. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, if patients have less than 12 months of amenorrhea, confirmation of menopause requires more than one FSH measurement.

- 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 studies guidance document (Clinical Trial 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.

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 study 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.
- Vasectomized 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.

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.
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. 1. If resolved to Grade ≤ 1 in ≤ 21 days, resume treatment at 1 reduced dose level of encorafenib and binimetinib. 2. 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: • 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.
QTcF > 500 ms and > 60 ms increase from baseline	Permanently discontinue.

Severity of Adverse Event	Dose Modifications
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 Hand-foot Skin Reactions)	
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.
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. 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

Severity of Adverse Event	Dose Modifications
	level or 1 reduced dose level based upon the Investigator's discretion.
Grade 3	1st or additional 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. 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).
Grade 4	Permanently discontinue encorafenib and binimetinib.
Other Adverse Reactions (including renal, haemorrhage). Additional renal guidance is provided in Section 7.3.9.	
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.

Severity of Adverse Event	Dose Modifications
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.
Recurrent Grade 3	Consider permanently discontinuing.
Recurrent Grade 4	Permanently discontinue.

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

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.
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.

Severity of Adverse Event	Dose Modifications
	• 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.
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.
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.
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.

Severity of Adverse Event	Dose Modifications
	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).
Grade 4	Permanently discontinue encorafenib and binimetinib.
Other Adverse Reactions (including haemorrhage)	
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.
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.
Recurrent Grade 3	Consider permanently discontinuing.
Recurrent Grade 4	Permanently discontinue.

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

Appendix 4. Response Evaluation Criteria in Solid Tumours (RECIST), Version 1.1

This scale is used for the assessment of extracranial response.

Measurability of Tumour at Baseline

Definitions

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

Measurable

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

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm);
- 10 mm caliper measurement by clinical examination (lesions which cannot be accurately measured with calipers should be recorded as non-measurable);
- 20 mm by chest X-ray.

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

Non-Measurable

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

Special Considerations Regarding Lesion Measurability

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

Bone lesions:

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

or MRI can be considered measurable lesions if the *soft-tissue component* meets the definition of measurability described above.

- Blastic bone lesions are non-measurable.

Cystic lesions:

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

Lesions with prior local treatment:

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

Specifications by Methods of Measurements

Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Method of Assessment

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

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

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

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

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

Endoscopy, laparoscopy: The utilization of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials were recurrence following complete response or surgical resection is an endpoint.

Tumour markers: Tumour markers *alone* cannot be used to assess *objective* tumour response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumour markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis.

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

Tumour Response Evaluation

Assessment of Overall Tumour Burden and Measurable Disease

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

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

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

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

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

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumour. As previously noted, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the *short* axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumour. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm X 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

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

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

Response Criteria

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

Evaluation of Target Lesions

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

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

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

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

Special Notes on the Assessment of Target Lesions

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

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

Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have

truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of Non-target Lesion

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

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

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

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

Special Notes on Assessment of Progression of Non-target Disease

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

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

When the patient has only non-measurable disease. This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as previously noted, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified, a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumour burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

New Lesions

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

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

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

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

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

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

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

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

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

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear

if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomised trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'.

Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs. Table A1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

Table A1: Time Point Response: Patients With Target (± Non-target) Disease

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

When patients have non-measurable (therefore non-target) disease only, Table A2 is to be used.

Table A2: Time Point Response: Patients With Non-target Disease Only

Non-target Lesions	New Lesions	Overall Response
CR	No	**CR**
Non-CR/non-PD	No	**Non-CR/non-PD**[a]
Not all evaluated	No	**NE**
Unequivocal PD	Yes or No	**PD**
Any	Yes	**PD**

a. 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Missing Assessments and Inevaluable Designation

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

Best Overall Response: All Time Points

The *best overall response* is determined once all the data for the patient is known.

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

Special Notes on Response Assessment

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

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

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

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

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

Appendix 5. Modified Response Evaluation Criteria in Solid Tumors (mRECIST), Version 1.1

This scale is used for the assessment of brain lesion response.

Modifications to RECIST v1.1 for Assessment of Brain Lesions

The modifications to RECIST v1.1 impact the number and the minimal size of the target brain lesions selected at baseline. Up to 5 lesions may be selected as target lesions; all brain lesions beyond these 5 target lesions will be regarded as nontarget lesions. Measurable lesions are defined as those that can be accurately measured in at least 1 dimension with the longest diameter ≥ 5 mm when evaluated with gadolinium-enhanced MRI.

Gadolinium-enhanced MRI is the only imaging modality accepted for the assessment of brain lesions.

- The technical specification of the MRI scanning sequence will be optimized for the evaluation of brain lesions, which must be measured in the same anatomic plane using the same imaging examinations. Whenever possible the same scanner should be used (Eisenhauer et al, 2009).
- As a modification to RECIST v1.1, target lesions as small as 5 mm may be selected, however the scanning should follow RECIST v1.1: contiguous slices of maximum thickness corresponding to half the size of the lesion. All measurements must be taken and recorded in millimeters (mm) using a ruler or calipers.
- Image Acquisition guidelines provide the slice thickness requirements that should be used following RECIST v1.1 criteria.

Evaluation of Target Brain Lesions

Definitions for assessment of target brain lesion(s) are as follows:

Complete Response (CR): Disappearance of all target lesions.

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

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum of diameters* recorded since the treatment started (e.g., percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase of at least 5 mm.

Not Evaluable (NE): Cannot be classified by 1 of the 4 preceding definitions.

Special Notes on the Assessment of Target Brain Lesions

If a target brain lesion disappears and reappears at a subsequent time point it should continue to be measured. The response at the time when the lesion reappears will depend upon the status of other lesions. For example, if the disease had reached a CR status then PD would be documented at the time of reappearance. However, if the response status were PR or SD, the diameter of the reappearing lesion should be added to the remaining diameters and response determined based on percent change from baseline and percent change from nadir.

Evaluation of Non-target Brain Lesions

Definitions for assessment of non-target brain lesion(s) are as follows:

Complete Response (CR): Disappearance of all non-target lesions.

Non-CR/Non-PD: The persistence of 1 or more non-target lesion(s) identified as a site of disease.

Progressive Disease (PD): Unequivocal progression of existing non-target lesions.

Not Applicable (NA): No non-target brain lesions at baseline.

Not Evaluable (NE): Cannot be classified by 1 of the 4 preceding definitions.

Special Notes on the Assessment of Non-target Brain Lesions

Non-target brain lesions that are not assessed at a particular timepoint based on the SoA (Table 3) should be excluded from the response determination (e.g., non-target response does not have to be “Not Evaluable”).

New Lesions

New brain malignancies denoting disease progression must be unequivocal. Lesions identified in follow up in an anatomical location not scanned at baseline are considered new lesions.

Any equivocal new lesion should continue to be followed. Treatment can continue at the discretion of the Investigator until the next scheduled assessment. If at the next assessment the new lesion is considered to be unequivocal, progression should be documented.

Time Point Response for Brain Lesions

Table A3 presents the intracranial response at an individual time point for all possible combinations of tumor response in target and non-target brain lesions, with or without the appearance of new brain lesions for patients with measurable (as defined in Section 7.2.1 and Section 7.2.2) intracranial disease at baseline.

Patients with a global deterioration of health status that requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having

"symptomatic deterioration." Objective response status is determined by evaluations of disease burden. Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (e.g., fine needle aspirate or biopsy) to confirm the CR.

Table A3: Evaluation of Brain Lesion Response

Target Lesions	Non-target Lesions	New Lesions	Response
CR	CR or NA	No	**CR**
CR	Non-CR/Non-PD or NE	No	**PR**
PR	Non-PD or NA or NE	No	**PR**
SD	Non-PD or NA or NE	No	**SD**
NE	Non-PD or NA or NE	No	**NE**
PD	Any	Yes or No	**PD**
Any	PD	Yes or No	**PD**
Any	Any	Yes	**PD**

Best Overall Brain Metastasis Response: All Time Points for Brain Lesions

The best overall brain metastasis response is defined as the best response recorded from the start of treatment until progression of brain metastasis and will be determined programmatically by the Sponsor based on the Investigator's assessment of brain metastasis response at each time point. Only tumor assessments performed before the start of any subsequent anticancer therapies and not later than 30 days after last dose of study drug will be considered in the assessment of best overall brain metastasis response. Clinical deterioration or clinical progression noted on the completion eCRF will not be considered as documented disease progression.

To be assigned a status of brain metastasis SD, follow-up disease assessment must meet the SD criteria at least once after the first dose of study treatment for a minimum of 6 weeks.

If the minimum time for SD is not met, the best response will depend on subsequent assessments. For example, if an assessment of PD follows the assessment of SD and SD does not meet the minimum time requirement, the best response will be PD. Alternatively, patients lost to follow up after an SD assessment who do not meet the minimum time criterion will be considered NE.

Appendix 6. Criteria for Evaluation of Global Response

This appendix provides definitions for global assessment of target and non-target lesion(s).

Evaluation of Target Lesions

Target lesion response is based on all (i.e., brain and extracranial) target lesions, up to a total of 10 lesions. The sum of longest diameters of all target lesions will be used to determine response. Definitions for assessment of response for target lesion(s), based on mRECIST v1.1 for brain lesion and RECIST v1.1 for extracranial lesions, are as follows:

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes must be < 10 mm on the short axis.

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

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to quality for PD.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as a reference the smallest sum of diameters recorded since the treatment started (i.e., percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of at least 5 mm.

Not Applicable (NA): No extracranial target lesions at baseline.

Not Evaluable (NE): Cannot be classified by 1 of the 5 preceding definitions.

Special Notes on the Assessment of Target Lesions

If lymph nodes are documented as target lesions, the short axis is added to the sum of the diameters (i.e., sum of diameters is the sum of the longest diameters for non-nodal lesions and the short axis for nodal lesions). When lymph nodes decrease to non-pathological size (i.e., short axis < 10 mm), they should still have a measurement reported in order not to overstate progression.

If at a given assessment time point all target lesions identified as baseline are not assessed, the sum of diameters cannot be calculated for purposes of assessing CR, PR or SD, or for use as the nadir for future assessments. However, the sum of the diameters of the assessed lesions and the percent change from nadir should be calculated to ensure that progression has not been documented. If an assessment of PD cannot be made, the response assessment should be NE.

All target lesions (nodal and non-nodal) should have their measurements recorded even when very small (e.g., 2 mm). If lesions are present but too small to measure, 5 mm should be

recorded and should contribute to the sum of the diameters unless it is likely that the lesion has disappeared, in which case 0 mm should be reported.

If a target lesion disappears and reappears at a subsequent time point it should continue to be measured. The response at the time when the lesion reappears will depend upon the status of the other lesions. For example, if the disease had reached a CR status then PD would be documented at the time of reappearance. However, if the response status was PR or SD, the diameter of the reappearing lesions should be added to the remaining diameters and response determined based on percent change from baseline and percent change from nadir.

Evaluation of Non-target Lesions

Non-target lesion response is based on all (that is, brain and extracranial) non-target lesions. Definitions for assessment of response for non-target lesions are as follows:

Complete Response (CR): The disappearance of all non-target lesions. All lymph nodes identified as a site of disease at baseline must be non-pathological (i.e., < 10 mm short axis).

Non-CR/Non-PD: The persistence of 1 or more non-target lesion(s) or lymph nodes identified as a site of disease at baseline ≥ 10 mm short axis.

Progressive Disease (PD): Unequivocal progression of existing non-target lesions.

Not Applicable (NA): No brain or extracranial non-target lesions at baseline.

Not Evaluable (NE): Cannot be classified by 1 of the 5 preceding definitions.

Special Notes on the Assessment of Non-target Lesions

In the presence of measurable disease, progression on the basis of solely non-target disease requires substantial worsening such that even in the presence of SD or PR in target disease, the global tumor burden has increased sufficiently to merit discontinuation of therapy.

In the presence of non-measurable-only disease, consideration should be given to whether or not the increase in global disease burden is comparable in magnitude to the increase that would be required to declare PD for measurable disease.

Sites of non-target lesions that are not assessed at a particular time point based on the SoA (Table 3) should be excluded from the response determination (i.e., non-target response does not have to be “Not Evaluable”).

Time Point Response

Table A4 presents the response at an individual time point for all possible combinations of tumor responses in all brain and extracranial target and non-target lesions with or without the appearance of new lesions.

Patients with a global deterioration of health status that requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Objective response status is determined by evaluations of disease burden. Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (e.g., fine needle aspirate or biopsy) to confirm the CR.

Table A4: Evaluation of Global Response

Target Lesions	Non-target Lesions	New Lesions	Global Response
CR	CR or NA	No	**CR**
CR	Non-CR/Non-PD or NE	No	**PR**
PR	Non-PD or NA or NE	No	**PR**
SD	Non-PD or NA or NE	No	**SD**
NE	Non-PD or NA or NE	No	**NE**
PD	Any	Yes or No	**PD**
Any	PD	Yes or No	**PD**
Any	Any	Yes	**PD**

Best Overall Global Response: All Time Points

The best overall global response is the best response recorded from the start of treatment until progression of brain metastasis or extracranial disease and will be determined programmatically by the Sponsor based on the Investigator's assessment of global response (brain metastasis and extracranial disease) at each time point. Only tumor assessments performed before the start of any subsequent anticancer therapies and not later than 30 days after last dose of study drug will be considered in the assessment of best overall global response. Clinical deterioration or clinical progression noted on the completion eCRF will not be considered as documented disease progression.

To be assigned a status of overall global stable disease (SD), follow-up disease assessment must meet the SD criteria at least once after the first dose of study treatment for a minimum of 6 weeks.

If the minimum time for SD is not met, the best response will depend on subsequent assessments. For example, if an assessment of PD follows the assessment of SD and SD does not meet the minimum time requirement, the best response will be PD. Alternatively, patients lost to follow up after an SD assessment who do not meet the minimum time criterion will be considered NE.

Appendix 7. Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

7.1 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 intervention, whether or not considered related to the study intervention.
- 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 intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., 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 intervention 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 and meet the requirements as per Section 7.4.8.1. 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 (e.g., 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.

7.2 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 (e.g., 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:

a. Results in death

b. 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.

c. 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 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.

d. 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 (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. 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 life-threatening 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).

7.3 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 intervention 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 intervention 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 (e.g., 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:

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.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up 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.

7.4 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.

Appendix 8. 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 patients’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. The ratio (R-value) of ALT (or AST when ALT is not available) activity to ALP activity expressed as multiples of ULN can be used to categorize the injury pattern of DILI as hepatocellular ($R \geq 5$), cholestatic ($R \leq 2$) or mixed (>2- <5) (CIOMS. 2020).

$$R = \frac{\text{ALT/ULN}}{\text{ALP/ULN}}$$

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 (e.g., 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.

Appendix 9. ECG Findings of Potential Clinical Concern

ECG Findings That May 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 May 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 May Qualify as Serious Adverse Events (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.
- **Additional clarifications for Canada:** QTcF prolongation >30 msec from baseline that is associated with an arrhythmic event (ventricular tachycardia, ventricular fibrillation or flutter, syncope, seizures, torsade de pointes, or sudden death).

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.

Appendix 10. 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).

10.10.1 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 criterion # 21. Active infection requiring systemic therapy.

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

10.10.2 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 (Section 1.3) 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 7.4.
- 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 10.10.3.1 of this appendix regarding pregnancy tests.

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

10.10.3 Alternative Facilities for Safety Assessments

10.10.3.1 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 7.3.7 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 patient'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.

10.10.3.2 Imaging

If the patient is unable to visit the study site for safety imaging assessments (e.g., ECHO 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.

10.10.3.3 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.

10.10.4 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.

10.10.5 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 7.4
- 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 10.10.3.1 of this appendix regarding pregnancy tests.

10.10.6 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 intervention with the study medical monitor.

10.10.7 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.

10.10.8 Steering Committee

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

Appendix 11. Protocol Amendment Summary of Changes

DOCUMENT HISTORY	
Document	**Date**
Amendment 4 (Version 4)	04 January 2021
Amendment 3 (Version 3)	07 August 2020
Amendment 2 (Version 2)	13 March 2020
Amendment 1 (Version 1)	08 April 2019
Original Version 0	14 November 2018

Amendment 4 (04 January 2021)

The purpose of this amendment is in response to requests from Health Canada for safety Section 7.4.6 *Cardiovascular and Death Events*, Appendix 8 *Liver Safety: Suggested Actions and Follow-up Assessments,* and Appendix 9 *ECG Findings of Potential Clinical Concern*. Details are provided in the table below.

Section # and Name	Description of Change	Brief Rationale
Section 7.4.6 Cardiovascular and Death Events	Section was revised to remove "not applicable" to further detail investigator's responsibilities for AE reporting.	Clarification of Safety reporting for cardiovascular and death events.
Appendix 8 Liver Safety: Suggested Actions and Follow-up Assessments	Added the following additional criteria and reference to CIOMS 2020; *The ratio (R-value) of ALT (or AST when ALT is not available) activity to ALP activity expressed as multiples of ULN can be used to categorize the injury pattern of DILI as hepatocellular (R ≥ 5), cholestatic (R ≤ 2) or mixed (>2- <5) (CIOMS 2020).* *R =ALT/ULN* *ALP/ULN*	Inclusion of Health Canada recommendations to inform investigators of the CIOMS standards regarding DILI, with regard to Hy's Law criteria.
Appendix 9 ECG Findings of Potential Clinical Concern	Added the following additional criteria; ***Additional clarifications for Canada****: QTcF prolongation >30 msec from baseline that is associated with an arrhythmic event (ventricular tachycardia, ventricular fibrillation or flutter, syncope, seizures, torsade de pointes, or sudden death).*	Inclusion of Health Canada recommendations for additional ECG criteria that may qualify as serious adverse events.

DOCUMENT HISTORY	
Document	**Date**
Amendment 3 (Version 3)	07 August 2020
Amendment 2 (Version 2)	13 March 2020
Amendment 1 (Version 1)	08 April 2019
Original Version 0	14 November 2018

Amendment 3 (07 August 2020)

The purpose of this amendment is to allow intra-patient dose escalation for patients that have tolerated the standard dose regiment of 450 mg QD encorafenib plus 45 mg BID binimetinib during the first 4 weeks of treatment (Cycle 1). Patients meeting a pre-defined safety criteria will be allowed to dose escalate to 600 mg QD encorafenib plus 45 mg BID binimetinib. In addition, the Adverse Event and Serious Adverse Events Section 7.4 has been revised to align with Pfizer standard operation procedures with SAE reporting directly to Pfizer Safety. Appendix 10. *Alternative Measures During Public Emergencies* has been added as a guidance document during public emergencies.

Section # and Name	Description of Change	Brief Rationale
Sponsor Signature Page Investigator Signature Page	Sponsor signature page and Investigator signature page has been removed from the protocol.	Sponsor signature page and Investigator Signature page will be separate from the protocol to align with Pfizer protocol standards.
1.1 Synopsis 3.0 Objectives and Endpoints	Updated PK objectives and endpoints to include metabolites for encorafenib and binimetinib.	Metabolites for encorafenib and binimetinib were added to the PK objectives and endpoints as these will be included in the PK analysis.
CCI [redacted]	[redacted]	[redacted]
2.2.3 Clinical Safety of Combination Encorafenib and Binimetinib	Uveitis, including iritis and iridocyclitis, was added as a risk based on updated safety data.	To include update safety/risk data.
2.2.5 Clinical Safety of Encorafenib 600 mg QD in the CMEK162X2110 Study	Added new section to describe the safety data and the determination of the MTD of the encorafenib 600 mg QD plus binimetinib 45 mg BID dosing regimen in the Phase 1b/2 CMEK162X2110 study.	Justification to allow intra-patient dose escalation up to 600 mg QD encorafenib for patients who tolerate the standard dosing regimen during the first 4 weeks (Cycle 1) of treatment in Phase 2.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 4.1 Overall Design 4.3 Justification for Dose 6.7.1 General Procedures for Dose Modifications 6.7.2 Intra-Patient Dose Escalation	Text added to allow patients to dose escalate from 450 mg QD encorafenib to 600 mg QD encorafenib after 4 weeks of tolerability at the 450 mg QD encorafenib provided pre-defined criteria are met.	In order to improve efficacy for patients with brain metastasis, intra-patient dose escalation of encorafenib will be allowed for patients who are able to tolerate the standard combination dose of encorafenib and binimetinib.
4.2 Discussion of Study Design	Added discussion to describe allowing intra-patient dose-escalation in Phase 2 for patients who tolerate the standard dosing regimen during the first 4 weeks (Cycle 1) of treatment.	Added this information to address the updated study design by including intra-patient dose escalation in this amendment.
4.3.2 High Dose Encorafenib	Section clarified.	Redundant information for the CMEK162X2110 study deleted with reference made to Section 2.2.5.
5.1 Inclusion Criterion #6 Inclusion Criterion #7d	Added clarification that prior SRS was allowed as long as there is 1 non irradiated measurable lesion. Defined total daily dose of corticosteroids	Added clarification to the Inclusion Criterion #6 that prior SRS was allowed as long as there is one non irradiated measurable lesion to align with Section 7.1.1. Clarified definition of stable or decreasing doses of corticosteroids.
6.1 Study Treatment Administered	Clarified QD arm for encorafenib	Clarified QD encorafenib dosing to account for those patients that qualify for dose escalation.
6.3.1 Patient Numbering	Changed the page for documenting reasons for patients failing to be randomized or starting study treatment from the Screening Disposition page to the eCRF.	Clarified the page for documenting reasons for patients not being randomized or starting treatment.
6.7 Dose Modification	For patients who require a dose modification, a clarification was added to prevent patients who dose reduce from 600 mg QD encorafenib to 450 mg QD encorafenib to re-escalate back to 600 mg QD encorafenib.	In order to ensure patient safety, patients who cannot tolerate the 600 mg QD encorafenib dose can be reduced to 450 mg QD encorafenib and will not be allowed to dose re-escalate back up to 600 mg QD encorafenib.
6.13 Withdrawal of Consent	New section added for patients who withdraw consent.	A separate section on patients who withdraw consent has been added to align with Pfizer standard operating procedures.
7.4 Adverse Events and Serious Adverse Events	The following Sections 7.4.1 to 7.4.5 were added to the Section 7.4	Adverse Events and Serious Adverse Events revised to align with Pfizer standard operating procedures.

Section # and Name	Description of Change	Brief Rationale
	replacing the previous Section 7.4.1 to 7.4.5. 7.4.1 Time Period and Frequency for Collecting AE and SAE information, 7.4.2 Methods of Detecting AEs and SAEs, 7.4.3 Follow-up of AEs and SAEs, 7.4.4 Regulatory Reporting Requirements for SAEs, 7.4.5 Exposure During Pregnancy or Breastfeeding and Occupational Exposure. The follow Sections were added: 7.4.6 Cardiovascular and Death Events 7.4.7 Disease-Related event/and or Disease-Related Outcomes Not Qualifying as AEs and SAEs. 7.4.8 Adverse Events of Special Interest 7.4.9 Medical Devices Deficiencies 7.4.10 Medication Errors	
7.5 Product Complaints	Added clarification to report product complaints within 1 business day.	Added to align with Pfizer mandatory requirements for the investigator to notify Pfizer about a product complaint with 1 business day of discovery
7.6 Treatment Overdose	Clarified per Pfizer standard operational procedures.	Additional clarifications to align with Pfizer standard operational procedures.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities 7.5 Product Complaints 7.6 Treatment of Overdose 7.7 Pharmacokinetic Assessments 7.7.1 Blood Sample Collection 7.8 Pharmacodynamics, CCI [redacted] 7.10 Patient-reported Outcomes, 7.11 Unscheduled Visits, 7.12 End of Treatment and/or Early Termination. Appendix 11. Protocol Amendment Summary of Changes.	Section numbering changes.	Due to moving the previous Section 7.5 Pregnancy to Section 7.4.5 Exposure During Pregnancy or Breastfeeding and Occupational Exposure per Pfizer standard operational procedures, section numbers have changed. Due to the addition of Appendices 7-10, the previous Appendix 7. Protocol Amendment Summary of Changes was renumbered to Appendix 11.
7.7 Pharmacokinetic Assessments and Table 13	Due to Section changes, Section 7.8 Pharmacokinetic Assessments has been renumbered to Section 7.7. The PK sampling for alternate PK Blood Sample Timing Table 13 has been adjusted to collect samples at Cycles 1, 2 and 3.	In order to capture possible changes in drug exposure due to intra-patient encorafenib dose escalation, PK of encorafenib and binimetinib will be characterized at the standard starting dose of 450 mg QD encorafenib plus 45 mg BID binimetinib and the escalated dose of 600 mg QD encorafenib plus 45 mg BID binimetinib in Phase 2. These PK data allow meaningful exposure response analysis to be conducted for all patients with and without including standard dose and intra-patient escalation.
8.3 Analysis Sets	Deleted Per-protocol analysis set CCI [redacted] Minor updates on Safety Set and PK Set	Per-protocol Set is not recommended per Pfizer SAP template. CCI [redacted] Minor updates on Safety Set and PK set for clarity
[redacted]	[redacted]	CCI [redacted]
8.4.3 Safety Analyses	Deleted body weight, ECOG PS, dermatologic, ECHO/MUGA and ophthalmic examination data descriptive summary	Per Pfizer TLF reduction initiative, these safety parameters will not be summarized descriptively in the tables. Only listings will be presented.

Section # and Name	Description of Change	Brief Rationale
8.4.4 Pharmacokinetic Analysis	Revised the list of PK parameters to be estimated and reported, when feasible and appropriate.	To include essential PK parameters including but not limited to C_{max}, C_{trough}, AUC and meanwhile allow flexibility for calculation while the data permit.
[redacted]	[redacted]	CCI [redacted]
9.7.1 Data Sharing	New Section added	Data sharing section added to align with Pfizer standard operating procedures.
Appendix 7. Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting. Appendix 8. Liver Safety: Suggested Actions and Follow-up Appendix 9. ECG Findings of Potential Clinical Concern Appendix 10. Alternative Measures During Public Emergencies	Added per Pfizer standard operating procedures. Previous Appendix 7 Protocol Amendment Summary of Changes moved to Appendix 11.	Adverse Events and Serious Adverse Events Appendix 7, 8, and 9 added to align with Pfizer standard operating procedures. The Alternative Measures During Public Emergencies Appendix 10 was added as guidance to be followed during public emergencies, including the COVID-19 pandemic.

DOCUMENT HISTORY	
Document	**Date**
Amendment 2 (Version 2)	13 March 2020
Amendment 1 (Version 1)	08 April 2019
Original Version 0	14 November 2018

Amendment 2 (13 March 2020)

The primary purpose of this amendment is to revise patient eligibility criteria based on investigator feedback and changes in standard of care for the treatment of asymptomatic brain metastases. Additionally, the study design was updated to allow for flexibility regarding if the high-dose regimen is not tolerated and to simplify the overall study design. This amendment is considered substantial based the change of the patient population and overall study design.

Additional language added for laboratory safety assessments, as required by Health Canada.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis Table 1 Primary and Select	Primary and Secondary Objectives revised and clarified.	Objectives clarified to account for the scenario that if the high-dose is

Section # and Name	Description of Change	Brief Rationale
Secondary Objectives and Endpoints, 3. Objectives and Endpoints Table 4		determined not to be safe during the Safety Lead-in phase, analysis will be completed on the standard dose.
1.1 Synopsis Table 2 Key Study Design Elements, 4.1 Overall Design, 4.2 Discussion of Study Design	Approximately 110 patients will be enrolled in the study (9 in the safety lead-in and 100 in Phase 2), patients will be stratified by baseline tumor burden in the brain (1 to 2 brain lesions vs. ≥ 3 brain lesions) and prior local therapy (yes vs. no), design change.	The study design has been revised with pick the winner approach and interim analysis no longer being explored.
1.2. Schema Figure 1: Study Schema	Study Schema revised to reflect the change in study design for the Phase 2 portion of the study.	Pick the winner study design approach and the requirement for an interim analysis are not needed for the revised study design.
1.3. Schedule of Activities, (SoA) Table 3	IWRS clarified, Karnofsky Status added to the SoA, coagulation and urinalysis requirements during the treatment period clarified.	Clarification. Karnofsky Status was missing from SoA and added with the ECOG PS. On treatment coagulation assessment clarified for patients that are on anticoagulation treatment should have parameters monitored throughout the study as clinically indicated. Urinalysis simplified and can now be assessed as clinically indicated.
2.1.3. Systemic Treatment for *BRAF*-mutant Melanoma Brain Metastasis, 2.2.1. Encorafenib, and 2.2.2. Binimetinib	Clarified market approval for binimetinib and encorafenib	Added approvals by EMA and other authorities.
5.1. Inclusion Criteria #3, #5, and #6.	Clarification to (#3) diagnosis, (#5) tumor tissue, and (#6) brain lesions	Clarifications to Inclusion Criteria.
5.1 Inclusion Criterion #7	(#7a) Patients may receive prior local therapy for brain metastasis, (#7c) Patients on prior immunotherapy are permitted, (#7d) Patients on corticosteroids can be included if on a stable dose for at least 2 weeks prior to enrollment.	Modification regarding allowable prior local therapy based on investigator feedback regarding standard of care treatment for patients with asymptomatic brain metastases including patients using corticosteroids.
5.2. Exclusion Criteria #1, #2, #11, and #20	(#1) Clarified patients with symptomatic brain metastasis. (#2) Added clarification to exclude patients on prophylactic or preventive anti-epileptic therapy. Moved requirements for patients using corticosteroids for brain metastasis to Inclusion criterion # 7d. (#11) added clarification for	Added example of symptomatic brain metastasis. Clarified requirements regarding patients on anti-epileptic therapy. Added clarification to major surgery and other malignancies.

Section # and Name	Description of Change	Brief Rationale
	major surgery. (#20) Clarification to other malignancies.	
5.2. Exclusion Criterion #7	Patients have had prior local therapy including craniotomy or WBRT are permitted, therefore added clarification to acceptable recovery window before enrollment.	Modification regarding allowable prior local therapy based on investigator feedback regarding standard of care treatment for patients with asymptomatic brain metastases.
5.2. Exclusion Criterion #9	Patients treated in the adjuvant setting with BRAF or MEK inhibitor(s) change from < 12 months to < 6 months prior to enrollment. Patients treated in the adjuvant setting with BRAF or MEK inhibitors changed from ≥ 12 months to ≥ 6 months prior to enrollment are eligible.	Modification regarding allowable prior therapy of BRAF or MEK inhibitor (s) based on investigator feedback regarding standard of care treatment for patients with metastatic disease.
6.3. Randomization	Clarified the IWRS will be used to enroll patients (randomization and cohort assignment), for study drug assignment, and for ordering study drug supplies.	Clarification.
6.5.2. Prohibited Concomitant Therapy	Clarification added regarding palliative radiation therapy to target lesions.	Note added to clarify palliative radiation therapy to target lesions is prohibited.
6.6 High-dose Safety Assessment	Clarification	Clarification to high-dose determination of safe as opposed to tolerable to be consistent with study objectives.
6.7.1. General Procedures for Dose Modification	Revised dose modifications to clarify dose re-escalation and dose reductions.	Updated as per the current local prescribing instructions for encorafenib and binimetinib.
7.1. Screening Procedures	Clarified the requirement for baseline scans during the screening period. Baseline scans from other institutions are acceptable, provided the sites obtain copies of the radiological scans.	To ensure that all baseline scans are available for central review.
7.1.1. Baseline Documentation of Intracranial Target and non-Target Lesions	New Section added	Additional details added for baseline documentation of intracranial target lesions.
7.1.2. Baseline Documentation of Extracranial Target and non-Target Lesions	New Section added	Additional details added for baseline documentation of extracranial target lesions.
7.2.1. Radiological Tumor Evaluation	Clarification to screening MRI of brain and spine.	Added clarification that brain and spine MRI is required at screening to be consistent with the Schedule of Activities.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities, Inclusion Criterion #4, 7.2.6 *BRAF* Testing, CCI [redacted]	Clarified *BRAF*V600 tissue testing by local PCR or NGS-based assay. Optional tumor biopsy added to EOT. Additional serum blood samples will be collected on C1D1, C2D1, C3D1 and EOT.	Serum blood samples will be collected on C1D1, C2D1, C3D1 and EOT for analysis of potential proteomic or metabolomic factors and signatures.
7.3.5. Vital Signs	Vital signs clarified from oral temperature to temperature.	Clarification.
7.3.7. Clinical Safety Laboratory Assessments and Appendix 2 (Recommended Dose Modifications for Encorafenib)	Added the following sentence: "Electrolyte abnormalities including magnesium should be corrected and cardiac risk factors for QT prolongation (e.g., congestive heart failure, bradyarrhythmias) should be controlled."	Additional language required by Health Canada prior to subjects being dosed in Canada.
7.8.1. Blood Sample Collection	Added PK sample schedule Table 13 to be collected from all Phase 2 patients if the high-dose regimen is determined not to be safe, as a result, the original Table 13 was renumbered to Table 14.	If the high-dose is determined not to be safe, PK sample collection will proceed with a reduced PK schedule detailing collection times for the standard dose Arm A.
2.4. Benefit/Risk Assessment, 8.1. Statistical Hypothesis, 8.2. Sample Size Determination, Phase 2, 8.3. Analysis Sets, 8.4. Statistical Analysis, 8.5. Interim Analysis	Interim analysis removed. Sample size determination for Phase 2 revised for the new study design. Table 14 *Operating characteristic of the Phase 2 interim analysis* has been removed. In Table 15, the Full Analysis Set was updated to only include patients in the randomized Phase 2 (Arms A and B).	The study design was simplified removing the Pick the Winner approach and the interim analysis. Sample size adjusted for new study design. The study design was simplified removing the interim analysis changing the full analysis set. The study design was simplified, and the interim analysis is no longer necessary.
Administrative Change	In some instances, references to Array have been changed to Sponsor.	Responsibility for some study functions has been modified from "Array BioPharma" to the more general "Sponsor" as a result of Array BioPharma, Inc. becoming a wholly owned subsidiary of Pfizer, Inc.

Amendment 1 (08 April 2019)

This amendment modifies the eligibility criterion pertaining to hepatic function to require eligible patients to have total bilirubin $\leq 1.5 \times$ ULN. Per US National Cancer Institute guidelines on classification of hepatic impairment, total bilirubin levels of $\leq 1.5 \times$ ULN would limit the study population to patients with normal hepatic function or mild hepatic impairment. Patients with elevated bilirubin may be admitted to the study on a case-by-case basis following review and agreement by the Medical Monitor if there is documented

evidence that the elevation is not due to decreased hepatic function, which could affect encorafenib and/or binimetinib exposures.

Section # and Name	Description of Change	Brief Rationale
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.
1.3 Schedule of Activities, (SoA) Table 3	ECHO/MUGA assessment on Cycle 1 Day 1 removed.	ECHO/MUGA is performed at Screening and throughout the study. Removal of the Cycle 1 Day 1 ECHO/MUGA avoids the possibility that a patient might undergo these tests in close proximity. This is consistent with other Array-sponsored studies of encorafenib/binimetinib in combination.
5.1 Inclusion Criteria	Inclusion criterion 9e was modified to require eligible patients to have total bilirubin ≤ 1.5 × ULN. Patients with documented Gilbert syndrome or hyperbilirubinemia due to non-hepatic cause may be enrolled following discussion and agreement with the Array Medical Monitor.	This change limits the study population to patients with normal hepatic function or mild hepatic impairment per US NCI guidelines.