Clinical Study ARRAY-162-202

An Open-label Phase 1b/2 Study of Binimetinib Administered in Combination with Nivolumab or Nivolumab Plus Ipilimumab in Patients with Previously Treated Microsatellite-stable (MSS) Metastatic Colorectal Cancer with *RAS* Mutation

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IND Number:	CCI [redacted]

Array BioPharma Inc.

3200 Walnut Street
Boulder, CO 80301
Phone: (303) 381-6600
Fax: (303) 386-1240

SIGNATURE PAGE (SPONSOR)

I have read and understand the contents of the clinical protocol for Clinical Study ARRAY-162-202 dated 02 March 2018 and agree to meet all obligations of Array BioPharma Inc. as detailed in all applicable regulations and guidelines. In addition, I will ensure that the Investigators are informed of all relevant information that becomes available during the conduct of this study.

PPD

PPD

PPD MD Date

PPD

Array BioPharma Inc.

PRINCIPAL INVESTIGATOR AGREEMENT

I have read and understand the contents of the clinical protocol for Clinical Study ARRAY-162-202 dated 02 March 2018 and will adhere to the study requirements as presented, including all statements regarding confidentiality. In addition, I will conduct the study in accordance with the requirements of this protocol and also protect the rights, safety, privacy and well-being of study patients in accordance with the following:

- International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use Harmonised Tripartite Guideline for Good Clinical Practice (GCP) E6(R1)
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations
- Requirements for reporting serious adverse events (SAEs) defined in Section 10.9 of this protocol
- Terms outlined in the Clinical Study Site Agreement

My signature also acknowledges that:

- Neither my subinvestigators nor I are members of the Ethics Committee (EC) reviewing this protocol, or
- I and/or my subinvestigators are members of the EC, but I/we will not participate in the initial review or continuing review of this study

Name of Principal Investigator	Signature of Principal Investigator

Date

PROTOCOL SYNOPSIS

Title	An Open-label Phase 1b/2 Study of Binimetinib Administered in Combination with Nivolumab or Nivolumab plus Ipilimumab in Patients with Previously Treated Microsatellite-stable (MSS) Metastatic Colorectal Cancer with *RAS* Mutation
Protocol Number	ARRAY-162-202
Phase	1b/2

Objectives	**Primary:**
	• Phase 1b:
	  ○ Determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of binimetinib administered in combination with nivolumab
	  ○ Determine the MTD and RP2D of binimetinib administered in combination with nivolumab plus ipilimumab
	• Phase 2: Assess the preliminary antitumor activity of the treatment combinations based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
	Secondary:
	Both Phases:
	• Further assess the preliminary antitumor activity of the treatment combinations based on RECIST version 1.1
	• Characterize the safety profile of the treatment combinations
	• Characterize the pharmacokinetics (PK) of binimetinib in both treatment combinations
	Exploratory:
	Both Phases:
	• Obtain preliminary estimates of progression-free survival (PFS) and overall survival (OS)
	CCI [redacted]

Endpoints	**Primary:**
	• Phase 1b:
	  ○ Incidence of dose-limiting toxicities (DLTs) resulting from binimetinib in combination with nivolumab
	  ○ Incidence of DLTs resulting from binimetinib in combination with nivolumab plus ipilimumab
	• Phase 2: Objective response rate (ORR) per RECIST v1.1
	Secondary:
	• Phase 1b only: ORR per RECIST v1.1
	Both Phases:
	• Duration of response (DOR) per RECIST v1.1
	• Rate of complete response (CR) per RECIST v1.1
	• Incidence and severity of adverse events (AEs) graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03, and changes in clinical laboratory parameters
	• Sparse plasma concentrations for binimetinib
	Exploratory:
	Both Phases:
	• PFS per RECIST v 1.1
	• OS
	CCI [redacted]

Design	This is a multicenter, open-label Phase 1b/2 study to determine the MTD and RP2D and schedule of binimetinib, and to assess the safety, efficacy, and PK of binimetinib administered in combination with nivolumab or

	nivolumab plus ipilimumab in patients with previously treated MSS metastatic colorectal cancer (mCRC) with documented *RAS* mutation. The study will include a dose-finding period in Phase 1b followed by a randomized Phase 2 period. The total number of patients enrolled in Phase 1b of the study will depend on the number of dose levels tested and the number of patients treated in each cohort before the MTD has been determined for each arm. Approximately 90 patients are planned. A maximum of approximately 42 patients will be enrolled in Phase 1b and a minimum of approximately 48 patients will be enrolled in Phase 2. Randomization into Phase 2 will continue until at least 33 patients have received the doublet and the triplet, respectively, at the RP2D (Phase 1b and Phase 2 combined). One treatment cycle is defined as 28 days (4 weeks) for all arms. Individual treatments will be dosed on the schedules as outlined below. Phase 1b of the study will consist of dose-finding cohorts in Arm 1A and Arm 1B. All dose-escalation and de-escalation decisions will be driven by the modified toxicity probability interval (mTPI-2) design (Guo et al. 2017). • Patients assigned to Arm 1A (Doublet) will be dosed with 480 mg nivolumab every 4 weeks (Q4W) and 45 mg twice daily (BID) of binimetinib initially as starting Dose Level 4. In the event that this dose level is not tolerated, lower dose levels, or an intermittent binimetinib dosing schedule, may be tested per Table 1 below. • Patients assigned to Arm 1B (Triplet) will be dosed with the RP2D of binimetinib from Arm 1A plus 480 mg nivolumab Q4W and 1 mg/kg ipilimumab Q8W. Dose de-escalation will proceed if the treatment is not tolerated. Intermittent dose schedules for binimetinib may also be evaluated as per Table 1 below. There will be a period of at least 7 days between Cycle 1 Day 1 (C1D1) of the first patient and C1D1 of the second patient enrolled during Phase 1b (Arms 1A and 1B). Intra-patient dose escalation will not be permitted. Note: In both arms, there will be flexibility to evaluate intermittent dosing schedule of binimetinib (30 or 45 mg BID; e.g., 3 weeks on/1 week off) if continuous dosing is not tolerated (Table 1) depending on the time of onset of DLTs. In Phase 1b: The target DLT probability for Cycle 1 is 30%, with an equivalence interval, i.e., an acceptable interval, of 25% to 35%. Dosing in

<table>
<tr><td></td><td>Phase 1b will continue within an arm until 9 patients (from the dose-determining set) have been treated at one dose level with a recommendation to stay (or a recommendation to escalate if there is not a higher dose level or if the tolerability of the next dose level is unacceptable), or the maximum sample size within a Phase 1b arm (n=21) has been reached. If further safety evaluations are required, additional patients may be added to a cohort.

Toxicities will only be considered DLTs if they occur in Cycle 1 although overall safety including later cycles will be considered for dose escalations and for each RP2D determination.

Patients are required to complete Cycle 1 (≥ 75% of the planned cumulative dose of binimetinib) to be considered evaluable for MTD determination unless discontinuation occurred due to a DLT (i.e, in the dose-determining set).

Phase 2 of the study will consist of 2 arms to investigate the safety and clinical activity of the RP2Ds established from Phase 1b: Arm 2A (nivolumab in combination with binimetinib) and Arm 2B (nivolumab plus ipilimumab in combination with binimetinib).</td></tr>
<tr><td>Treatment Regimens</td><td><u>Phase 1b</u>:

Table 1: Dosing Scheme for Phase 1b

<table>
<tr><th>Arm</th><th>Dose Level (*Starting Dose Level)</th><th>Binimetinib</th><th>Nivolumab</th><th>Ipilimumab</th></tr>
<tr><td rowspan="4">1A (Doublet)</td><td>4*</td><td>45 mg BID</td><td rowspan="4">480 mg Q4W</td><td rowspan="4">N/A</td></tr>
<tr><td>3</td><td>45 mg BID 3W on / 1W off</td></tr>
<tr><td>2</td><td>30 mg BID</td></tr>
<tr><td>1</td><td>30 mg BID 3W on / 1W off</td></tr>
<tr><td rowspan="4">1B (Triplet)[a]</td><td>4</td><td>45 mg BID</td><td rowspan="4">480 mg Q4W</td><td rowspan="4">1 mg/kg Q8W</td></tr>
<tr><td>3</td><td>45 mg BID 3W on / 1W off</td></tr>
<tr><td>2</td><td>30 mg BID</td></tr>
<tr><td>1</td><td>30 mg BID 3W on / 1W off</td></tr>
</table>
[a] The starting Dose Level of Arm 1B (Triplet) will be the RP2D of binimetinib from Arm 1A. If tolerated, the RP2D of binimetinib from Arm 1A will be considered the RP2D for Arm 1B. If not tolerated, any dose level below the RP2D for Arm 1B may be explored.

<u>Phase 2</u>:

Arm 2A: Patients randomized to the nivolumab and binimetinib arm will receive nivolumab administered as 480 mg Q4W as a 30-minute (± 5 minutes) intravenous (IV) infusion on Day 1 of each treatment cycle and</td></tr>
</table>

	the recommended dose of binimetinib in Arm 1A of Phase 1b. Arm 2B: Patients randomized to the nivolumab, ipilimumab, and binimetinib arm will receive nivolumab administered as 480 mg Q4W as a 30-minute (± 5 minutes) IV infusion on Day 1 of each treatment cycle, ipilimumab IV as a dose of 1 mg/kg Q8W as a 30-minute IV infusion (± 5 minutes), and the recommended dose of binimetinib in Arm 1B of Phase 1b.
Study Population	This study will be conducted in adult patients with MSS mCRC with a *RAS* mutation. Participants in both Phase 1b and Phase 2 must have received at least one prior line of systemic therapy in the metastatic setting and were unable to tolerate the prior first-line therapy, experienced disease progression during or after the prior treatment regimen for mCRC, or progressed during or within 6 months of completing adjuvant chemotherapy. Participants must also have received no more than 2 prior lines of systemic therapy in the metastatic setting. Maintenance therapy given in the metastatic setting will not be considered a separate regimen.
Duration of Study Participation	Following a screening period of up to 28 days, patients will receive the doublet or triplet treatment regimens in 28-day cycles until disease progression, unacceptable toxicity, withdrawal of consent, initiation of subsequent anticancer therapy, the patient is lost to follow-up, or death. Patients will be monitored for OS until 1 year after the randomization date of the last patient enrolled, or until withdrawal of consent for such follow up, lost to follow up, or death.
Eligibility Criteria for Prescreening	**Prescreening Inclusion Criteria:** Patients must meet all of the following inclusion criteria to be eligible for participation in the prescreening period: 1. Provide a signed and dated Prescreening informed consent form (ICF). 2. Male or female ≥ 18 years of age at the time of signing the Screening ICF. 3. Measurable, histologically/cytologically confirmed mCRC per RECIST v1.1. 4. Have willingness and ability to participate in the study. 5. Able to provide a sufficient amount (tumor block or minimum of 6 slides) of representative tumor specimen (primary or metastatic, archival or newly obtained) for central laboratory testing of *RAS* mutation status and MSS.

	a. If a fresh tissue sample is provided, a blood sample is required. 6. Have received no more than 2 prior lines of systemic therapy in the metastatic setting (maintenance therapy given in the metastatic setting will not be considered a separate regimen). Generally, treatments that are separated by an event of progression are considered different regimens. 7. Have received prior systemic treatment as recommended by National Comprehensive Cancer Network (NCCN) or European Society for Medical Oncology (ESMO) guidelines, including fluoropyrimidines, oxaliplatin, irinotecan or bevacizumab in the metastatic setting or similar treatments, as per local guidelines. 8. No known contraindications to study treatment. **Prescreening Exclusion Criteria** Patients meeting any of the following criteria are not eligible for enrollment in the study: 1. Prior treatment with any MEK inhibitor. 2. Prior treatment with an anti-programmed death-1 (PD-1), anti-PD-L1, anti-PD-L2, anti-CD137, or anti- cytotoxic T-cell lymphoma-4 antigen (CTLA-4) antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways. 3. Any untreated central nervous system (CNS) lesion. However, patients are eligible if: a) all known CNS lesions have been treated with radiotherapy or surgery, and b) patients remained without evidence of CNS disease progression ≥ 4 weeks after treatment, and c) patients must be off corticosteroid therapy for ≥ 3 weeks. 4. Patients with an active, known or suspected autoimmune disease, with the following exceptions: patients with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll. 5. Partial or complete bowel obstruction. 6. Impaired gastrointestinal function or disease that may significantly alter the absorption of binimetinib (e.g., ulcerative diseases, uncontrolled vomiting, malabsorption syndrome, small bowel resection with decreased intestinal absorption) or baseline diarrhea ≥ Grade 1. 7. Known history of retinal vein occlusion (RVO).

	8. Concurrent or previous other malignancy within 5 years of study entry, except cured basal or squamous cell skin cancer, superficial bladder cancer, prostate intraepithelial neoplasm, carcinoma in-situ of the cervix, or other noninvasive or indolent malignancy 9. Known history of Gilbert's syndrome. 10. Severe uncontrolled medical illness. 11. Psychiatric illness inhibiting informed consent or protocol compliance. 12. Pregnant or breastfeeding females. 13. History of severe hypersensitivity reactions to monoclonal antibodies (mAbs). 14. History of allergy or intolerance (unacceptable AEs) to study drug components or polysorbate-80-containing infusions.
Eligibility Criteria for Screening	**Screening Inclusion Criteria** Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study: 1. Patients must meet all Prescreening inclusion criteria. 2. Provide a personally signed and dated Screening ICF. 3. mCRC categorized as MSS by immunohistochemistry (IHC) or polymerase chain reaction (PCR)-based local assay at any time prior to Screening or by the central laboratory (Section 7.1.1). 4. *RAS* mutation per local assay at any time prior to Screening or by the central laboratory. 5. Have received at least one prior line of systemic therapy in the metastatic setting as recommended by National Comprehensive Cancer Network (NCCN) or European Society for Medical Oncology (ESMO) guidelines, including fluoropyrimidines, oxaliplatin, irinotecan or bevacizumab, or similar treatments, as per local guidelines, and meets at least one of the following criteria: a. were unable to tolerate the prior first-line regimen b. experienced disease progression during or after prior first-line regimen for metastatic disease c. progressed during or within 6 months of completing adjuvant chemotherapy Note: Generally, treatments that are separated by an event of progression are considered different regimens. 6. Eastern Cooperative Oncology Group (ECOG) performance status (PS)

	of 0 or 1. 7. Female patients are either postmenopausal for at least 1 year, are surgically sterile for at least 6 weeks; if a female patient is of childbearing potential, she must agree to follow instructions for acceptable or highly effective method(s) of contraception for the duration of study treatment and for 5 months after the last dose of study treatment with nivolumab (i.e., 30 days [duration of ovulatory cycle] plus the time required for the investigational drug to undergo approximately 5 half-lives) (Section 5.3). 8. Non-sterile male patients who are sexually active with female partners of childbearing potential must agree to follow instructions for acceptable or highly effective method(s) of contraception for the duration of study treatment and for 7 months after the last dose of study treatment with nivolumab (i.e., 90 days [duration of sperm turnover] plus the time required for the investigational drug to undergo approximately 5 half-lives) (Section 5.3). 9. Adequate renal and bone marrow function as measured by the following Screening laboratory values: a. White blood cells (WBC) $\geq$ 2000/µL b. Neutrophils $\geq$ 1500/µL c. Platelets $\geq$ 100 $\times 10^3$/µL d. Hemoglobin $\geq$ 9.0 g/dL e. Serum creatinine $\leq$ 1.5 $\times$ upper limit of normal (ULN) or calculated creatinine clearance > 50 mL/min (using the Cockcroft Gault formula) or estimated glomerular filtration rate > 50 mL/min/1.73 m^2 (using the Modification of Diet in Renal Disease [MDRD] Study formula) 10. Adequate hepatic function characterized by the following Screening laboratory values: a. Serum total bilirubin $\leq$ 1.5 $\times$ ULN and < 2 mg/dL Note: Patients who have a total bilirubin level > 1.5 $\times$ ULN will be allowed if their indirect bilirubin level is $\leq$ 1.5 $\times$ ULN. b. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) $\leq$ 2.5 $\times$ ULN, or $\leq$ 5 $\times$ ULN in presence of liver metastases 11. Adequate cardiac function as follows: a. Left ventricular ejection fraction (LVEF) $\geq$ 50% or above institutional normal value as determined by a MUGA scan or echocardiogram

	b. QTcF interval ≤ 480 msec (preferably the mean from triplicate electrocardiograms [ECGs]) 12. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures including computed tomography (CT)/magnetic resonance imaging (MRI) scans. **Screening Exclusion Criteria** Patients meeting any of the following criteria are not eligible for enrollment in the study: 1. Patients must not meet any of the Prescreening exclusion criteria. 2. Treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to first day of study treatment: a. The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) and topical steroids are allowed. Patients who have received acute and/or low-dose systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea or chronic use of ≤ 10 mg/day of prednisone or dose-equivalent corticosteroid) may be enrolled in the study after discussion with and approval by the Sponsor's Medical Monitor. 3. Impaired gastrointestinal function or disease that may significantly alter the absorption of binimetinib (e.g., ulcerative diseases, uncontrolled vomiting, malabsorption syndrome, small bowel resection with decreased intestinal absorption) or baseline diarrhea ≥ Grade 1. 4. History of thromboembolic or cerebrovascular events ≤ 6 months prior to starting study treatment, including transient ischemic attacks, cerebrovascular accidents, deep vein thrombosis or pulmonary emboli. 5. Uncontrolled hypertension defined as persistent systolic blood pressure ≥ 150 mmHg or diastolic blood pressure ≥ 100 mmHg despite current therapy. 6. Concurrent neuromuscular disorder that is associated with the potential of elevated creatine kinase (CK) (e.g., inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy). 7. 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).

	8. Clinically significant cardiac disease, including, but not limited to, any of the following: a. Congestive heart failure requiring treatment (New York Heart Association Grade ≥ 2). b. Clinically significant and uncontrolled atrial fibrillation. c. History of acute coronary syndromes including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty, or stenting < 6 months prior to screening. d. Symptomatic chronic heart failure, history or current evidence of clinically significant cardiac arrhythmia and/or conduction abnormality < 6 months prior to screening except controlled atrial fibrillation and paroxysmal supraventricular tachycardia. 9. Residual CTCAE ≥ Grade 2 toxicity from any prior anticancer therapy, with the exception of Grade 2 alopecia or Grade 2 neuropathy. 10. Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at sites where mandated locally. 11. Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection, and/or detectable virus.
Pharmacokinetics	Peripheral venous blood (3 mL) will be collected from all patients on Cycle 1 Day 1 at 1.5 hours post-binimetinib dose, on Cycle 1 Day 15 pre-binimetinib dose and 1.5 hours post-binimetinib dose, and on Cycles 2-5 Day 15 pre-binimetinib dose during treatment for quantitation of binimetinib and active metabolite AR00426032.
Biomarkers	Peripheral blood and tumor tissue (fresh or archival) will be collected prior to therapy and at selected time points on treatment (tumor biopsy optional). Residual sample material available after completion of the designated analyses may be used in the future for identification of additional pharmacodynamic or predictive markers or to enhance understanding of disease biology unless prohibited by local laws or regulations. Samples will be de-identified to ensure patient privacy.
Sample Size Determination	For the dose-finding period of this study (Phase 1b), the primary objective is to determine the RP2D of binimetinib in combination with nivolumab with or without ipilimumab. The total number of patients enrolled in the dose-finding period will depend on the number of dose levels tested and the number of patients treated in each cohort before the RP2D has been determined. Approximately 90 patients are planned. A maximum of approximately

	42 patients will be enrolled in Phase 1b and a minimum of approximately 48 patients will be enrolled in Phase 2. In Phase 1b, a maximum of approximately 21 patients will be treated in each arm, with a target of 9 patients at the MTD. In the Phase 2 period of the study, a minimum of approximately 24 patients will be treated in each arm. Randomization into Phase 2 will continue until at least 33 patients have received the doublet and the triplet, respectively, at the RP2D (Phase 1b and Phase 2 combined). The primary analysis of the response rate and efficacy endpoints will include all Phase 2 patients plus those treated at the same dose/schedule in Phase 1b; thus, it is expected that a minimum of 33 patients in each arm will be available for the primary efficacy evaluation. In the doublet arm, a response rate of 5% or less will be considered unacceptably low. Hence, the null hypothesis that the response rate is at most 5% will be tested against the alternative hypothesis that the response rate is greater than 5%. The targeted response rate is 20%. With these assumptions, and a 2-tailed alpha = 0.10 significance level, 33 patients will provide approximately 86% power. In the triplet arm, a response rate of 10% or less will be considered unacceptably low. Hence, the null hypothesis that the response rate is at most 10% will be tested against the alternative hypothesis that the response rate is greater than 10%. The targeted response rate is 30%. With these assumptions, and a two-tailed alpha = 0.10 significance level, 33 patients will provide approximately 91% power. The study is not adequately powered to compare the response rate between treatment arms; these comparisons will be descriptive only.

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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
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the concentration-time curve
BCRP	breast cancer resistance protein
BID	twice daily
BNP	brain natriuretic peptide
BOR	best overall response
BRAF	B-RAF proto-oncogene, serine/threonine kinase
BSA	body surface area
BSC	best supportive care
BUN	blood urea nitrogen
C1D1	Cycle 1 Day 1 or CXDX
CA 19-9	cancer antigen 19-9
CAPOX	capecitabine and oxaliplatin
C_{avgss}	average steady-state exposures
CEA	carcinoembryonic antigen
cHL	classical Hodgkin's lymphoma
CI	confidence interval
CK	creatine kinase
C_{max}	maximum concentration
C_{maxss}	steady-state peak concentrations
C_{minss}	steady-state trough concentrations
CMS	consensus molecular subtypes
CNS	central nervous system

Abbreviation or special term	Explanation
CR	complete response
CRA	clinical research associate
CRC	colorectal cancer
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-cell lymphoma-4 antigen
CV	curriculum vita
CYP	cytochrome P450
DDS	Dose-determining Set
DLT	dose-limiting toxicity
dMMR	DNA mismatch repair
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
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture system
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ER	exposure-response
ESMO	European Society for Medical Oncology
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDG-PET	fluorodeoxyglucose positron emission tomography
FOLFIRI	leucovorin, 5-FU and irinotecan
FOLFOX	leucovorin , 5-FU and oxaliplatin
FSH	follicle-stimulating hormone

Abbreviation or special term	Explanation
5-FU	5-fluorouracil
GCP	Good Clinical Practice
GI	Gastrointestinal
H&N	head and neck
HBV	hepatitis B virus
HCV	hepatitis C virus
HDPE	high-density polyethylene
HFSR	rash, hand foot skin reaction
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
IB	Investigator's Brochure
IC_{50}	≥ 50% inhibition of MEK activity
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
Ig	Immunoglobulin
IHC	immunohistochemistry
ILD	interstitial lung disease
imAE	immune-mediated adverse event
INR	international normalized ratio
CCI	[redacted]
IRB	Institutional Review Board
irPR	immune-related partial response
irSD	immune-related stable disease
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous(ly)
IWRS	interactive web response system
KRAS	V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
LC-MS-MS	liquid chromatography tandem mass spectrometry
LH	luteinizing hormone
LLN	lower limit of the normal reference range
LVEF	left ventricular ejection fraction

Abbreviation or special term	Explanation
mAb	monoclonal antibody
MAP	mitogen activated protein
MAPK	mitogen activated protein kinase
mCRC	metastatic colorectal cancer
MDRD	Modification of Diet in Renal Disease (Study)
MedDRA	Medical Dictionary for Regulatory Activities
MEK	mitogen/extracellular signal regulated kinase
MHC	major histocompatibility complex
MLR	mixed lymphocyte reaction
mOS	median overall survival
MRI	magnetic resonance imaging
MSI	microsatellite instability
MSI-H	high-frequency microsatellite instability
MSS	microsatellite stable
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
MUGA	multi-gated acquisition
mWHO	Modified World Health Organization (criteria)
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGS	next generation sequencing
NSCLC	non-small cell lung cancer
OCT	optical coherence tomography
ORR	objective response rate (overall response rate)
OS	overall survival
PAS	PK Analysis Set
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed death-1
PDF	portable document format
PD-L1	programmed death-ligand 1
PE	pulmonary embolism

Abbreviation or special term	Explanation
pERK	phosphorylated ERK
PFS	progression-free survival
P-gp	P-glycoprotein
pH	hydrogen ion concentration
PK	pharmacokinetic(s)
PO	oral(ly)
PPK	population pharmacokinetics
PPS	Per-protocol Set
PR	partial response
PS	performance status
PT	prothrombin time
QXW	every X weeks (X varies based on number of weeks specified)
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	red blood cell
RCC	renal cell cancer
RECIST	Response Evaluation Criteria in Solid Tumors
RPED	retinal pigment epithelial detachment
RP2D	recommended Phase 2 dose
RVO	retinal vein occlusion
SAE	serious adverse event
SAP	statistical analysis plan
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SOC	standard of care
SOP	standard operating procedure
SS	safety set
SUSAR	suspected unexpected serious adverse event
$t_{1/2}$	terminal half-life
T3	Triiodothyronine
T4	Thyroxine
TCGA	The Cancer Genome Atlas
T_{max}	time of maximum plasma concentration
TME	tumor microenvironment

Abbreviation or special term	Explanation
TNF	tumor necrosis factor
TSH	thyroid-stimulating hormone
UC	urothelial carcinoma
UGT	UDP-glucuronosyl transferase
ULN	upper limit of normal
US	United States
vs	version
VEGF	vascular endothelial growth factor
VTE	venous thromboembolism
WBC	white blood cell
WES	whole exosome sequencing
WHO	World Health Organization

SUMMARY OF CHANGES FOR PROTOCOL VERSION 4.0

Rationale

The objective of this amendment is to (1) specify that all patients must have received prior systemic treatment as recommended by National Comprehensive Cancer Network (NCCN) or European Society for Medical Oncology (ESMO) guidelines, including fluoropyrimidines, oxaliplatin, irinotecan or bevacizumab in the metastatic setting or similar treatments, as per local guidelines; (2) add a delay of at least 7 days between Cycle 1 Day 1 (C1D1) of the first patient and C1D1 of the second patient enrolled during Phase 1b (Arms 1A and 1B); (3) add a post-treatment 150-day safety follow-up assessment; and (4) decrease the burden of visual field testing for sites and patients. Other minor changes or clarifications have also been made as described below.

Changes to the Protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strikethrough font for deletions and underlined font for insertions.

Summary of Changes for Protocol Version 4.0: Section added to summarize this amendment.

Protocol Synopsis: Section was updated to match the body of the protocol.

Section 2.1 was modified to describe likely outcomes relating to standard-of-care therapies after the first-line setting as well as potential outcomes of the study regimen.

Title for Section 2.4 was changed to “Risk-benefit Assessment Summary.”

Section 2.4 was modified to provide an overview of the informed consent process and to describe likely outcomes relating to standard-of-care therapies after the first-line setting as well as potential outcomes of the study regimen.

Sections 3.1.2, 3.1.3 and 3.2.3 were modified to clarify that all elements of the sections apply to both Phase 1b and Phase 2 of the study.

Title for Section 4.1.1 was changed to add the following: “and Dose De-Escalation/Escalation”.

Section 4.1.1 was modified to include a statement that there will be a period of at least 7 days between C1D1 of the first patient and C1D1 of the second patient enrolled during Phase 1b (Arms 1A and 1B).

Section 4.1.1 was modified to include the statement "The Sponsor's Medical Monitor and the Investigators will review, at a minimum, all the available data from Cycle 1 once 3 to 6 evaluable patients in subsequent cohorts have been treated for at least 1 cycle", which was moved from Section 4.1.1.1 to improve organization.

Section 4.1.1.1 was modified to remove the statement "The Sponsor's Medical Monitor and the Investigators will review, at a minimum, all the available data from Cycle 1 once the first 3 to 6 evaluable patients in a cohort have been treated for at least 1 cycle", which was moved to Section 4.1.1.

Section 5.2.1.1 was modified to include a new prescreening inclusion criterion (criterion 7) that requires that all patients must have received prior systemic treatment as recommended by NCCN or ESMO guidelines, including fluoropyrimidines, oxaliplatin, irinotecan or bevacizumab in the metastatic setting or similar treatments, as per local guidelines. Wording of an existing prescreening criterion (criterion 5) was also adjusted to specify that patients must have willingness and ability to participate in the study.

Section 5.2.2.1 (criterion 5) was modified to specify that the required line(s) of prior systemic therapy were consistent with recommendations by NCCN or ESMO guidelines, including fluoropyrimidines, oxaliplatin, irinotecan or bevacizumab in the metastatic setting or similar treatments, as per local guidelines.

Section 6.3.1 was updated to include a ± 5-minute window around the 30-minute nivolumab infusions and to clarify this time does not include the time required to flush the IV lines.

Section 6.3.3 was updated to include a ± 5-minute window around the 30-minute ipilimumab infusions and to clarify this time does not include the time required to flush the IV lines.

Section 6.4.1.4 was modified to align with guidelines in the nivolumab prescribing information.

Section 7.2.5.1 was updated: (1) to remove visual field testing as part of the full ophthalmic examination; (2) to state that visual field testing will only be performed when clinically indicated; and (3) to allow visual field testing to be performed by either an optometrist or ophthalmologist.

Table 11 Footnote "A" was updated to remove visual field testing as part of the full ophthalmic examination and to instead state that visual field testing will be performed when clinically indicated.

Tables 12 to 15 have been updated: (1) to add a 150-day safety follow-up assessment; (2) to remove visual field testing as part of the full ophthalmic examination; and (3) to state that visual field testing will only be performed when clinically indicated.

Section 8.4.2 was updated to remove tumor assessments at this visit (C2D15) as they are to be performed every 8 weeks (±7 days) from C1D1 through Week 24, then every 12 weeks (±7 days) thereafter.

Section 8.5.1 was updated to clarify that tumor assessments are to be performed in subsequent cycles every 8 weeks (±7 days) from C1D1 through Week 24, then every 12 weeks (±7 days) thereafter.

Section 8.7.2 was updated to remove tumor assessments at this visit (C2D15) as they are to be performed every 8 weeks (±7 days) from C1D1 through Week 24, then every 12 weeks (±7 days) thereafter.

Section 8.8.1 was updated to clarify that tumor assessments are to be performed in subsequent cycles every 8 weeks (±7 days) from C1D1 through Week 24, then every 12 weeks (±7 days) thereafter.

Section 8.9.2 was updated to remove details of survival follow-up, which have been moved into a separate section.

Section 8.9.3 was updated to remove details of survival follow-up, which have been moved into a separate section.

Section 8.9.4 was added to describe the events of the 150-day safety follow-up assessment.

Section 8.9.5 was added to clarify tumor assessment follow-up visits.

Section 8.9.6 was added to clarify survival follow-up.

Section 10.3 was updated with administrative changes/corrections.

Section 10.6 was updated with administrative changes/corrections.

Section 10.9 was updated to reflect the 150-day safety follow-up assessment.

References were updated.

SUMMARY OF CHANGES FOR PROTOCOL VERSION 3.0

Rationale

At the time of this protocol amendment, the study had been initiated at 3 study centers, 1 patient had received study drug and 1 patient was in screening.

The objective of this amendment is to add immunohistochemistry (IHC) as a permitted method of local MSS determination.

Changes to the Protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strikethrough font for deletions and underlined font for insertions.

Summary of Changes for Protocol Version 3.0: Section added to summarize this amendment.

Protocol Synopsis: Section has been updated to match the body of the protocol.

Section 5.2.2.1: Screening Inclusion Criterion 3 modified to include IHC as a permitted method of local MSS determination.

Section 7.1.1: Section modified to include IHC as a permitted method of local MSS determination and to specify the mismatch repair proteins that must be assayed and reported.

Section 8.0: Table 11 modified to include IHC as a permitted method of local MSS determination.

Section 8.1: Section modified to include IHC as a permitted method of local MSS determination.

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and health authorities. The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein do not affect the informed consent.

SUMMARY OF CHANGES FOR PROTOCOL VERSION 2.0

Rationale

At the time of this protocol amendment, the study had been initiated at 1 study center and 1 patient has been screened.

The main objectives of this amendment are:

- To modify eligibility criteria as follows:
  - Allow progression within 6 months of completing adjuvant chemotherapy prior to enrollment (previously 3 months)
  - Permit use of estimated glomerular filtration rate measurement per Modification of Diet in Renal Disease (MDRD) Study formula (previously only allowed a qualifying creatinine or calculated creatinine clearance measurement)
- To specify that permanent discontinuation of nivolumab will also result in permanent discontinuation of ipilimumab
- To clarify permitted binimetinib treatment modifications
- To update protocol instructions regarding documentation of adverse events to align with current Sponsor language
- Administrative changes (clarifications and corrections)

Changes to the Protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strikethrough font for deletions and underlined font for insertions.

Summary of Changes for Protocol Version 2: Section added to discuss this amendment.

Protocol Synopsis: Section has been updated to match the body of the protocol.

Protocol Synopsis, Study Design: Redundant presentation of study objectives was deleted.

Section 2.1.1: Section updated to reflect the approval of nivolumab for the treatment of colorectal cancer.

Section 2.2.3.1: Section updated with administrative changes.

Section 2.3.1.1: Section updated with administrative changes.

Section 2.3.1.2: Section updated with administrative changes.

Section 2.3.2.3: Section heading updated with administrative changes.

Section 4.1: Figure 2 updated with administrative changes.

Section 4.1.1: Clarification added that de-escalation decisions will also be guided by the modified toxicity probability interval (mTPI-2) design.

Section 4.1.1, Table 2: Clarification added to footnote.

Section 4.1.1: Table 3 expanded to provide mTPI-2 dose-escalation and de-escalation guidance for a broader range of cohort sizes; paragraph referencing TPI-2 algorithm removed, as it is no longer necessary given the expanded table.

Section 4.1.1.1: Clarification added that de-escalation decisions will also be guided by the mTPI-2 design.

Section 4.1.1.1.1: Removed statement allowing doses of ipilimumab and/or nivolumab to be reduced.

Section 4.1.1.2: Table 4 updated to clarify that relevant CK comparator value for assessment of dose-limiting toxicities is the baseline, rather than the screening, value.

Section 5.1: Estimated number of study centers participating in Phase 1b was reduced to 5 (previously 12 to 15).

Section 5.2.1.1: Prescreening Inclusion Criterion 3 modified to specify use of RECIST v1.1.

Section 5.2.1.1: Prescreening Inclusion Criterion 6 modified to specify that the maximum of 2 permitted prior therapies refers to systemic therapy in the metastatic setting.

Section 5.2.1.2: Prescreening Exclusion Criterion 4 wording modified for clarity.

Section 5.2.2.1: Screening Inclusion Criterion 5 modified to specify that the requirement regarding prior therapy refers to systemic therapy in the metastatic setting, and criterion 5c modified to allow progression within 6 months of completing adjuvant chemotherapy (previously 3 months).

Section 5.2.2.1: Screening Inclusion Criteria 9e modified to allow estimated glomerular filtration rate measurement per Modification of Diet in Renal Disease (MDRD) Study formula (previously only allowed a qualifying creatinine or calculated creatinine clearance measurement).

Section 6.1: Corrected to state that manual assignment of patient numbers will be performed in Phase 2 as well as Phase 1b.

Section 6.3.2: Reference to binimetinib capsules removed (binimetinib is provided as tablets).

Section 6.3.2: Statements regarding ipilimumab and nivolumab administration timing were removed, as they are not relevant to this section.

Section 6.3.3: Timing of ipilimumab administration in relation to nivolumab administration clarified, and stipulation added that permanent discontinuation of nivolumab will also result in permanent discontinuation of ipilimumab.

Section 6.4.1.3: Duration of ipilimumab dose interruption necessitating permanent discontinuation specified as > 18 weeks to ensure consistency in the protocol.

Section 6.4.1.4: Stipulation added that permanent discontinuation of nivolumab will also result in permanent discontinuation of ipilimumab.

Section 6.4.2: Permitted binimetinib dose modifications were clarified in text and via addition of Table 5; instructions pertaining to binimetinib treatment after interruption of more than 28 days and after discontinuation of nivolumab (and, if applicable, ipilimumab) were clarified.

Section 6.4.2: Added a restriction to permit only a single dose re-escalation after dose reduction due to toxicity.

Section 6.4.2: Table 7 footnote updated with administrative changes.

Section 6.4.2: Incorrect statement describing conditions required for re-escalation of binimetinib dose was removed; the correct information is presented earlier in the section.

Section 7.1.1: Section modified to specify time window for central confirmation of locally determined MSS disease and *RAS* mutation.

Section 7.1.2: Section modified to specify that collection of fresh tumor biopsy must include blood sample and corrected to state that manual assignment of patient numbers will be performed in Phase 2 as well as Phase 1b.

Section 7.2.1: Statement regarding severity grading scale was removed, as it is presented elsewhere.

Section 7.2.2: Table 9 was modified to include amylase and lipase, changes in which may meet criteria for dose-limiting toxicities, and was updated with administrative changes.

Section 7.2.2.1: Section modified to correct typographical error and to specify that assessment of renal function for a given patient should use the same method throughout the study.

Section 7.2.2.3: To address inconsistency within protocol, section modified to state that serum or urine pregnancy tests are permitted at post-screening assessments.

Section 7.2.3: Modified section to clarify that all vital signs assessments will include blood pressure, pulse and temperature.

Section 7.2.4.1: Section deleted, as ipilimumab dosing in this study is not dependent on body surface area.

Section 7.4: Numbering of section headings corrected (Sections previously numbered 7.4.1.1 through 7.4.1.4 have become Sections 7.4.1 through 7.4.4).

Section 7.5.1: To address inconsistency within protocol, section modified to specify tumor response assessments after Week 24 are to be performed every 12 weeks.

Section 8.0, Table 11: Corrected to state that manual assignment of patient numbers will be performed in Phase 2 as well as Phase 1b; to address inconsistencies within protocol, table modified to specify that women sterile by oophorectomy alone require LH, FSH and/or estradiol testing, and to specify that assignment of patient number in Phase 1b will occur during prescreening.

Section 8.0, Tables 12-15:

- To address inconsistency within protocol, tables modified to specify tumor response assessments after Week 24 are to be performed every 12 weeks.
- Study days on which binimetinib is dispensed in Cycle 1 corrected for consistency with the body of the protocol.
- References to binimetinib capsules removed (binimetinib is provided as tablets).
- Timing of ophthalmic examinations in Cycle 1 (Tables 12 and 13) and Cycle 2 (Table 15) modified for consistency across treatment groups and with body of protocol.
- Terminology clarified around blood sample collected with optional tumor biopsy.
- Guidance regarding timing of PK blood draw in relation to ipilimumab infusion added to footnote q (Tables 13 and 15 only).

Section 8.2: To address inconsistency within protocol, text modified to specify that women sterile by oophorectomy alone require LH, FSH and/or estradiol testing at screening.

Section 8.3.1: Figure 3 added to clarify sequence of events on Cycle 1 Day 1 for Arms 1A and 2A.

Section 8.6.1: Figure 4 added to clarify sequence of events on Cycle 1 Day 1 for Arms 1B and 2B, and timing of ipilimumab was specified to occur after 1.5-hour PK sample collected.

Section 8.8.1: Sequence of listed activities modified for clarity.

Section 8.9: Statement regarding timing of tumor assessments removed, as the information is presented elsewhere.

Section 9.2: Duration of ipilimumab dose interruption necessitating permanent discontinuation changed to > 18 weeks to ensure consistency in the protocol; clinical progression per Investigator discretion added as a potential reason for treatment discontinuation.

Section 10.0: Section heading updated to reflect updated Sponsor language.

Section 10.2: Section updated to include characterization of immune-mediated adverse events.

Section 10.6: Sponsor language regarding documentation of adverse events updated.

Section 10.7: Sponsor language regarding documentation of adverse events updated.

Section 10.8: Sponsor language regarding documentation of adverse events updated.

Section 10.9: Sponsor language regarding documentation of adverse events updated.

Section 10.10: Section updated to reflect updated Sponsor terminology.

Section 11.1: Rationale added for why Phase 2 enrollment may exceed the protocol-specified minimum of approximately 48 patients, and erroneous statement that 90 patients are required to complete the study was removed.

Section 11.4: Clarification added that de-escalation decisions will also be guided by the mTPI-2 design.

Section 11.4, Table 16: Clarification added to footnote.

References: Unnecessary literature citation deleted.

Appendix 7: Numbering of section headings corrected.

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and health authorities. The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the informed consent. Sites are required to update and submit for approval a revised informed consent that takes into account the changes described in this protocol amendment.

1.0 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

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

Prior to study initiation, the Principal Investigator at each site must provide to Array BioPharma Inc. (Array BioPharma/Sponsor) a signed protocol signature page, a fully executed and signed United States (US) Food and Drug Administration (FDA) Form 1572 (or equivalent) and a Qualified Investigator Undertaking form for Investigators at Canadian sites, a current curriculum vita (CV), medical license and a financial disclosure form. Financial disclosure forms, current CVs and medical licenses must also be provided for all subinvestigators listed on Form 1572 who will be directly involved in the treatment or evaluation of patients in this study.

The study will be administered and monitored by employees or representatives of Array BioPharma and/or a contract research organization (CRO) in accordance with all applicable regulations. Clinical research associates (CRAs) will monitor each site on a periodic basis and perform verification of source documentation for each patient. The Array BioPharma Drug Safety Department (and/or the CRO, if applicable) will be responsible for ensuring timely reporting of expedited serious adverse event (SAE) reports to regulatory authorities and Investigators.

2.0 INTRODUCTION

2.1 Metastatic Colorectal Cancer

Colorectal cancer is a serious, life-threatening condition. In 2015, colorectal cancer accounted for 774,000 deaths world wide (WHO 2017). In the US and Europe, it is the second and fourth most common cancer type, respectively. Approximately 130,000 new cases are diagnosed per year in the US and it is the second leading cause of cancer mortality (Siegel et al. 2015). In Europe, approximately 450,000 new cases are diagnosed per year and colorectal cancer was responsible for 215,000 deaths in 2012. A quarter of patients initially present with metastases and the majority of patients will eventually develop metastatic disease (Van Cutsem et al. 2016). Standard systemic therapy in patients with unresectable metastatic colorectal cancer (mCRC) includes combination regimens with cytotoxic and targeted agents. In the last decade, substantial advances in the treatment of mCRC have resulted in an improvement in overall survival (OS) from 10 to 12 months to more than 20 months (Grothey and Goldberg 2004). This improvement has occurred with the addition of irinotecan, oxaliplatin, bevacizumab, cetuximab, and panitumumab to the standard treatment with 5-fluorouracil (5-FU)/folinic acid (leucovorin).

First-line treatment options for patients with mCRC are partially determined by performance status, age and the presence or absence of specific genomic alterations in the tumor. Treatments in the US and EU are predominantly 5-FU- and leucovorin-containing regimens in combination with either oxaliplatin or irinotecan (FOLFOX or FOLFIRI) with a biologic agent such as bevacizumab. Both the FOLFOX and FOLFIRI regimens are considered to be equivalent with a median first-line progression-free survival (PFS) of 8.5 months for FOLFIRI and 8 months for FOLFOX (Mayer et al. 2015). If a *KRAS* or *NRAS* mutation in exons 2, 3 or 4 is absent (i.e., "*RAS* wild-type"), an epidermal growth factor receptor (EGFR) inhibitor (cetuximab or panitumumab) is indicated (Tournigand et al. 2004; Lea et al. 2007). In Europe, based on a similar efficacy and safety profile, the combination of capecitabine and oxaliplatin (CAPOX) is an alternative to standard 5-FU/LV and oxaliplatin-based regimens (Van Cutsem et al. 2015).

Second line and subsequent treatment choices are limited and dependent on therapy chosen in the first line. For those patients who were previously treated with FOLFOX or another 5-FU containing therapy, the median PFS for patients receiving FOLFIRI is approximately 4.5 months (Peeters et al. 2010). Bevacizumab and ziv-aflibercept have indications for second-line treatment in combination with chemotherapy and have demonstrated slight improvement in median OS (mOS), but for both biologic agents, the improvement in mOS is less than 2 months when comparing the investigational agent with standard of care (SOC) to SOC alone: 11.2 vs. 9.8 months for bevacizumab (Avastin Package Insert [PI]. 12/2016) and 13.50 vs. 12.06 months for ziv-aflibercept (Zaltrap PI. 6/2016). Single-agent cetuximab also has demonstrated an

improvement in median OS of less than 2 months (6.1 vs. 4.6 months) in patients who have previously received chemotherapy when compared to best supportive care (BSC) (Erbitux PI. 10/2016). In patients who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-vascular endothelial growth factor (VEGF) therapy, and, if *RAS* wild type, an EGFR directed therapy, the multikinase inhibitor regorafenib has demonstrated an improvement in mOS of 1.4 months (6.4 vs. 5 months) when compared to BSC (Stivarga PI. 4/2017). Another treatment option is tipiracil/trifluoridine (TAS-102), which demonstrated an improvement in mOS from 5.3 months with placebo to 7.1 months, with an objective response rate (ORR) of 1.6% (Mayer et al. 2015). The median PFS was 2.0 months in the tipiracil/trifluoridine group and 1.7 months in the placebo group.

Despite numerous treatment options for mCRC after first-line therapy, the overall benefit of these treatments is limited, with low response rates and minimal OS benefits of generally less than 2 months. Options are even further limited in patients with *RAS* mutated disease as the entire class of EGFR-directed therapies is not indicated for these patients. New options are, therefore, needed to improve outcomes for these patients.

2.1.1 Treatment with Immune Checkpoint Inhibitors in MSS versus MSI-H Disease

Immune checkpoint blockade has shown benefit in several cancer types, including melanoma, non-small cell lung cancer, renal cell, head and neck, classical Hodgkin's and bladder cancer (Ott et al. 2017). Additional indications with and without combination chemotherapy or targeted kinase inhibitors are likely (Sharma et al, 2015). Nivolumab administered as monotherapy or in combination with ipilimumab has demonstrated impressive benefit in metastatic CRC with high microsatellite instability (MSI-H) (RR: 26% in single-agent nivolumab-treated patients, and, 33% in combination with ipilimumab) (Boland et al. 2017; Opdivo US PI 2017). Although MSI-H mCRC shows sensitivity to immunotherapy, these patients represent only a small fraction (4%) of the mCRC population (Overman et al. 2016).

Data indicate that the majority (~96%) of CRC patients have tumors with a microsatellite-stable (MSS) phenotype. In this population, immunotherapeutic agents have been largely ineffective (Diaz et al. 2013). While the high mutational load of MSI tumors have been well documented in whole exosome sequencing (WES) studies, with some research suggesting the number of mutations in MSI tumors is 10 to 50 times higher than in MSS tumors (Llosa et al. 2015), MSS CRC exhibits a demonstrable level of neoantigens and mutational burden capable of being recognized by the immune system (Giannakis et al. 2017). Moreover, The Cancer Genome Atlas (TCGA) data has revealed a sizeable number of CRC tumors are both MSS *and* hypermutated (22%; The Cancer Genome Atlas Network 2012). Although MSS CRC lesions have mutations which can enhance susceptibility to immunotherapy, the tumor microenvironment is relatively

immunosuppressive, inhibiting the activation of T cell dependent anti-tumor immune responses and yielding a more immunologically quiescent tumor (Angelova et al. 2016; O'Toole et al. 2014; Xiao and Freeman. 2015). Two recent clinical studies support these observations: a single-agent study of pembrolizumab comparing MSI-H versus MSS mCRC patients found an ORR of 57% vs. 0%, respectively (Le et al. 2015), and a combination immunotherapy study of nivolumab with ipilimumab in a similar patient population found an ORR of 26% vs. 5%, respectively (Overman et al., 2016). Thus in comparison to MSI-H CRC, patients with MSS CRC were less likely to respond to immune checkpoint blockade.

2.1.2 RAS mutation in mCRC

The *RAS* oncogene is mutated in 30-40% of CRC. Mutations in specific codons within exons 2, 3 or 4 of *RAS* lead to constitutive activation of mitogen activated protein kinase (MAPK) pathway, causing cell growth, division and dysplasia. Patients with activating mutations in *RAS* have more limited treatment options as the use of anti-EGFR monoclonal antibodies (cetuximab and panitumumab) is not effective due to the dominant (downstream) activity of *RAS* in the MAPK pathway (Douillard et al. 2010; Douillard et al. 2014).

Activating RAS mutation leads to MAPK pathway activation which reduces immune cell infiltration and inflammatory mediators in the tumor microenvironment (Loi et al., 2016; Zelenay et al. 2016; Hugo et al. 2015). A bioinformatics analysis of CRC data in The Cancer Genome Atlas (TCGA) involving two-dimensional hierarchical clustering to define an immune signature comprising 28 genes showed that *RAS* mutation predicts for a relatively poor immune infiltration (Lal et al. 2016). In addition to effects on the TME and immune cell infiltration, RAS mutation may contribute to immune escape mechanisms by downregulating MHC class I required for antigen processing in tumor cells, and pharmacologic inhibition of MAPK signaling can improve peptide/MHC target recognition and killing by T cells (Brea et al. 2016; Atkins et al. 2004; Seliger et al. 1998). Thus, CRC with RAS mutation represents a clinical setting where MAPK pathway inhibition may positively modulate the efficacy of checkpoint inhibition.

2.2 Investigational Medicinal Products: Nivolumab, Ipilimumab and Binimetinib,

Nivolumab (also referred to as BMS-936558-01 and BMS-936558) and ipilimumab (also referred to as BMS-734016, MDX-010 and MDX-CTLA4) continue to be investigated in the oncology setting including mCRC.

Nivolumab is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-

L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens.

OPDIVO™ (nivolumab) is approved for use in multiple countries including the US (Dec 2014), the European Union (Jun 2015), and Japan (Jul 2014).

Ipilimumab is a fully human monoclonal immunoglobulin (Ig) G1κ that binds to the cytotoxic T-cell lymphoma-4 antigen (CTLA-4) antigen expressed on a subset of T cells from human and nonhuman primates. CTLA-4 is a negative regulator of T-cell activity. Ipilimumab is a mAb that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor-infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce Treg function, which may contribute to a general increase in T-cell responsiveness, including the anti-tumor response.

YERVOY™ (ipilimumab) 3 mg/kg has been approved for use in advanced melanoma in over 47 countries, including the US (25 Mar 2011), the European Union (13 Jul 2011), and Australia (Jul 2011). Yervoy 10 mg/kg is approved as adjuvant treatment of unresectable or metastatic melanoma in the US.

Binimetinib (also known as MEK162 or ARRY-438162) is a potent and selective allosteric, adenosine-triphosphate (ATP)-uncompetitive inhibitor of MEK1 and MEK2 that is active in inhibiting Ras/Raf/Erk pathway signalling and growth of cancer cells (KRAS-mutant, BRAF-mutant and wild-type) in the low nanomolar range. In oncology settings, binimetinib is currently being investigated both as a single agent and in combination with other agents in patients with selected advanced or metastatic solid tumors, including biliary cancer, CRC, and melanoma.

2.2.1 Nonclinical Safety Pharmacology and Toxicology of Binimetinib

Acute, subchronic, chronic and reproductive toxicity, genotoxicity and phototoxicity studies were completed in rats and monkeys to support the chronic administration of binimetinib to adult patients. There was no evidence of a genotoxic potential in vitro or in vivo. The adverse effects of mitogen/extracellular signal regulated kinase (MEK) inhibitors in humans are similar to those observed in rats and monkeys, with the exception of ocular findings (only seen in humans). These adverse effects include gastrointestinal intolerance, diarrhea, and rash (skin findings in rats only). In vitro and in vivo phototoxicity studies conducted in mice indicate that binimetinib has a low risk of weak phototoxic potential at therapeutic doses. Furthermore, there has been no evidence of phototoxicity or photosensitivity in humans being treated with binimetinib for cancer or for rheumatoid arthritis.

Given the embryo-lethal effects seen in rats and rabbits and the teratogenic effects seen in rabbits, binimetinib should not be used in pregnant women. Women of childbearing potential must be advised to use acceptable or highly effective contraception methods (Section 5.3).

For details regarding nivolumab clinical pharmacology and safety pharmacokinetics, refer to local labeling for OPDIVO™.

For details regarding ipilimumab clinical pharmacology and safety pharmacokinetics, refer to local labeling for YERVOY™.

For details regarding binimetinib clinical pharmacology and safety pharmacokinetics, please refer to the current binimetinib Investigator's Brochure (IB).

2.2.2 Pharmacokinetics of Binimetinib

Nonclinical in vitro and in vivo data indicated that binimetinib is metabolized by multiple routes but primarily by glucuronidation pathways (mainly via UDP-glucuronosyl transferase [UGT] 1A1, 1A3 and 1A9) and to a lesser extent by oxidation pathways (mainly via cytochrome p450 [CYP] 1A2 and 2C19). In vitro, binimetinib reversibly inhibits CYP2B6, but in vivo inhibition of CYP2B6 is anticipated to be insignificant. It is not considered a time-dependent inhibitor of CYP1A2, CYP2C9, CYP2D6, and CYP3A. Binimetinib has also induced CYP3A in vitro; however, in a drug-drug interaction study in healthy subjects, binimetinib did not alter the exposure of midazolam, indicating this induction is not clinically relevant.

In vitro experiments indicate that binimetinib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Inhibition of P-gp or BCRP is unlikely to result in a clinically important increase in binimetinib concentrations as binimetinib exhibits moderate to high passive permeability.

Binimetinib is rapidly absorbed after oral administration with a median time (T_{max}) to reach the maximum concentration (C_{max}) around 1.5 hours at steady state. The mean terminal half-life ($t_{1/2}$) in healthy subjects is approximately 10 hours.

For further details on the pharmacokinetics (PK) and metabolism of binimetinib, please refer to the current binimetinib IB.

2.2.3 Clinical Safety of Binimetinib

As of 20 January 2017, a total of 2750 healthy subjects and patients have received at least one dose of binimetinib either as monotherapy or in combination with other agents. This includes 229 healthy subjects, 164 patients with rheumatoid arthritis, 17 patients with hepatic dysfunction,

6 patients with renal dysfunction, and 2334 patients with advanced cancer. Please refer to the binimetinib IB for a detailed discussion of the safety profile of binimetinib.

2.2.3.1 Single-agent Binimetinib in Oncology

Available clinical data indicate a predictable safety profile consistent with that reported for other allosteric MEK1/2 inhibitors. The most frequent treatment-emergent AEs by MedDRA preferred term (PT) in patients receiving binimetinib include rash, dermatitis acneiform, nausea, vomiting, diarrhea, peripheral edema, fatigue, and creatine kinase (CK) elevation. Other clinically relevant toxicities are retinal events, increased blood pressure, decreased ejection fraction, and noninfectious pneumonitis/interstitial lung disease, all of which should be monitored closely with appropriate diagnostic evaluations. These observed AEs are generally reversible and manageable by appropriate supportive medical care and/or dose modifications.

The experience of binimetinib in patients with advanced cancer as a single agent includes 889 patients who have received at least 1 dose of binimetinib in 7 clinical studies. Safety results are summarized in the IB as pooled data for 4 of these studies and individually for 3 trials.

Pooled data from 4 clinical studies includes 566 patients with advanced solid tumors, primarily patients with melanoma, but also patients with biliary, colorectal, lung, pancreatic, and other solid tumors, treated at doses of 30 mg BID to 80 mg BID of binimetinib as a single agent. Of these patients, 427 patients with melanoma in two studies were treated at the recommended dose of 45 mg BID. The median age of patients in the pooled studies of single-agent binimetinib in advanced cancer was 61.5 years, 61.8% were male, and 89.0% were Caucasian. AEs were reported most frequently (> 20.0% of patients) under the PTs of diarrhea (44.7%), blood CK increased (40.3%), edema peripheral (41.2%), rash (36.6%), dermatitis acneiform (36.2%), nausea (34.3%), fatigue (30.0%) and vomiting (25.3%). Adverse events were reported most frequently (> 5.0% of patients) as Grade 3/4 in severity under the PTs of blood CK increased (18.9%) and hypertension (6.5%) and 22.3% of patients experienced AEs that resulted in permanent discontinuation of binimetinib treatment. The most common PTs leading to discontinuation of binimetinib were ejection fraction decreased (2.7%), blood CK increased (1.8%), RVO and dermatitis acneiform (1.2% each), and AST increased (1.1%).

Adverse Reactions with Binimetinib at the Recommended Dose

The safety of binimetinib monotherapy at the recommended dose of 45 mg BID was evaluated in 2 studies of patients with metastatic melanoma (n=427). In this pooled evaluation, for the purposes of describing adverse reactions, preferred terms describing a similar pathophysiology are grouped under a single Adverse Reaction (e.g., Left Ventricular Dysfunction includes the

preferred terms of "left ventricular dysfunction," "ejection fraction decreased," and "ejection fraction abnormal").

A number of selected Adverse Reactions associated with binimetinib were identified from pooled data from these 2 studies and are described below.

Cardiac Disorders

Left Ventricular Dysfunction (Includes preferred terms of left ventricular dysfunction, ejection fraction decreased, and ejection fraction abnormal)

Left ventricular dysfunction occurred in 10% (44/427) of patients and was Grade 3 in 4.4% (19/427) of patients. No Grade 4 events were reported.

It was the most frequent cause of treatment discontinuation, which was required in 3.3% of patients. Median time of onset of left ventricular dysfunction was 1.4 months.

Vascular Disorders

Hypertension (Includes preferred terms of hypertension, increased blood pressure, hypertensive crisis, orthostatic hypertension)

New onset or increased hypertension was reported in 16% (68/427) of patients and was reported as Grade 3 in 8% (34/427) of patients. No Grade 4 events were reported. Hypertensive events requiring additional therapy were reported for 13.1% of patients. Median time of onset of first grade ≥ 3 hypertension event was 1 month.

Venous thromboembolism (Includes preferred terms of pulmonary embolism, deep vein thrombosis, mesenteric vein thrombosis, portal vein thrombosis, thrombophlebitis, and others)

Venous thromboembolism (VTE) occurred in 4.2% (18/427) of patients, including 1.4% (6/427) of patients with pulmonary embolism. VTE was reported as Grade 1/2 in 2.5% (11/427) of patients and Grade 3/4 in 1.6% (7/427) of patients. Grade 3 pulmonary embolism was reported in below 1% (3/427) of patients.

Hemorrhage (includes preferred terms of epistaxis, retinal hemorrhage, hematuria, hemoptysis, gastrointestinal hemorrhages, and others)

The observed events are predominantly mild to moderate, whereas Grade 3/4 hemorrhagic events were reported in comparable frequency with the control arm in a Phase 3 trial (1.5 % vs 1.8%,

respectively). In melanoma patients treated at the recommended dose of binimetinib, the most frequent hemorrhage events were epistaxis, reported in 2.8%, retinal hemorrhage in 1.6%, and hematuria in 1.4% of patients.

Eye Disorders

Retinal events including serous retinopathy (also referred to as retinal pigment epithelial detachment [RPED] or chorioretinopathy) and retinal vein occlusion are class effects reported with MEK inhibitors.

With the recognition of this class-related toxicity, clinical programs for MEK inhibitors have included extensive monitoring (including optical coherence tomography [OCT]) to fully evaluate the retinal effects of MEK inhibitors, better defining the overall rate of this toxicity.

Retinal Pigment Epithelium Detachment (includes preferred terms of retinal pigment epithelial detachment, retinal detachment, detachment of retinal pigment epithelium, detachment of macular retinal pigment epithelium, subretinal fluid and others)

RPED was reported in 32% (135/427) of patients. RPED was reported as Grade 1 (asymptomatic) in 18% (78/427) of patients, Grade 2 in 12% (52/427) of patients, and Grade 3 in 1.2% (5/427) of patients. No Grade 4 events were reported. For patients who developed RPED, the median time to onset was 22 days (range: 1 to 251 days). This is consistent with data reported by Urner-Bloch et al. In their reports on patients with MEK inhibitor-related RPED, RPED generally appeared during the first 4 weeks of treatment, and in some cases during the first few days of treatment. Patients reported mild and only short-lived visual symptoms. Optical coherence tomography revealed neuroretinal elevations. Central retinal thickness and volume showed dose-dependent increases after the start of treatment, followed by a marked decrease despite continued treatment, which was associated with symptom resolution. No vascular abnormalities were found with fluorescein and indocyanine green angiography. Retinopathy was mild, self-limiting and tolerable as visual function was not seriously impaired (Urner-Bloch et al. 2014; Urner-Bloch et al. 2016).

Visual Impairment (includes preferred terms of visual impairment, vision blurred and reduced visual acuity**)**

Visual impairment occurred in 13% (56/427) of patients and was generally reversible.

Retinal Vein Occlusion (RVO)[1]

Retinal vein occlusion was reported in 1.6% (9/566) of treated patients across all studies; 0.9% (5/566) were reported as Grade 3/4. For patients who developed RVO, the median time to onset was 2.9 months.

Respiratory, Thoracic and Mediastinal Disorders

Pneumonitis/Interstitial lung disease[1]

Across all studies, pneumonitis and interstitial lung disease were respectively reported in 0.9% (5/566) and 0.4% (2/566) of treated patients; while 0.2% (1/566) of each were reported as Grade 3/4. The median time to first grade ≥ 2 event was 2.5 months.

Investigations

Blood Creatine Phosphokinase Increased

Blood creatine phosphokinase increased was reported as an AE in 43.3% of patients. In the majority of cases it was asymptomatic. It was the most frequent cause of dose adjustment or interruption, which was required in 18.3% of patients. Median time of onset of the first grade ≥ 2 events was 1 month.

Liver Transaminases Increase

The incidence of AEs reported as Grade 3 or 4 increases in liver laboratory tests among patients receiving binimetinib were: 2.3% (10/427) for alanine aminotransferase (ALT) and 2.1% (9/427) for aspartate aminotransferase (AST).

[1] *: The rate of rare events was calculated using the larger pool of 566 patients in order to capture all relevant events.

Musculoskeletal and Connective Tissue Disorders

Rhabdomyolysis[2]

Across clinical trials of binimetinib, rhabdomyolysis was reported in 0.4% (2/566) of treated patients. In one patient, fatal rhabdomyolysis was characterized by CK elevation, muscle symptoms, and evidence of renal dysfunction.

Skin and Subcutaneous Tissue Disorders

Rash (Includes preferred terms of rash, rash maculo-papular, rash papular, rash erythematous, rash follicular, and others)

Rash occurred in 44% of patients. Rash was reported as Grade 1 in 22% (95/427) of patients, Grade 2 in 18% (75/427) of patients, and Grade 3 in 4% (17/427) of patients. No Grade 4 events were reported.

Acneiform Dermatitis

Acneiform dermatitis is a characteristic rash associated with MEK inhibition. Acneiform dermatitis occurred in 41% (173/427) of patients. Acneiform dermatitis was reported as Grade 1 in 20% (85/427) of patients, Grade 2 in 18% (77/427) of patients, and Grade 3 in 2.6% (11/427) of patients. No Grade 4 events were reported.

Infections and Infestations

Skin Infection (Includes preferred terms of skin infection, rash pustular, folliculitis, erysipelas, paronychia and others)

Skin infection, often secondary to other dermatologic reactions, occurred in 23% (98/427) of patients. Skin infection was reported as Grade 1 in 9.6% (41/427) of patients, Grade 2 in 8.9% (38/427) of patients, and Grade 3 in 4.4 % (19/427) of patients. No Grade 4 events were reported.

[2] The rate of rare events was calculated using the larger pool of 566 patients in order to capture all relevant events.

Gastrointestinal Disorders

Diarrhea, Nausea, and Vomiting (Includes preferred terms of vomiting, retching)

Diarrhea, nausea, and vomiting occurred in 43%, 30%, and 20% of patients, respectively. Gastrointestinal events required dose adjustment or study drug interruption in 11% of patients and led to discontinuation of binimetinib in 1.2% of patients. Prophylaxis was not used in clinical trials.

Study ARRAY-162-311

Study ARRAY-162-311 (MILO) is an ongoing multinational, randomized, open-label Phase 3 study to evaluate single-agent binimetinib vs. physician's choice of selected chemotherapies in patients with low-grade serous carcinomas of the ovary, fallopian tube, or primary peritoneum. The study enrollment was discontinued after the planned interim analysis showed that the hazard ratio for PFS crossed the predefined futility boundary. As of the cutoff date of 20 January 2016 for the primary analysis, a total of 303 patients (201 binimetinib and 102 physician's choice) were randomized to treatment. The Safety Set included all patients who were enrolled in the study and received any dose of study drug (binimetinib or physician's choice therapy), and was comprised of 200 patients in the binimetinib arm and 94 patients in the physician's choice arm. The most frequently reported AEs (≥ 20% of all patients) in the binimetinib arm, regardless of relationship to study drug, by PT, included diarrhea (70%), nausea (55%), vomiting (54%), blood CK increased (50%), fatigue (48%), peripheral edema (46%), acneiform dermatitis (46%), abdominal pain (32%), ejection fraction decreased (28%), dry skin (28%), constipation (26%), alopecia (25%), stomatitis (23%), decreased appetite (22%), rash maculo-papular (22%), pruritus (20%), and vision blurred (20%). The rate of Grade 3 or higher AEs in the binimetinib arm was 76%, with blood CK increased accounting for a large percentage of these AEs. AEs with Grade 3 or higher severity reported for ≥ 10% of patients included blood CK increased (26%), hypertension (10%), and vomiting (10%).

Adverse events that led to permanent discontinuation of study drug occurred in 31% of patients in the binimetinib arm. Adverse events leading to binimetinib discontinuation in at least 5 patients were ejection fraction decreased (4%), vomiting (3%), intestinal obstruction and RVO (2% each).

Gastrointestinal obstruction events (intestinal obstruction, large intestinal obstruction, small intestinal obstruction, colonic obstruction, and gastrointestinal obstruction) were reported at a higher incidence in the binimetinib group (26 patients [13%]) versus the physician's choice group (7 patients [7%]); most of these events resolved with conservative supportive care. This

observed difference with binimetinib treatment was not seen in melanoma and may be related to underlying risk factors present in ovarian cancers with extensive intraperitoneal involvement such as peritoneal carcinomatosis, prior abdomino-pelvic surgery, or a history of abdominal adhesions. The majority of gastrointestinal obstruction events did not result in gastrointestinal perforation, and although events of obstruction and perforation have been seen in other trials of binimetinib, association with binimetinib treatment seems to be confined to this particular clinical setting. In the CRC expansion of a Phase 1 study, bowel obstruction (small bowel obstruction) was seen in 2 out of 46 (4.3%) patients.

Safety Conclusions

The overall safety profile of binimetinib is consistent with the known safety profile of other drugs in this class. In general, AEs can be managed with interruption, dose modification and occasionally require discontinuation of binimetinib in conjunction with established medical interventions.

2.3 Rationale for the Study

2.3.1 Study Design

Recent preclinical studies have shown that the use of a MEK1/2 inhibitor can increase the number of CD8+ T cells within tumors, in addition to increasing MHC class I expression (Ebert et al. 2016; Mimura et al. 2014). By combining MEK inhibition with anti-PD-L1 antibodies, there is documented evidence of remarkable tumor regression even where either agent alone was only modestly effective. Further studies have been conducted in a clinical setting with the combination of cobimetinib (MEK1/2 inhibitor) and atezolizumab (anti-PD-L1 antibody) in metastatic treatment refractory tumors (preliminary results were presented at the 2016 American Society of Clinical Oncology [ASCO] meeting; Bendell et al. 2016). A response rate of 17% was identified in largely *KRAS*-mutant MSS CRCs. Many of these responses were shown to be durable indicating great promise for the combination of MEK1/2 inhibition with immune targeted agents, even in the MSS setting.

Nivolumab is a fully human monoclonal IgG4 antibody that binds to the PD-1 cell surface membrane receptor, a negative regulatory molecule expressed by activated T and B lymphocytes. Blockade of the PD-1 pathway by nivolumab was studied using the mixed lymphocyte reaction (MLR). PD-1 blockade resulted in a reproducible enhancement of both proliferation and interferon release in the MLR. The effect of nivolumab on antigen-specific recall response was investigated using a cytomegalovirus-restimulation assay with human peripheral blood mononuclear cells (PBMCs), and was evaluated by enzyme-linked immunosorbent assay (ELISA). Nivolumab 3 mg/kg monotherapy is currently approved for the treatment of advanced

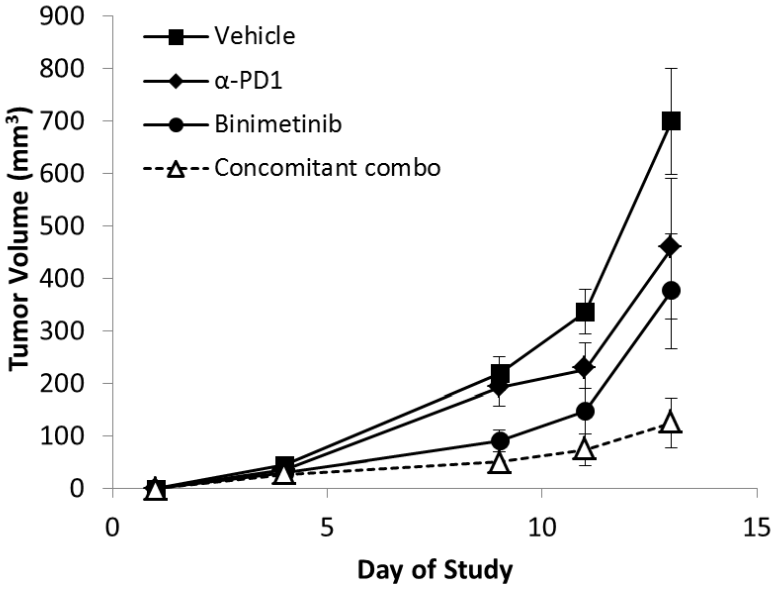
melanoma and lung cancer, metastatic renal carcinoma, and Hodgkin lymphoma, and is being studied in several Phase 3 and 2 clinical trials in advanced and metastatic solid and hematologic malignancies.

Ipilimumab is a fully humanized IgG1 mAb binding to CTLA-4. Ipilimumab is an approved therapy for metastatic melanoma and has demonstrated improved OS as monotherapy and in combination with dacarbazine (Hodi et al. 2010; Robert et al. 2011). It has been studied in combination with multiple standards of care therapies including chemotherapy for squamous and non-squamous non-small cell lung cancer (NSCLC) and radiotherapy for hormone-resistant prostate cancer (ipilimumab IB v.11). Ipilimumab is currently also approved as adjuvant therapy in Stage 3 melanoma.

Nonclinical studies have shown that MEK inhibition increases tumor responsiveness to immunotherapy through multiple mechanisms including: increasing the number of active immune cells (e.g., CD8+ cells) in the tumor by inhibition of activation induced cell death, reducing the expression of immune suppressive factors in the tumor microenvironment factors and increasing the expression of human leukocyte antigen (HLA)-class I molecules (Ebert et al 2016; Liu et al, 2015).

For example, in the syngeneic CT26 colorectal allograft tumor model, combining binimetinib with an anti-PD1 antibody resulted in enhanced tumor growth inhibition relative to treatment with either drug as a single agent (Figure 1).

Figure 1: Binimetinib Enhances αPD-1 Anti-Tumor Activity in Immunocompetent CRC Model



In light of the nonclinical data and the increased clinical efficacy observed with combination approaches in other tumor types, adding binimetinib may potentially offer patients the benefit of treatment for mCRC, and may have specific benefit in the population with *RAS*-mutant tumors.

2.3.1.1 Rationale for the Doublet Combination (Nivolumab and a MEK Inhibitor)

Combined PD-1 Blockade and MEK Inhibition

To build on the hypothesis that a combined immunotherapy approach will be necessary to significantly impact MSS mCRC, a MEK inhibitor will be combined with nivolumab in Arm 1A and combined with nivolumab and ipilimumab in Arm 1B.

While MSI-H tumors have significant levels of immune cell infiltration (Ohrling et al. 2010), lesions from MSS mCRC patients generally have fewer infiltrative CD8+ T-cell populations (Chirica et al. 2015). Immuno-oncologic approaches with checkpoint inhibition alone might not be sufficient in patients who have limited tumor immune cell infiltration. In the fraction of patients whose tumors are resistant to anti-PD-L1 mAb therapy, CD8+ T cells localize at the edge of the tumors, whereas they accumulate in the tumor mass in patients who respond to PD-L1 blockade, suggesting that, in addition to PD-L1 inhibition, strategies aimed at promoting T cell accumulation in the tumor mass are essential for the induction of therapeutic immunity (Salmon et al. 2016).

The mitogen activated protein (MAP) kinase (MAPK) pathway is one of the most frequently disregulated pathways in cancer. The signaling molecule MEK is a key intermediate in the MAPK pathway. Two MEK isoforms (MEK1 and MEK2) are known, both of which phosphorylate ERK1 and/or ERK2 downstream of *RAS* and *BRAF*. MEK has been well characterized as a critical mediator of the constitutively active mutant form of *KRAS*, KRASG12D, in many cancers (Ebert et al. 2016). The MEK pathway is presumed to be upregulated in a large fraction of colorectal tumors due to mutation of several components of the pathway, most notably *KRAS*, *NRAS*, *HRAS*, and *BRAF*. In addition to *RAS* and *RAF* mutations, many tumors are activated by amplification or overexpression of upstream pathway components (Hoeflich et al. 2012). Importantly, there is likely a role of the activated MAPK pathway in immune evasion by tumors (see Section 2.1.2).

Early experience with MEK-inhibition in mCRC demonstrated no single-agent activity for this class of agents (Rinehart et al. 2004). However, MEK inhibitors have been combined preclinically with anti-PD-1 and anti-CTLA-4 agents to provide additional efficacy in mouse models (Liu et al. 2015). Using melanoma cell lines, the MEK inhibitor trametinib increased expression of HLA-I and/or II expression in 5 of 6 lines tested, and a similar effect was found in an in vivo mouse model which demonstrated that the combination of trametinib with anti–PD-1 increased tumor-infiltrating CD8+ T cells in CT26 tumors and potentiated antitumor activity with PD-1 blockade (Sorich et al. 2014; Brahmer et al. 2010). MEK inhibition alone in immunocompetent mice harboring a colon carcinoma cell line with mutant KRASG12D who were treated with the MEK inhibitor G-38963 (which is similar to cobimetinib) can result in intratumoral CD8+T cells accumulation and class I MHC upregulation (Ebert et al. 2016). These increased up to 4-fold among several mouse and human tumor cell lines as determined by flow cytometry. In further experiments in preclinical models, MEK inhibition synergized with anti-PD-1 to promote durable tumor regression while promoting the effector phenotype and longevity of tumor-infiltrating CD8+ T cells (Ebert et al. 2016; Ohrling et al. 2010).

2.3.1.2 Rationale for the Triple Combination in Arms 1B and 2B: Binimetinib with Nivolumab and Ipilimumab

Promising preclinical data combining MEK inhibition with PD-1 and/or CTLA-4 blockade have been published by Liu et al., (2015) and Ebert et al., (2016). Particularly in Ebert et al., it was found that a syngeneic mouse model of colon cancer treated with a MEK inhibitor and either an anti-CTLA-4 or anti-PD-1 antibody showed substantial tumor regression after 3 weeks of exposure, and also demonstrated that CTLA-4 blockade is as effective as PD-1 blockade in this model.

In clinical studies, the additive activity of ipilimumab over nivolumab single-agent has been shown in both MSI-H and MSS treatment-refractory mCRC patients. Among 77 patients with MSI-H mCRC (Overman et al. 2016), the response rate for PD-1 blockade alone was 26%, yet was 33% when PD-1 and CTLA-4 blockade were combined. Moreover, among those with MSS disease, the response rate for PD-1 blockade alone was 0%, but was 5% when PD-1 and CTLA-4 blockade were combined.

In addition to colorectal studies, cumulative data from other cancer types suggest nivolumab in combination with ipilimumab is more efficacious than single agent immunotherapy treatment. Although the minimum follow-up period of 28 months has not been reached, landmark results from the Checkmate-067 Phase 3 trial among advanced treatment-naïve melanoma patients treated with the combination of nivolumab and ipilimumab shows 2-year OS of 64% versus 59% or 45% for patients assigned to either nivolumab or ipilimumab monotherapy, respectively (Larkin et al. 2017). This finding highlights the distinct advantage of combination immune blockade treatment. Preclinical data from Figure 1 as well as studies outlined above which show clear effects on immune cell infiltration and major histocompatibility complex (MHC) upregulation following MEK inhibition, present a compelling argument for exploring the treatment of MEK inhibition of binimetinib in combination with anti-PD-1 (nivolumab) and CTLA-4 (ipilimumab) checkpoint blockade.

2.3.2 Rationale for Dose Selection

2.3.2.1 Rationale for Nivolumab Doses

Nivolumab monotherapy has been extensively studied in multiple tumor types, including melanoma, NSCLC, renal cell carcinoma (RCC), classical Hodgkin's lymphoma (cHL), head and neck (H&N) and urothelial carcinoma (UC), using body weight normalized dosing (mg/kg), and has been safely administered at doses up to 10 mg/kg every 2 weeks (Q2W). Nivolumab is currently approved for the treatment of various tumors, including melanoma, NSCLC, RCC, cHL, squamous cell carcinoma of the head and neck (SCCHN), and UC, using a regimen of either nivolumab 240 mg Q2W or nivolumab 3 mg/kg Q2W.

The nivolumab dose of 480 mg Q4W was selected for this study based on clinical data and modeling and simulation approaches using population PK (PPK) and exposure-response (ER) analyses examining relationships between nivolumab exposures and efficacy (e.g. OS, ORR) and safety responses, using data from studies in multiple tumor types (melanoma, NSCLC, and RCC) with body weight-normalized dosing (mg/kg). The PPK analyses have shown that exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered Q2W, and no clinically meaningful differences in PK across ethnicities and tumor types were

observed. Nivolumab clearance and volume of distribution were found to increase as body weight increases but less than proportionally with increasing weight, indicating that milligram-per-kilogram dosing represents an over-adjustment for the effect of body weight on nivolumab PK.

Using the PPK and ER models, nivolumab exposures and probabilities of efficacy responses and risks of AEs were predicted following nivolumab 480 mg Q4W and compared to those following nivolumab 3 mg/kg Q2W. The overall distributions of average nivolumab steady-state exposures (C_{avgss}) are comparable following administration with either nivolumab 480 mg Q4W or nivolumab 3 mg/kg Q2W. Nivolumab 480 mg Q4W is predicted to result in approximately 43% greater steady-state peak concentrations (C_{maxss}) compared to nivolumab 3 mg/kg Q2W. Although the C_{maxss} of nivolumab is expected to be greater following nivolumab 480 mg Q4W compared to nivolumab 3 mg/kg Q2W, the predicted C_{maxss} following nivolumab 480 mg Q4W is well below the median C_{maxss} achieved following administration of nivolumab 10 mg/kg Q2W, a safe and tolerable dose level.

Exposure-safety analysis demonstrated that the exposure margins for safety are maintained following nivolumab 480 mg Q4W, and the predicted risks of AEs leading to discontinuation or death, AEs ≥ Grade 3, and immune-related AEs ≥ Grade 2, are predicted to be similar following nivolumab 480 mg Q4W relative to nivolumab 3 mg/kg Q2W across tumor types. Safety analyses using available data following nivolumab 3 mg/kg Q2W and 10 mg/kg Q2W administration indicated there were no differences in AE profiles across body weight groups. Finally, initial evidence indicates that the nivolumab 480 mg Q4W schedule is well tolerated.

Nivolumab 480 mg Q4W is predicted to have approximately 16% lower steady-state trough concentrations (C_{minss}) compared to nivolumab 3 mg/kg Q2W. While these exposures are predicted to be lower, they are on the flat part of the exposure-response curves and are not predicted to affect efficacy (Wang et al 2017). Exposure-efficacy analyses of multiple PK measures and efficacy endpoints (e.g. OS, ORR) indicated that following administration of nivolumab 480 mg Q4W efficacy is predicted to be similar to that following administration of nivolumab 3 mg/kg Q2W across multiple tumor types. Based on these data, nivolumab 480 mg Q4W is expected to have similar efficacy and safety profiles to nivolumab 240 mg Q2W or nivolumab 3 mg/kg Q2W.

2.3.2.2 Rationale for Binimetinib Doses up to 45 mg BID

In a Phase 1 dose escalation study, 60 mg twice daily (BID) was initially declared the maximum tolerated dose (MTD) for binimetinib. Following completion of the dose-escalation phase, 74 patients were enrolled in an expansion phase, including 31 patients in a *KRAS*-mutant CRC

cohort, 15 patients in a *BRAF*-mutant CRC cohort and 28 patients in a biliary cancer cohort. After initiation of the expansion phase, AEs resulting in reduction of binimetinib dose were reported at a 3-fold higher incidence in patients in the 60 mg BID dose group compared with the 45 mg BID dose group; thus, 45 mg BID was determined to be the recommended Phase 2 dose (RP2D).

Nonclinical data with MEK inhibitors support a continuous dosing schedule to consistently inhibit MEK activation. The in vivo EC_{50} for MEK inhibition based on inhibition of phospho-ERK, a downstream marker of MEK activity, is ~60 ng/mL. Prediction of mean plasma concentrations vs time using a cross-study human PPK model for binimetinib indicate that the 45 mg BID dosing regimen should result in ≥ 50% inhibition of MEK activity (IC_{50})at steady state for the majority of human patients. This amount of target engagement is consistent with nonclinical models of efficacy and expectations for clinical activity.

Doses less than 45 mg BID are expected to result in fewer patients maintaining plasma concentrations above the MEK IC_{50}, potentially resulting in less efficacy. This expectation is consistent with observed exposure response analysis results.

Analyses exploring the relationship between exposure and efficacy in a Phase 3 Study in unresectable metastatic melanoma in which binimetinib was administered at 45 mg BID, showed that efficacy was observed across the range of observed exposures with a trend towards greater efficacy both in terms of PFS and ORR with higher exposures. This supports the conclusion that binimetinib 45 mg BID maximizes the potential for benefit while providing a tolerated starting dose.

2.3.2.3 Rationale for Ipilimumab Dosing Schedule

In a Phase 1b trial evaluating the safety and tolerability of nivolumab in patients with chemotherapy-naïve advanced NSCLC (Study NCT01454102; Hellman et al. 2016), ipilimumab 1 mg/kg using Q6W and Q12W schedules were assessed and were found to be safe in combination with nivolumab 3 mg/kg Q2W. Both the Q6W and Q12W arms were associated with improved and manageable tolerability compared to the arms with more frequent ipilimumab dosing (Q3W). Both arms also had encouraging efficacy in all participants and enhanced benefit in participants with PD-L1 expression, with Q6W arm having numerically higher median PFS compared to the Q12W arm. There were some imbalances observed between the Q6W and Q12W arms, as follows:

- There were more never smokers in the Q6W arm than in the Q12W arm. Current and former smokers have been shown to respond better to immunotherapy.

- Participants on the Q6W schedule progressed, died or came off treatment more frequently in the first 3 months; however, this did not appear to be related to the schedule.
    - Overall treatment-related AEs leading to discontinuation as rates were 11% and 13% in the Q12W and Q6W arm, respectively. While there were more AEs leading to discontinuation in the first 3 months in the Q6W arm (n=3) vs the Q12W arm (n=1), 2 of the 3 participants who discontinued < 3 months on Q6W discontinued before receiving the 2nd dose of ipilimumab; therefore, these discontinuations are unlikely to be due to the more frequent dosing on the Q6W arm.
    - There were early clinical progressors and (unrelated) deaths in the Q6W arm compared to the Q12W arm (8% and 15%), which were more likely due to imbalances in baseline characteristics, rather than differences in treatment schedule.

With both schedules showing a similar safety and efficacy profile, the Q8W schedule was chosen for this trial for scheduling purposes as Q8W works well with nivolumab and binimetinib dosing schedules.

2.3.2.4 Rationale for the Doses of Nivolumab and Ipilimumab in Combination

Study NCT01454102: Non-Small Cell Lung Cancer

In a multi-arm Phase 1b trial evaluating the safety and tolerability of nivolumab in patients with chemotherapy-naïve advanced NSCLC, nivolumab was adminstered as either a monotherapy or in combination with other agents, including ipilimumab, at different doses and schedules (Hellman et al. 2016). The primary endpoint of the study was safety with secondary endpoints of ORR and 24-week PFS. Exploratory endpoints included OS and efficacy by PD-L1 expression. In the study, patients were tested for PD-L1 expression and 68% of participants in the Q12W cohort and 77% of patients in the Q6W cohort expressed PD-L1. Participants were randomized to nivolumab 3 mg/kg (N3) Q2W + ipilimumab 1 mg/kg (I1) Q12W (n=38), nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W (n=39) and nivolumab 3 mg/kg Q2W (n=52). The confirmed ORR was 47% (N3 Q2W + I1 Q12W), 39% (N3 Q2W + I1 Q6W) and 23% (N3 Q2W). The median duration of response (DOR) was not reached (Hellman et al. 2016).

The rate of treatment-related AEs in the Q12W (82%) and Q6W (72%) arms were comparable to monotherapy (72%). In the study, Grade 3/4 AEs were 37%, 33%, and 19% for the Q12W, Q6W and nivolumab monotherapy arms, respectively. Treatment-related Grade 3-4 AEs lead to discontinuation in 5% and 8% of patients in the Q12W and Q6W cohorts, respectively and were similar to nivolumab monotherapy. There were no treatment-related deaths. The treatment-related select AEs in patients administered the optimized dosing scheduled (3 mg/kg of nivolumab Q2W plus 1 mg/kg of ipilimumab Q6W) were skin related (36%), gastrointestinal

(23%), endocrine (20%), and pulmonary (5%), and there were ≤ 5% treatment-related Grade 3/4 AEs per category.

Study NCT01472081: Metastatic Renal Cell Cancer

The combination of nivolumab with ipilimumab at different doses and schedules was evaluated in another Phase 1, dose-finding trial (Study NCT01472081). Patients with mRCC (favorable/intermediate Memorial Sloan Kettering Cancer Center score; Karnofsky performance status ≥ 80%; untreated or any number of prior therapies) were randomized to receive nivolumab 3 mg/kg + ipilimumab 1 mg/kg (arm N3 + I1) or nivolumab 1 mg/kg + ipilimumab 3 mg/kg (arm N1 + I3) Q3W for 4 doses then nivolumab 3 mg/kg Q2W until progression/toxicity. The primary objective was to assess safety/tolerability; secondary objective was to assess antitumor activity. Patients were randomized to N3 + I1 (n = 21) and N1 + I3 (n = 23). Most patients (n = 34; 77%) had prior systemic therapy (N3 + I1: 16; N1 + I3: 18). The confirmed ORR was 43% (N3 + I1) and 48% (N1 + I3). Duration of response (DOR) was 4.1+ to 42.1+ weeks (7 of 9 responses ongoing) in N3 + I1, and 12.1+ to 35.1+ weeks (9 of 11 responses ongoing) in N1 + I3. Best response of stable disease (SD) was seen in 5 (24%) patients (N3 + I1) and 8 (35%) patients (N1 + I3). Median PFS was 36.6 weeks (N3 + I1) and 38.3 weeks (N1 + I3); these data are still immature, with 11 of 21 events reported for N3 + I1 and 10 of 23 events reported for N1 + I3.

Treatment-related AEs were seen in 83/94 patients (88%), including 39/47 (83%) in N3 + I1 and 44/47 (94%) in N1 + I3. The most frequently reported drug-related AEs in patients treated with 3 mg/kg nivolumab + 1 mg/kg ipilimumab included fatigue (23 patients, 48.9%), rash and pruritus (12 subjects, 25.5% each), and diarrhea and nausea (11 patients, 23.4% each); the majority were Grade 1-2. The most frequently reported drug-related AEs in patients treated with 1 mg/kg nivolumab + 3 mg/kg ipilimumab included fatigue (30 patients, 63.8%); nausea and diarrhea (20 patients, 42.6% each), and lipase increased (16 patients, 34.0%). The majority were Grade 1-2 (Nivolumab IB version 15, June 2016).

Treatment-related AEs leading to discontinuation (21% vs 11%), and treatment-related SAEs (34% vs 21%) all occurred more commonly in subjects in the N1 + I3 arm than in the N3 + I1 arm, respectively (Nivolumab IB version 15, June 2016).

Study NCT01024231: Unrectable or Metastatic Melanoma

In a Phase 1 study in patients with unresectable or metastatic melanoma, ascending doses of nivolumab have been studied concomitantly with ascending doses of ipilimumab (Study NCT01024231). In each arm of this multi-arm study, ipilimumab was administered Q3W for 4 doses with nivolumab administered Q3W for 8 doses. Starting at Week 24, ipilimumab and

nivolumab were administered Q12W for 8 doses. The 3 initial dose-escalation cohorts consisted of Cohort 1 (nivolumab 0.3 mg/kg plus ipilimumab 3 mg/kg; n=14), Cohort 2 (nivolumab 1.0 mg/kg plus ipilimumab 3 mg/kg; n=17) and Cohort 3 (nivolumab 3.0 mg/kg plus ipilimumab 3 mg/kg; n=6). Later, the study was amended to include Cohort 2a which evaluated nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (n=16).

As of the 15 February 2013 data cut-off, of the 52 patients evaluable for response, 21 patients (40%) had an objective response by modified World Health Organization (mWHO) criteria. In Cohort 1 (0.1 mg/kg nivolumab + 3 mg/kg ipilimumab), 3 out of 14 evaluable patients had an objective response by mWHO (21%); 1 complete response (CR) and 2 partial responses (PRs) with an additional PR by immune-related mWHO criteria (irPR) (Wolchok et al. 2009). In Cohort 2 (1 mg/kg nivolumab + 3 mg/kg ipilimumab), 9 out of 17 evaluable patients had an objective response by mWHO (53%; 3 CRs, 18%), 6 PRs (35%) with 2 additional patients experiencing immune-related SD (irSD). In Cohort 2a (3 mg/kg nivolumab + 1 mg/kg ipilimumab), 6 out of 15 response evaluable patients had an objective response rate by mWHO (40%; 1 CR, 7%), 5 PRs, 33%) and 2 irSDs and 1 irPR. In Cohort 3 (3 mg/kg nivolumab + 3 mg/kg ipilimumab), 3 out of 6 evaluable patients had an objective response by mWHO (50%; 3 PRs with 1 additional irPR and 1 irSD.

Preliminary analysis revealed 16 of the 52 evaluable patients (31%) had > 80% reduction in the size of target tumor lesions by the Week 12 evaluation. This is compared to < 2% for 3 mg/kg ipilimumab monotherapy based on a Phase 3 study in patients with previously treated, unresectable or metastatic melanoma (N=540; Study NCT00094653), and < 3% for nivolumab monotherapy based on a Phase 1 study in patients with various advanced or recurrent metastatic cancers (N=94, 0.1-10 mg/kg; Study NCT00730639).

The following dose-limiting toxicities (DLTs) were observed: Cohort 1 - Grade 3 elevated AST/ALT (1 patient); Cohort 2 - Grade 3 uveitis (1 patient) and Grade 3 elevated AST/ALT (1 patient); Cohort 3 - Grade 4 elevated lipase (2 patients) and Grade 3 elevated lipase (1 patient). Based on these data, Cohort 2 was identified as the MTD and Cohort 3 exceeded the MTD.

A total of 53 melanoma patients were treated with nivolumab combined with ipilimumab across Cohorts 1, 2, 2a, and 3. At least one AE regardless of causality has been reported in 98% of patients treated. The most common (reported at > 10% incidence) treatment-related AEs (any Grade %; Grade 3-4 %: 93; 53) are rash (55; 4), pruritus (47; 0), vitiligo (11; 0), fatigue (38; 0), pyrexia (21, 0), diarrhea (34; 6), nausea (21, 0), vomiting (11, 2), ALT increased (21; 11), AST

increased (21; 13), lipase increased (19; 13), amylase increased (15, 6), headache (11, 0), and cough (13, 0).

The majority of AEs leading to discontinuation (regardless of causality) were Grade 3 or 4 (reported in 11 of 53 patients, 21%). Grade 3 events included lipase increased, ALT increased, AST increased, troponin I increased, colitis, diverticular perforation, pancreatitis, tachycardia, renal failure acute, choroiditis, autoimmune disorder, and pneumonitis. One patient each discontinued due to Grade 4 events of blood creatinine increased and AST increased. No drug-related deaths were reported (Wolchok et al. 2013).

2.3.2.5 Rationale for Infusion Times for Nivolumab and Ipilimumab

Long infusion times place a burden on patients and treatment centers. Establishing that nivolumab and ipilimumab can be safely administered using shorter infusion times will diminish the burden, provided that there is no change in the safety profile. Previous clinical studies of nivolumab and ipilimumab monotherapies and the combination of nivolumab and ipilimumab have used a 60-minute infusion duration for nivolumab and a 90-minute infusion duration for ipilimumab (1 - 3 mg/kg dosing for both). However, both nivolumab and ipilimumab have been administered at up to 10 mg/kg with the same infusion duration (i.e. 60 minutes).

Establishing that nivolumab can be safely administered using a shorter infusion time (30 minutes) is under investigation. Previous clinical studies of nivolumab monotherapy have used a 60-minute infusion duration wherein nivolumab has been safely administered up to 10 mg/kg over long treatment periods. Infusion reactions including high-grade hypersensitivity reactions have been uncommon across nivolumab clinical program. In a Phase 2 dose-ranging study of nivolumab in patients with advanced or metastatic clear-cell RCC, a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg and 18.5% at 10 mg/kg) (Martín-Algarra et al. 2016). All the events were Grade 1 - 2 and were manageable. An infusion duration of 30 minutes for 3 mg/kg nivolumab (30% of the dose provided at 10 mg/kg) is not expected to present any safety concerns compared to the prior experience at 10 mg/kg nivolumab dose infused over a 60-minute duration. The safety of nivolumab 3 mg/kg administered as a 30-minute infusion was assessed in a Phase 3 study in patients (n=322) with previously treated, advanced NSCLC (Study NCT02066636). Overall, there were no clinically meaningful differences in the frequency of hypersensitivity/infusion-related reactions (of any cause or treatment-related) in patients administered nivolumab over a 30-minute infusion compared with that reported for patients with the 60-minute infusion. Also, as discussed in Section 2.3.2.1, the C_{maxss} for nivolumab 480 mg Q4W, even when infused over 30 minutes instead of 60 minutes, is expected to be well below

the median C_{maxss} achieved following administration of nivolumab 10 mg/kg Q2W, a safe and tolerable dose level. Thus, it is expected that nivolumab can be safely infused over 30 minutes.

Similarly, ipilimumab at 10 mg/kg has been safely administered over 90 minutes. In a Phase 2 study in patients with advanced Stage 2 or Stage 4 melanoma where ipilimumab was administered up to a dose of 10 mg/kg, on-study drug related hypersensitivity events (Grade 1/2) were reported in 1 patient (1.4%) in the 0.3 mg/kg and in 2 patients (2.8%) in the 10 mg/kg group (Study NCT00289640). There were no drug-related hypersensitivity events reported in the 3 mg/kg group. Across the 3 treatment groups, no Grade 3/4 drug-related hypersensitivity events were reported and there were no reports of infusion reactions. Ipilimumab 10 mg/kg monotherapy has also been safely administered as a 90-minute infusion in a large Phase 3 study in patients with prostate cancer (Study NCT00861614) and as adjuvant therapy for patients with Stage 3 melanoma (Study NCT00636168). A retrospective analysis of 138 patients treated with 10 mg/kg of ipilimumab monotherapy as a 90-minute infusion determined that few (6/138; 4.3%) patients experienced infusion reactions (Momtaz et al. 2015). As part of this study, 120 patients were treated prospectively with 3 mg/kg ipilimumab infused over 30 minutes, i.e., approximately one-third of the 10 mg/kg dose, and 7 patients (5.8%) had an infusion-related reaction; it was concluded that 3 mg/kg ipilimumab can be infused safely over 30 minutes with an acceptably low incidence of infusion-related reactions.

Overall, infusion reactions, including high-grade hypersensitivity reactions, have been uncommon across clinical studies of nivolumab, ipilimumab, and nivolumab/ipilimumab in combination. Furthermore, a 30-minute break after the first infusion for the combination cohort will ensure the appropriate safety monitoring before the start of the second infusion. Overall, a change in safety profile is not anticipated with 30-minute infusions of either nivolumab or ipilimumab.

2.3.2.6 Rationale for Duration of Therapy

The optimal duration of immunotherapy is currently unknown. However, because immunotherapy engages the immune system to control the tumor, continuous treatment as is required with targeted agents or cytotoxic therapy may not be necessary.

Accumulating evidence from different clinical trials in different tumor types with nivolumab or nivolumab combined to ipilimumab indicates that most of the responses are generally occurring early, with a median time to response of 2-4 months (Brahmer et al. 2015; Borghaei et al. 2015). A recent analysis in a melanoma study suggests the majority of patients who discontinue nivolumab and/or ipilimumab for toxicity maintain disease control in the absence of further treatment (Schadendorf et al. 2016).

For these reasons, in this current study, treatment with nivolumab or nivolumab with ipilimumab will be given for up to 24 months in the absence of disease progression or unacceptable toxicity. Patients who complete 24 months of treatment and have subsequent disease progression may reinitiate nivolumab or nivolumab with ipilimumab at the same dose and schedule given previously on study and continue such treatment for up to 1 additional year.

2.3.3 Risks for Overall Safety of Combination Therapy

The safety profile of each agent proposed for the triplet combination is well defined. Nivolumab and ipilimumab are already commercially available for the treatment of several advanced and metastatic tumor types. The safety and efficacy of binimetinib has been evaluated as a single agent and in combination. As of 20 January 2016, a total of 2555 healthy subjects and patients have received at least 1 dose of binimetinib and are therefore eligible for inclusion in the overall safety population of binimetinib, which comprises 220 healthy subjects, 164 patients with rheumatoid arthritis, 12 patients with hepatic dysfunction and 2159 patients with advanced cancer.

With regards to the effect of MEK inhibition on T-cell mediated responses, nonclinical studies have shown that inhibition of MEK in the setting of cancer leads to enhancement of the immune response. This immune-mediated activity of MEK inhibitors is due to a positive effect on tumor antigen-specific T-cells maintaining their activation state (preventing exhaustion-induced T-cell death) leading to synergy with checkpoint inhibitors (Ebert et al 2016). Thus, MEK inhibition enhances the activity of tumor antigen-primed t-cells (post-naïve t-cells) without adversely effecting naïve T-cell priming. Based on the latter biological effects, the potential for augmented toxicity related to immune activation is unlikely.

For the combination of nivolumab with ipilimumab, related AEs of Grade 3-4 severity have been limited to toxicities in gastrointestinal, skin, liver, and endocrine system expected based on the mechanism of action of both compounds. It has been observed in a several previous trials that the toxicity of the nivolumab + ipilimumab combination correlated with the ipilimumab dose (Wolchok et al. 2013; Postow et al. 2015; Reardon et al. 2016; Wolchok et al. 2016). With increasing doses of ipilimumab there has been an increase in frequency of AEs, and potentially the severity of these events; however, no novel toxicities have been demonstrated versus either agent alone. In the proposed regimen for this clinical study, the dose of ipilimumab will be cumulatively lower than on prior cohorts studied in the proposed indication as well as the approved dose level for the combination for the treatment of advanced and metastatic melanoma. The toxicity profile with lower doses of ipilimumab has been established to be very similar to that of nivolumab monotherapy (Hellmann et al. 2016).

The safety of the combination of nivolumab, with binimetinib and ipilimumab has not been established. Based on reported data from the co-administration of an anti-PD-L1 agent (atezolizumab) and a MEK inhibitor (cobimetinib) characterized as well tolerated at full single-agent doses for both agents in a Phase 1 study (Bendell et al. 2016) it is hypothesized that if there were to be an increase in toxicity with the 3-agents administered in combination, it is not expected to be significantly different than that seen in the combination of nivolumab with the higher dose of ipilimumab, which has been tolerable. No new toxicities are anticipated (Bendell et al. 2016); however, overlapping toxicities may occur and may include dermatologic reactions, diarrhea, bowel obstruction, ileus, liver toxicity, pneumonitis/interstitial lung disease (ILD). These can be monitored and managed with appropriate dose modification.

Overall, it is anticipated that these regimens will be well tolerated for this patient population and that the potential toxicities are well understood and can be appropriately monitored and managed.

Please refer to the IB and/or the locally approved prescribing information for nivolumab and ipilimumab for additional guidance and to the current binimetinib Investigator's Brochure (IB).

2.4 Risk-benefit Assessment Summary

The proposed study will be conducted in adult patients with advanced mCRC with MSS and a *RAS* mutation, a clinical setting in which therapy after first line has limited value (Section 2.1).

This trial studies a novel combination of a targeted therapeutic and 2 immunotherapy agents that inhibit two different immune checkpoint targets. In patients with MSS mCRC, the combination of a different MEK inhibitor (cobimetinib) and atezolizumab, a PD-L1 directed antibody, produced a modest 8% ORR but a median OS of 10 months in a heavily pretreated population in which the majority of patients had ≥ 5 prior lines of therapy (Bendell et al. 2018).

The potential for immunotherapy to produce meaningful benefits for patients, particularly those with an intact immune response, is maximized by offering it to patients earlier in their treatment when the immune suppressive effects of prior therapy and of advanced metastatic cancer are less pronounced. Given the limited benefit of SOC options after first-line therapy, it is not unreasonable for an appropriately informed patient to opt to delay these SOC treatment options in favor of participation in a clinical trial. This paradigm of a "window of opportunity" type trial allows for the testing of new treatments in settings where there is an opportunity to properly evaluate their potential value (Glimelius et al. 2011).

Patients participating in the trial will go through an informed consent process and be required to sign an informed consent document. This process will provide patients with information on their treatment options, including all SOC options available to them, and allow them to make a decision in conjunction with their physician with regard to trial participation.

Potential risks of the combination are discussed in Section 2.3.3. The safety profile of each agent proposed for the triplet combination is well defined. The safety and efficacy of binimetinib has been evaluated as a single agent and in combination in over 2500 exposures. Nivolumab and ipilimumab are already commercially available for the treatment of several advanced and metastatic tumor types. It has been observed in several previous trials that the toxicity of the nivolumab + ipilimumab combination correlated with the ipilimumab dose (Wolchok et al. 2013; Postow et al. 2015; Reardon et al. 2016; Wolchok et al. 2016). The toxicity profile with lower doses of ipilimumab, such as those being used in this study, has been established to be very similar to that of nivolumab monotherapy (Hellmann et al. 2016).

The safety of the combination of nivolumab with binimetinib and ipilimumab has not been established. Based on reported Phase 1 data from the co-administration of an anti-PD-L1 agent (atezolizumab) and a MEK inhibitor (cobimetinib) characterized as well tolerated at full single-agent doses for both agents (Bendell et al. 2016), it is hypothesized that if there were to be

an increase in toxicity with the 3 agents administered in combination, it is not expected to be significantly different than that seen in the combination of nivolumab with the higher dose of ipilimumab, which has been tolerable. No new toxicities are expected. Overall, it is anticipated that these regimens will be well tolerated for this patient population and that potential toxicities are well understood and can be appropriately monitored and managed.

Immunotherapy with a checkpoint inhibitor combined with a MEK inhibitor has shown activity in patients with MSS CRC after 5 or more lines of therapy (Bendell et al. 2018). The potential for benefit may be further optimized by allowing appropriately informed patients to enter the study earlier in the course of their disease. The potential for risk is appropriate for patients with advanced malignancy, and the risks associated with early disease progression and toxicity will be closely monitored. The overall assessment of benefit and risk is appropriate for the proposed study population.

3.0 STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Primary Objectives

- Phase 1b:
    - Determine the MTD and RP2D of binimetinib administered in combination with nivolumab
    - Determine the MTD and RP2D of binimetinib administered in combination with nivolumab plus ipilimumab
- Phase 2: Assess the preliminary antitumor activity of the treatment combinations based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1

3.1.2 Secondary Objectives

Both Phases:

- Further assess the preliminary antitumor activity of the treatment combinations based on RECIST version 1.1
- Characterize the safety profile of the treatment combinations
- Characterize the PK of binimetinib in both treatment combinations

3.1.3 Exploratory Objectives

Both Phases:

- Obtain preliminary estimates of PFS and OS

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3.2 Study Endpoints

3.2.1 Primary Endpoints

- Phase 1b:
    - Incidence of dose-limiting toxicities (DLTs) resulting from binimetinib in combination with nivolumab
    - Incidence of DLTs resulting from binimetinib in combination with nivolumab plus ipilimumab
- Phase 2: ORR per RECIST v1.1

3.2.2 Secondary Endpoints

- Phase 1b only: ORR per RECIST v1.1

Both Phases:

- DOR per RECIST v1.1
- Rate of CR per RECIST v1.1
- Incidence and severity of AEs graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03, and changes in clinical laboratory parameters
- Sparse plasma concentrations for binimetinib

3.2.3 Exploratory Endpoints

Both Phases:

- PFS per RECIST v 1.1
- OS

CCI

4.0 STUDY DESIGN

4.1 Study Design Overview

This is a multicenter, open-label Phase 1b/2 study to determine the MTD and RP2D and schedule of binimetinib, and to assess the safety, efficacy and PK of binimetinib administered in combination with nivolumab or nivolumab plus ipilimumab in patients with previously treated MSS mCRC with documented *RAS* mutation. The study will include a dose-finding period in Phase 1b followed by a randomized Phase 2 period (Figure 2).

Phase 1b Dose Determination:

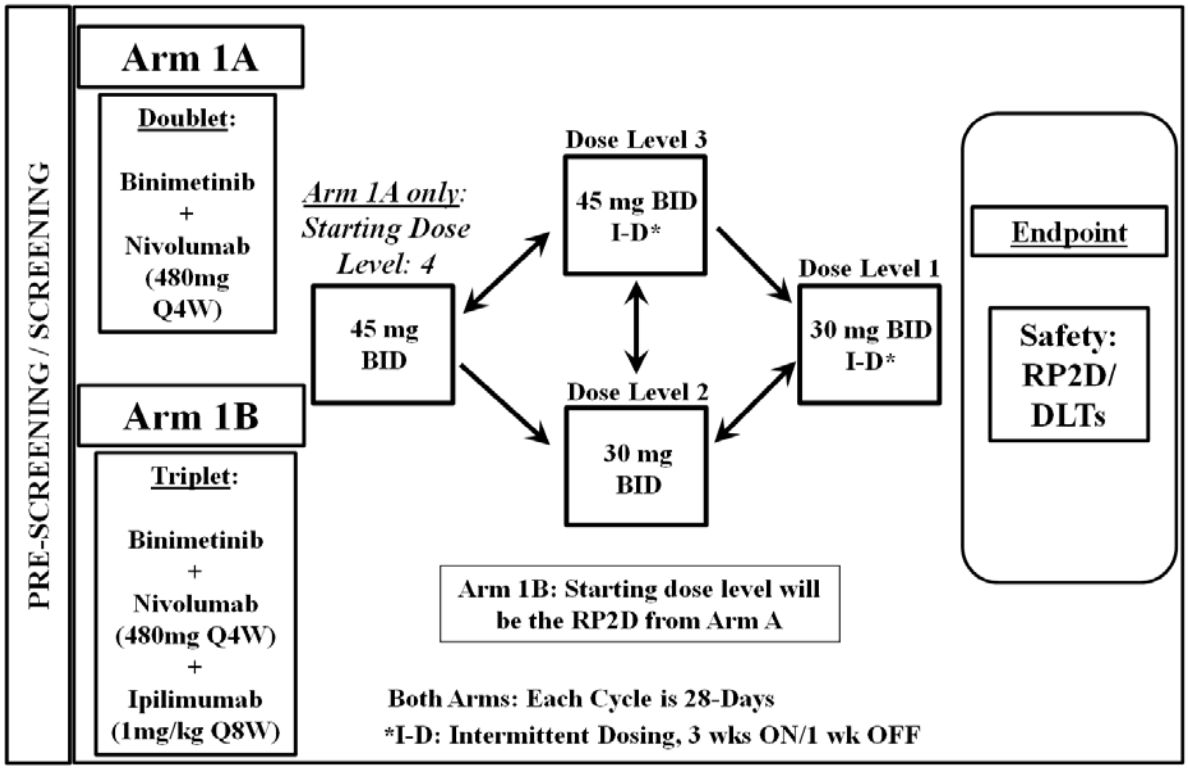
- Arm 1A - Binimetinib plus nivolumab (Doublet): To determine the MTD and RP2D and schedule of binimetinib in combination with nivolumab.
- Arm 1B - Binimetinib with nivolumab plus ipilimumab (Triplet): To determine the MTD and RP2D and schedule of binimetinib in combination with nivolumab + ipilimumab.

Phase 2 Efficacy Assessment:

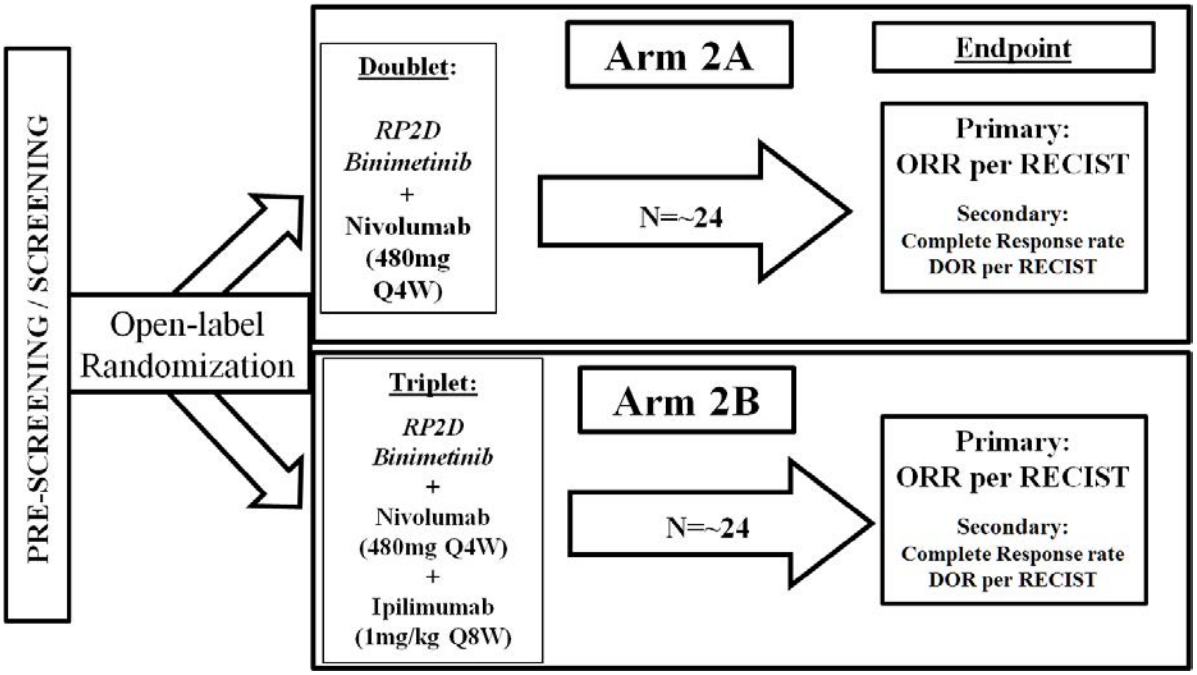
- Arm 2A - Binimetinib plus nivolumab (Doublet): To determine the efficacy of binimetinib in combination with nivolumab.
- Arm 2B - Binimetinib with nivolumab plus ipilimumab (Triplet): To determine the efficacy of binimetinib in combination with nivolumab + ipilimumab

Figure 2: Study Design Scheme for Phase 1b and Phase 2

Phase 1b



Phase 2



One treatment cycle is defined as 28 days (4 weeks) for all arms. Individual treatments will be dosed on the schedules as outlined below.

4.1.1 Phase 1b: Dose-Finding Period and Dose De-Escalation/Escalation

Phase 1b of the study will consist of dose-finding cohorts in Arm 1A and Arm 1B. Enrollment of patients in the dose-finding period and all dose-escalation and de-escalation decisions will be guided by the modified toxicity probability interval (mTPI-2) design (Guo et al. 2017). The mTPI-2 design is a model-based approach that is guided by a prespecified decision matrix that recommends escalating, reducing, or maintaining the same dose or stopping dose escalation based on the number of patients with DLTs observed in the dose level under evaluation (Section 4.1.1.2). Doses of binimetinib, nivolumab, and ipilimumab to be explored in the dose-finding period are presented in Table 2.

There will be a period of at least 7 days between C1D1 of the first patient and C1D1 of the second patient enrolled during Phase 1b (Arms 1A and 1B).

Table 2: Dosing Scheme for Phase 1b

Arm	Dose Level (*Starting Dose Level)	Binimetinib	Nivolumab	Ipilimumab
1A (Doublet)	4*	45 mg BID	480 mg Q4W	N/A
	3	45 mg BID 3W on / 1W off		
	2	30 mg BID		
	1	30 mg BID 3W on / 1W off		
1B (Triplet)[a]	4	45 mg BID	480 mg Q4W	1 mg/kg Q8W
	3	45 mg BID 3W on / 1W off		
	2	30 mg BID		
	1	30 mg BID 3W on / 1W off		

[a] The Starting Dose Level of Arm 1B (Triplet) will be the Recommended Phase 2 Dose (RP2D) of binimetinib from Arm 1A. If tolerated, the RP2D of binimetinib from Arm 1A will be considered the RP2D for Arm 1B. If not tolerated, any dose level below the RP2D for Arm 1B may be explored.

Arm 1A (Doublet):

The first patient enrolled will receive 480 mg nivolumab Q4W in combination with the Starting Dose Level of 45 mg BID binimetinib (Dose Level 4; Table 2). Subsequent patients will receive 480 mg nivolumab Q4W in combination with binimetinib at a dose and schedule that will be determined based on the cumulative toxicities observed in current and prior patients.

For binimetinib only: dose de-escalation and dose escalation will follow the mTPI-2 design (Guo et al. 2017). Dose escalation above 45 mg BID (Dose Level 4) is not permitted, nor is de-escalation below 30 mg BID intermittent schedule (Dose Level 1) permitted.

If 45 mg BID (Dose Level 4) is not tolerated during Cycle 1, dose de-escalation to either 30 mg BID (Dose Level 2) or 45 mg BID intermittent dosing (Dose Level 3) is permitted. Subsequent dose escalation or de-escalation of cohorts may only increase or decrease one dose level at a time, except de-escalation from 45 mg BID intermittent dosing (Dose Level 3) to 30 mg BID intermittent dosing (Dose Level 1), which may be permitted after discussion and upon agreement between the Sponsor's Medical Monitor and the Investigators (Figure 2).

Arm 1B (Triplet):

The first patient enrolled will receive 480 mg nivolumab Q4W with 1 mg/kg ipilimumab Q8W in combination with binimetinib. The binimetinib Starting Dose Level will be assigned once the RP2D from Arm 1A has been determined. Subsequent patients will receive 480 mg nivolumab Q4W with 1 mg/kg ipilimumab Q8W in combination with binimetinib, at a dose and schedule that will be determined based on the cumulative toxicities observed in current and prior patients.

For binimetinib only: dose de-escalation and dose escalation will follow the mTPI-2 design (Guo et al. 2017). Dose escalation above 45 mg BID (Dose Level 4) or above the RP2D determined in Arm 1A (if the RP2D is not 45 mg BID) is not permitted, nor is de-escalation below 30 mg BID intermittent schedule (Dose Level 1) permitted.

The Starting Dose Level of Arm 1B will be the RP2D of binimetinib from Arm 1A. If 45 mg BID (Dose Level 4) is the Starting Dose Level and is not tolerated during Cycle 1, dose de-escalation to either 30 mg BID (Dose Level 2) or 45 mg BID intermittent dosing (Dose Level 3) is permitted. Subsequent dose escalation or de-escalation of cohorts may only increase or decrease one dose level at a time, except de-escalation from 45 mg BID intermittent dosing (Dose Level 3) to 30 mg BID intermittent dosing (Dose Level 1), which may be permitted after discussion and upon agreement between the Sponsor's Medical Monitor and the Investigators (Figure 2).

At each dose level after the first 3 evaluable patients have completed Cycle 1, the Sponsor's Medical Monitor and the Investigators will meet to clinically assess the available data from the dose cohort. The decision to escalate, continue to enroll in the current cohort, or dose de-escalate will be based on available data combined with the recommendations of the mTPI-2 matrix (Table 3). The Sponsor's Medical Monitor and the Investigators will review, at a minimum, all

the available data from Cycle 1 once 3 to 6 evaluable patients in subsequent cohorts have been treated for at least 1 cycle.

Table 3: Guidance for Safety Review based on Observed Toxicity Outcomes

No. of Patients with DLTs	Number of Patients Treated																				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	D	D	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
2	-	D	D	D	D	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E
3	-	-	DU	DU	D	D	D	D	S	S	S	S	E	E	E	E	E	E	E	E	E
4	-	-	-	DU	DU	DU	D	D	D	D	D	S	S	S	S	S	E	E	E	E	E
5	-	-	-	-	DU	DU	DU	DU	DU	D	D	D	D	D	S	S	S	S	S	S	E
6	-	-	-	-	-	DU	DU	DU	DU	DU	DU	D	D	D	D	D	D	S	S	S	S
7	-	-	-	-	-	-	DU	DU	DU	DU	DU	DU	DU	D	D	D	D	D	D	D	S
8	-	-	-	-	-	-	-	DU	DU	DU	DU	DU	DU	DU	DU	DU	D	D	D	D	D
9	-	-	-	-	-	-	-	-	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	D	D
10	-	-	-	-	-	-	-	-	-	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
11	-	-	-	-	-	-	-	-	-	-	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
12	-	-	-	-	-	-	-	-	-	-	-	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
13	-	-	-	-	-	-	-	-	-	-	-	-	DU	DU	DU	DU	DU	DU	DU	DU	DU
14	-	-	-	-	-	-	-	-	-	-	-	-	-	DU	DU	DU	DU	DU	DU	DU	DU
15	-	-	-	-	-	-	-	-	-	-	-	-	-	-	DU	DU	DU	DU	DU	DU	DU
16	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	DU	DU	DU	DU	DU	DU
17	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	DU	DU	DU	DU	DU
18	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	DU	DU	DU	DU
19	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	DU	DU	DU
20	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	DU	DU
21	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	DU

D = De-escalate to the next lower dose; DLT = Dose-limiting toxicity; DU = De-escalate to the next lower dose and the current dose will not be revisited; E = Escalate to the next higher dose; S = Stay at the current dose.

Intra-patient dose escalation will not be permitted.

Note: In both arms, there will be flexibility to evaluate an intermittent dosing schedule of binimetinib (30 or 45 mg BID; e.g., 3 weeks on/1 week off) if continuous dosing is not tolerated depending on the time of onset of DLTs (Section 4.1.1.2). De-escalation may only decrease a maximum of 2 dose levels at a time. A reduction in dose levels from 45 mg BID (Dose Level 4) to 30 mg BID intermittent schedule (Dose Level 1) is not permitted.

The target DLT probability for Cycle 1 is 30%, with an equivalence interval, i.e., an acceptable interval, of 25% to 35%. Dosing in Phase 1b will continue within an arm until 9 patients have been treated at one dose level with a recommendation to stay (or a recommendation to escalate if there is not a higher dose level or if the tolerability of the next dose level is unacceptable), or the maximum sample size within a Phase 1b arm (n=21) has been reached. If further safety evaluations are required, additional patients may be added to a cohort.

If the first 2 patients in a previously untested dose level experience a DLT, the next cohort will be opened at the next lower dose level/schedule or an intermediate dose level. However, if the first 2 patients in a new cohort at a previously tested dose combination/schedule experience a DLT, further enrollment to that cohort will stop and the Sponsor's Medical Monitor and the Investigators will meet to discuss all available data for that dose level/schedule and determine if additional patients may be enrolled in the dose cohort or if a new cohort of patients will be enrolled at a lower dose level.

Toxicities will only be considered DLTs if they occur in Cycle 1 although overall safety including later cycles will be considered for dose escalations and for each RP2D determination.

Patients are required to complete Cycle 1 (≥ 75% of the planned cumulative dose of binimetinib) to be considered evaluable for MTD determination unless discontinuation occurred due to a DLT.

The dose-finding period of the study will evaluate the safety and tolerability of the combinations of nivolumab and binimetinib with or without ipilimumab for 1 cycle (the first 28 days of treatment in Phase 1b).

4.1.1.1 Tolerability Assessment

All dose-escalation and de-escalation decisions will be driven by the mTPI-2 design. For each dose-finding cohort, the tolerability assessment will be based upon occurrence of DLTs (see Section 4.1.1.2) in all patients. An End-of-Cohort meeting scheduled by the Sponsor between the Sponsor's Medical Monitor and the Investigators will occur after the last patient in each cohort

has completed at least 1 treatment cycle (28 days) for careful assessment of AEs before escalating to the next dose. Pending the documented outcome of the meeting, doses will be escalated or de-escalated as agreed by the Sponsor's Medical Monitor and the Investigators.

4.1.1.1.1 Special Considerations for Tolerability Assessment

If the first occurrence of a Grade 3 immune-mediated AE (imAE; see the nivolumab and ipilimumab IBs for further details) is reported in a given cohort outside of Cycle 1, enrollment in that cohort will continue at the same dose until the toxicity is evaluated. If a second Grade 3 imAE is reported or a first Grade 3 imAE is reported in addition to a previous DLT in a given cohort, enrollment of new patients in that cohort will be stopped until the Grade 3 imAE is evaluated. If the event is not a DLT (as determined by the Investigators in consultation with the Sponsor's Medical Monitor), then enrollment may be resumed, or the cohort may be expanded. If the Grade 3 imAE is deemed a DLT, the MTD has been exceeded and additional patients will be enrolled at the previous dose level or at an intermediate dose level.

Patients are required to complete Cycle 1 (≥ 75% of the planned cumulative dose of binimetinib) to be considered evaluable unless discontinuation occurred due to a DLT. Patients will be replaced if they have received less than 75% planned dose intensity ([administered dose in mg/planned dose in mg] x 100) of binimetinib for any reason other than an AE or abnormal laboratory value that is not related to disease, disease progression, intercurrent illness or concomitant medications/therapies before completing Cycle 1.

If an acceptable combination dose cannot be identified, following discussions between the Sponsor's Medical Monitor and the Investigators, the protocol may be amended.

4.1.1.2 Dose-limiting Toxicities

For purposes of tolerability decisions, a DLT is defined as any AE or abnormal laboratory value assessed as unrelated to disease, disease progression, intercurrent illness or concomitant medications/therapies occurring within the first 28 days of treatment that satisfies at least 1 of the criteria listed in Table 4.

Whenever a patient experiences toxicity that fulfills the criteria for a DLT, treatment with the study drug will be interrupted and the toxicity will be followed up.

Table 4: Criteria for Defining Dose-limiting Toxicities

Any of the following will be considered a DLT
• Any AE or laboratory value considered unrelated to underlying disease, disease progression, intercurrent illness or concomitant medications/therapies resulting in the inability to tolerate 75% dose intensity ([administered dose in mg/planned dose in mg] x 100) of binimetinib during Cycle 1
Laboratory/Investigation Abnormalities • Total bilirubin Grade ≥ 3 (>3.0 x ULN) • AST or ALT > 5 - 8 x ULN for > 5 consecutive days • AST or ALT > 8 x ULN • AST or ALT > 3 x ULN with concurrent total bilirubin > 2 x ULN (For patients with abnormal ALT, AST or total bilirubin at baseline, AST or ALT or total bilirubin elevated to ≥ 2 × baseline) without initial findings of cholestasis (elevated serum alkaline phosphatase ≥ 2 × ULN) or other reasons to explain the combination of increased aminotransferases and total bilirubin • Serum creatinine Grade ≥ 3 • CK elevation ≥ Grade 3 associated with an increase in creatinine ≥ 1.5 × the patient's baseline creatinine • ECG QTcF prolonged ≥ Grade 3 (on at least 2 separate ECGs) • Grade 3 or 4 increase in amylase and/or lipase associated with symptoms or clinical manifestations of pancreatitis • Grade 3 troponin associated with any sign of cardiac toxicity (as determined by a cardiac evaluation) • Grade 3 electrolyte abnormality (and Grade 4 hyperglycemia) that lasts > 72 hours, is clinically complicated, or does not resolve spontaneously or respond to conventional medical intervention Note: Isolated laboratory changes (e.g. alkaline phosphatase, cholesterol) or those due to sampling or laboratory errors without associated clinical signs or symptoms may be determined to not be DLTs upon review and agreement upon discretion of the Sponsor and Investigator.
Hematologic abnormalities • ANC Grade 4 for > 7 consecutive days • Platelet count Grade 3 with signs of clinically significant bleeding • Platelet count Grade 4 • Any other hematologic AE ≥ Grade 3 <u>except</u> lymphocyte count decrease (lymphopenia) ≥ Grade 3 unless clinically significant

Any of the following will be considered a DLT
Eye disorders • Retinopathy or retinal detachment Grade ≥ 3, confirmed by ophthalmic examination • Retinal vascular disorder including retinal vein occlusion (RVO), confirmed by ophthalmic examination • Any Grade 2 immune-related uveitis or eye pain or blurred vision or decreased visual acuity that does not improve to Grade 1 despite topical therapy OR requires systemic treatment • Any other eye disorder ≥ Grade 3 for > 21 consecutive days • Any other eye disorder Grade 4 confirmed by ophthalmic examination
Cardiac disorders • Absolute decrease of LVEF > 10% compared to Baseline and the LVEF is below the institution's lower limit of normal (LLN) • Symptomatic left ventricular systolic dysfunction Grade ≥ 3 • Other cardiac disorders Grade ≥ 3
Vascular disorders • Grade 3 hypertension for > 14 consecutive days • Grade 4 hypertension
General disorders, administration site conditions, other or immune system disorders • Grade 3 Fatigue for ≥ 7 consecutive days • Grade 3 Hypersensitivity reaction • Grade 3 Infusion reaction which does not return to ≤ Grade 1 within 6 hours • Grade 3 fever that lasts ≥ 72 hours, or is associated with hemodynamic compromise (including hypotension, or clinical or laboratory evidence of end organ perfusion impairment) • Grade 3 endocrinopathy which is not well-controlled by hormone replacement
Respiratory disorders • Interstitial lung disease/ pneumonitis Grade ≥ 2 • Bronchospasm Grade 3

Any of the following will be considered a DLT
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) • Grade 3 rash that does not improve to Grade 1 within 14 days, limits self-care, or which is associated with infection • Rash, HFSR, or photosensitivity CTCAE Grade 4
Gastrointestinal disorders [a] • Grade 3 Colitis • Grade 3 Diarrhea for ≥ 48 hours despite optimal use of antidiarrheal therapy, results in hospitalization, or does not resolve to Grade 1 spontaneously or with conventional medical intervention • Grade 4 Diarrhea • Nausea or vomiting Grade 3 for ≥ 48 hours despite optimal use of antiemetic therapy • Grade 4 Nausea/vomiting
Neurologic toxicity • Neurologic toxicity Grade 3
Other hematologic and nonhematolic toxicities • Any other Grade≥ 3 AE
NOTE: Tumor flare (defined as pain, irritation, or rash that localizes to site of known or suspected tumor) is NOT a DLT.

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CK = creatine kinase; DLT = dose-limiting toxicities; ECG = electrocardiogram; LLN = lower limit of normal; LVEF = left ventricular ejection fraction; QTcF = QT interval corrected for heart rate using Fridericia's formula; RVO = retinal vein occlusion.

[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.

4.1.2 Phase 2: Randomized Dose Cohorts

Phase 2 of the study will consist of two arms to investigate the safety and clinical activity of the RP2Ds established from Phase 1b, Arm 2A (nivolumab in combination with binimetinib) and Arm 2B (nivolumab plus ipilimumab in combination with binimetinib).

- Arm 2A: Patients randomized to the nivolumab and binimetinib arm will receive nivolumab administered as 480 mg Q4W as a 30-minute IV infusion on Day 1 of each treatment cycle and the recommended dose of binimetinib in Arm 1A of Phase 1b.
- Arm 2B: Patients randomized to the nivolumab, ipilimumab, and binimetinib arm will receive nivolumab administered as 480 mg Q4W as a 30-minute IV infusion on Day 1 of each treatment cycle, ipilimumab administered as 1 mg/kg Q8W as a 30-minute IV infusion, and the recommended dose of binimetinib determined in Arm 1B of Phase 1b.

Dosing calculations for ipilimumab should be based on the body weight assessed at baseline. It is not necessary to re-calculate subsequent doses if the patient weight is within 10% of the weight used to calculate the initial dose.

4.1.2.1 Measures to Minimize Bias

During the randomized Phase 2 period of the study, treatments will be assigned according to a computerized central randomization list using an interactive web response system (IWRS) (see Section 6.2) in order to minimize any possible bias.

4.2 Duration of Treatment

Patients may continue receiving study drug as long as none of the treatment discontinuation criteria are met (see Section 9.2), with the following exceptions: In the absence of disease progression, nivolumab or ipilimumab may be dosed continuously for a maximum of 2 years.

Continuing study treatment beyond disease progression for any patient is only to be considered under special circumstances when it is believed that the patient may clinically benefit from continued treatment beyond progression. If it is judged by the Investigator in consultation with the Sponsor, to be in the best interest of the patient, the patient may remain on study treatment as long as the patient continues to receive benefit from the study treatment per Investigator assessment. Circumstances in which treatment beyond disease progression might be appropriate include mixed responses or the appearance of new brain metastases treatable with stereotactic radiotherapy or surgery but not requiring whole brain radiotherapy.

Dosing beyond progression is not allowed in the following cases:

- Patients with clear evidence of disease progression at multiple sites or clear evidence of new lesions outside the central nervous system
- Patients with rapid progression of disease at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention
- Patients who have clinically relevant worsening of laboratory values
- Patients who have a clinically significant decline in performance status at time of progression.

4.3 End of Study

End of study will be defined as the point when all patients have the opportunity to be followed for at least 1 year after the randomization date of the last patient enrolled. The Sponsor will notify all applicable regulatory agencies in accordance with local requirements when the study has ended. After the end of the study, access to study drugs will be provided only in accordance with local regulations and requirements.

4.4 Safety Review

Safety Review will be performed by the Sponsor's Medical Monitor and the Investigators. This team will be responsible for ongoing review of safety data during the study in order to evaluate the safety and tolerability of the combinations of nivolumab and binimetinib, and nivolumab and binimetinib plus ipilimumab.

For the dose-finding cohorts, after the last patient in a given cohort has completed at least 1 cycle of study treatment, the Sponsor's Medical Monitor and the Investigators will meet to review all safety data and decide whether to continue or halt dose escalation, expand individual dose levels to gain additional safety data, determine the MTD and/or RP2D, or explore other dose levels/schedules.

In addition to end-of cohort meetings, safety meetings between the Sponsor's Medical Monitor and the Investigators will be scheduled periodically during Phase 2 of the study to review safety data for ongoing patients and patients who are being monitored during the follow-up period.

5.0 PATIENT POPULATION

5.1 Number of Patients

Approximately 90 adult patients are planned. A maximum of approximately 42 patients will be enrolled in Phase 1b at approximately 5 study centers, and a minimum of approximately 48 patients will be enrolled in Phase 2 at approximately 30 study centers. The total number of patients enrolled in Phase 1b of the study will depend on the number of dose levels tested and the number of patients treated in each cohort before the RP2D has been determined for each arm.

5.2 Selection of Patients

The eligibility criteria described in this study protocol are designed to identify patients for whom study treatment is considered appropriate. All relevant medical conditions should be considered when deciding whether a patient is suitable for enrollment in the study.

Eligibility will be determined separately for molecular tumor testing during a Prescreening Phase and for enrollment/randomization in the study during a Screening Phase. Questions regarding patient eligibility should be addressed to the Sponsor or delegate prior to enrollment/randomization. Patients will be considered enrolled in the study once they have signed the Screening informed consent form (ICF).

5.2.1 Eligibility Criteria for Prescreening

5.2.1.1 Prescreening Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for participation in the prescreening period:

1. Provide a signed and dated Prescreening ICF.
2. Male or female ≥ 18 years of age at the time of signing the Screening ICF.
3. Measurable, histologically/cytologically confirmed mCRC per RECIST v1.1.
4. Have willingness and ability to participate in the study.
5. Able to provide a sufficient amount (tumor block or minimum of 6 slides) of representative tumor specimen (primary or metastatic, archival or newly obtained) for central laboratory testing of *RAS* mutation status and MSS.
   a. If a fresh tissue sample is provided, a blood sample is required.
6. Have received no more than 2 prior lines of systemic therapy in the metastatic setting (maintenance therapy given in the metastatic setting will not be considered a separate regimen). Generally, treatments that are separated by an event of progression are considered different regimens.

7. Have received prior systemic treatment as recommended by National Comprehensive Cancer Network (NCCN) or European Society for Medical Oncology (ESMO) guidelines, including fluoropyrimidines, oxaliplatin, irinotecan or bevacizumab in the metastatic setting or similar treatments, as per local guidelines.
8. No known contraindications to study treatment.

5.2.1.2 Prescreening Exclusion Criteria

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

1. Prior treatment with any MEK inhibitor.
2. Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.
3. Any untreated central nervous system (CNS) lesion. However, patients are eligible if: a) all known CNS lesions have been treated with radiotherapy or surgery, and b) patients remained without evidence of CNS disease progression ≥ 4weeks after treatment, and c) patients must be off corticosteroid therapy for ≥ 3 weeks.
4. Patients with an active, known or suspected autoimmune disease, with the following exceptions: patients with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
5. Partial or complete bowel obstruction.
6. Impaired gastrointestinal function or disease that may significantly alter the absorption of binimetinib (e.g., ulcerative diseases, uncontrolled vomiting, malabsorption syndrome, small bowel resection with decreased intestinal absorption) or baseline diarrhea ≥ Grade 1.
7. Known history of RVO.
8. Concurrent or previous other malignancy within 5 years of study entry, except cured basal or squamous cell skin cancer, superficial bladder cancer, prostate intraepithelial neoplasm, carcinoma in-situ of the cervix, or other noninvasive or indolent malignancy
9. Known history of Gilbert's syndrome.
10. Severe uncontrolled medical illness.
11. Psychiatric illness inhibiting informed consent or protocol compliance.
12. Pregnant or breastfeeding females.
13. History of severe hypersensitivity reactions to mAbs.

14. History of allergy or intolerance (unacceptable AEs) to study drug components or polysorbate-80-containing infusions.

5.2.2 Patient Eligibility at Screening

5.2.2.1 Screening Inclusion Criteria

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

1. Patients must meet all Prescreening inclusion criteria.
2. Provide a personally signed and dated Screening ICF.
3. mCRC categorized as MSS by immunohistochemistry (IHC) or polymerase chain reaction (PCR)-based local assay at any time prior to Screening or by the central laboratory (Section 7.1.1).
4. *RAS* mutation per local assay at any time prior to Screening or by the central laboratory.
5. Have received at least 1 prior line of systemic therapy in the metastatic setting as recommended by National Comprehensive Cancer Network (NCCN) or European Society for Medical Oncology (ESMO) guidelines, including fluoropyrimidines, oxaliplatin, irinotecan or bevacizumab, or similar treatments, as per local guidelines, and meets at least one of the following criteria:
   a. were unable to tolerate the prior first-line regimen
   b. experienced disease progression during or after prior first-line regimen for metastatic disease
   c. progressed during or within 6 months of completing adjuvant chemotherapy

   Note: Generally, treatments that are separated by an event of progression are considered different regimens.
6. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.
7. Female patients are either postmenopausal for at least 1 year, are surgically sterile for at least 6 weeks; if a female patient is of childbearing potential, she must agree to follow instructions for acceptable or highly effective method(s) of contraception for the duration of study treatment and for 5 months after the last dose of study treatment with nivolumab (i.e., 30 days [duration of ovulatory cycle] plus the time required for the investigational drug to undergo approximately 5 half-lives) (Section 5.3).

8. Non-sterile male patients who are sexually active with female partners of childbearing potential must agree to follow instructions for acceptable or highly effective method(s) of contraception for the duration of study treatment and for 7 months after the last dose of study treatment with nivolumab (i.e., 90 days [duration of sperm turnover] plus the time required for the investigational drug to undergo approximately 5 half-lives) (Section 5.3).
9. Adequate renal and bone marrow function as measured by the following Screening laboratory values:
    a. White blood cells (WBC) ≥ 2000/µL
    b. Neutrophils ≥ 1500/µL
    c. Platelets ≥ 100 $\times 10^3$/µL
    d. Hemoglobin ≥ 9.0 g/dL
    e. Serum creatinine ≤ 1.5 × upper limit of normal (ULN) or calculated creatinine clearance > 50 mL/min (using the Cockcroft Gault formula) or estimated glomerular filtration rate > 50 mL/min/1.73 m^2 (using the Modification of Diet in Renal Disease [MDRD] Study formula)
10. Adequate hepatic function characterized by the following Screening laboratory values:
    a. Serum total bilirubin ≤ 1.5 × ULN and < 2 mg/dL
    Note: Patients who have a total bilirubin level > 1.5 × ULN will be allowed if their indirect bilirubin level is ≤ 1.5 × ULN.
    b. ALT and/or AST ≤ 2.5 × ULN, or ≤ 5 × ULN in presence of liver metastases
11. Adequate cardiac function as follows:
    a. LVEF ≥ 50% or above institutional normal value as determined by a MUGA scan or ECHO
    b. QTcF interval ≤ 480 msec (preferably the mean from triplicate electrocardiograms (ECGs)
12. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures including computed tomography (CT)/magnetic resonance imaging (MRI) scans.

5.2.2.2 Screening Exclusion Criteria

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

1. Patients must not meet any of the Prescreening exclusion criteria.

2. Treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to first day of study treatment:
    a. The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) and topical steroids are allowed. Patients who have received acute and/or low-dose systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea or chronic use of ≤ 10 mg/day of prednisone or dose-equivalent corticosteroid) may be enrolled in the study after discussion with and approval by the Sponsor's Medical Monitor.
3. Impaired gastrointestinal function or disease that may significantly alter the absorption of binimetinib (e.g., ulcerative diseases, uncontrolled vomiting, malabsorption syndrome, small bowel resection with decreased intestinal absorption) or baseline diarrhea ≥ Grade 1.
4. History of thromboembolic or cerebrovascular events ≤ 6 months prior to starting study treatment, including transient ischemic attacks, cerebrovascular accidents, deep vein thrombosis or pulmonary emboli.
5. Uncontrolled hypertension defined as persistent systolic blood pressure ≥ 150 mmHg or diastolic blood pressure ≥ 100 mmHg despite current therapy.
6. Concurrent neuromuscular disorder that is associated with the potential of elevated CK (e.g., inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy).
7. 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).
8. Clinically significant cardiac disease, including, but not limited to, any of the following:
    a. Congestive heart failure requiring treatment (New York Heart Association Grade ≥ 2).
    b. Clinically significant and uncontrolled atrial fibrillation.
    c. History of acute coronary syndromes including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty, or stenting < 6 months prior to screening.
    d. Symptomatic chronic heart failure, history or current evidence of clinically significant cardiac arrhythmia and/or conduction abnormality < 6 months prior to screening except controlled atrial fibrillation and paroxysmal supraventricular tachycardia.
9. Residual CTCAE ≥ Grade 2 toxicity from any prior anticancer therapy, with the exception of Grade 2 alopecia or Grade 2 neuropathy.

10. Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at sites where mandated locally.
11. Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection, and/or detectable virus.

5.3 Lifestyle Guidelines - Contraception

Female patients are either postmenopausal (defined as without menses for at least 12 consecutive months before screening AND a follicle-stimulating hormone [FSH] value > 30 IU/L at Screening), are surgically sterile for at least 6 weeks, or if of childbearing potential, must agree to use acceptable or highly effective methods of contraception to avoid pregnancy for the duration of study treatment through 5 months after the last dose of study treatment with nivolumab (i.e., 30 days [duration of ovulatory cycle] plus the time required for the investigational drug to undergo approximately 5 half-lives).

Non-sterile male patients who are sexually active with female partners of childbearing potential must agree to use acceptable or highly effective methods of contraception to avoid fathering a child for the duration of study treatment and for 7 months after the last dose of study treatment with nivolumab (i.e., 90 days [duration of sperm turnover] plus the time required for the investigational drug to undergo approximately 5 half-lives).

Please refer to the IB and/or the locally approved prescribing information for nivolumab and ipilimumab for additional guidance (as applicable).

The following methods have been determined to be highly effective and are permitted under this protocol for use by the patient and his/her partner (Clinical Trials Facilitation Group Guidelines 2014)[a]:

- Complete abstinence from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient
- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - Oral (It is recommended that patients experiencing vomiting or diarrhea should be counseled to use non-oral methods of contraception.)
    - Intravaginal
    - Transdermal

- Progestogen-only hormonal contraception associated with inhibition of ovulation:
    - Oral (It is recommended that patients experiencing vomiting or diarrhea should be counseled to use non-oral methods of contraception.)
    - Injectable
    - Implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner (considered highly effective provided the vasectomized male has received medical assessment of surgical success and that the male is a female patient's sole sexual partner)

[a] Section 2.2.5 of the Clinical Trials Facilitation Group Guidelines 2014 states that the choice of contraceptive methods may be adapted in special circumstances dictated by factors such as study duration, fertility of study population, and seriousness of the treated medical condition. Acceptable birth control methods that result in a failure rate of more than 1% per year include:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- A combination of male condom with either cap, diaphragm or sponge with spermicide (double-barrier methods)
- Male or female condom with or without spermicide
- Cap, diaphragm or sponge with spermicide

6.0 STUDY TREATMENT AND CONCOMITANT MEDICATIONS/THERAPIES

The term "study drug" is used to refer to nivolumab, binimetinib, and ipilimumab, collectively. In addition to the information provided in this protocol, refer to the IB and/or the locally approved prescribing information for nivolumab and ipilimumab for additional guidance (as applicable) for the management of patients concerning contraindications, duration of contraception, special warnings and precautions, and concomitant medications that are contraindicated or that must be used with caution.

6.1 Patient Numbering

In Phase 1b and Phase 2 of the study, patients will be manually assigned a patient study number at prescreening.

In Phase 2 of the study, patients who sign informed consent to participate in Screening will be assigned a unique number by interactive web response system (IWRS). Once a patient is enrolled in the study, that patient will be identified only by the assigned patient number. Once assigned, the patient number must not be reused for any other patient.

6.2 Allocation to Treatment

In Phase 1b, patients will first enroll into Cohort 1 of Arm 1A (45 mg BID binimetinib) (Table 2 and Section 4.1.1.1). Enrollment in Arm 1A will continue until the RP2D has been determined. At this time, new patients may be enrolled into Cohort 1 of Arm 1B.

In Phase 2, patients will be randomized in a 1:1 ratio to receive either nivolumab and binimetinib (Arm 2A) or nivolumab and binimetinib plus ipilimumab (Arm 2B).

The randomization schedule will be created and managed by a statistician not assigned to support the study and treatments will be assigned according to a computerized central randomization list using an IWRS.

6.3 Doses and Schedule of Administration

The investigational products in this study are nivolumab and binimetinib (Arms 1A and 2A) and nivolumab, binimetinib, and ipilimumab (Arms 1B and 2B) (Table 2).

6.3.1 Administration of Nivolumab

Nivolumab will be administered IV on a Q4W schedule as a fixed dose and not by body weight or body surface area (BSA). Nivolumab may be diluted in 0.9% sodium chloride solution.

Nivolumab will be administered at the study site according to institutional standards. The initial nivolumab dose is 480 mg administered as a 30-minute (± 5 minutes) IV infusion (not including time required to flush the IV lines). Close monitoring is required during the infusion and for at least 1 hour after the end of the infusion. If an infusion reaction occurs while nivolumab is being administered, the infusion should be stopped immediately, and the patients should be closely monitored and treated in line with institutional standards. Any rechallenge with nivolumab following an infusion reaction should be first discussed with the Sponsor.

Antiemetic premedications should not be routinely administered prior to dosing of nivolumab. See Section 6.4.1.5 for premedication recommendations following a nivolumab-related infusion reaction.

Doses of nivolumab that are omitted for AEs or any other reason should not be made up. If nivolumab is discontinued, the frequency of study visits may be decreased after discussion with Sponsor.

6.3.2 Administration of Binimetinib

Binimetinib will be administered orally (PO) on a BID schedule (Table 2). Binimetinib should be taken without regard to food. Patients should be instructed to swallow the tablets whole and not to chew or crush them.

- **BID Dosing**: Patients should be instructed to take binimetinib tablets 12 ± 2 hours apart with a large glass of water (~250 mL) 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.

On days when a blood collection is scheduled at the investigational site, patients will take the morning dose of binimetinib at the site, after the collection, under the supervision of the Investigator or designee. On the evening of the visit day, patients will take binimetinib at home. On all other days, patients will take binimetinib at home. Predose PK samples for binimetinib analysis should be collected just prior to intake of binimetinib.

If a patient vomits at any time after dosing, the dose of study drug should not be re-administered. If vomiting occurs within the first 4 hours post dosing with binimetinib, the exact time of vomiting should be recorded whenever possible (Section 7.3).

Binimetinib will be co-administered at the start of the nivolumab infusion (± 5 minutes).

The pharmacist or study nurse will ensure that the appropriate dose is dispensed and will provide the patient with at least the appropriate number of binimetinib tablets for the number of doses to be taken prior to the next scheduled visit. The site personnel will train the patient and/or the patient's caregiver on dosing procedures for the study drug.

Patients will receive a diary to document self-administered dosing of binimetinib in each cycle to include the dose of study drug taken, the date of dosing (and times if applicable), and if any doses were missed and the reason for the missed dose. One diary will be provided per cycle. Patients will be instructed to return unused binimetinib and the patient diary to the site at the end of each cycle. Patient compliance and accountability must be performed every 4 weeks (Table 12 [Phase 1b Arm 1A], Table 13 [Phase 1b Arm 1B], Table 14 [Phase 2 Arm 2A] and Table 15 [Phase 2 Arm 2B]).

The Investigator or responsible site personnel should instruct the patient to take binimetinib per protocol (promote compliance). The dosage prescribed and dispensed to the patient and all dose changes and all missed doses during the study must be recorded in the electronic case report form (eCRF).

6.3.3 Administration of Ipilimumab

Ipilimumab will be administered IV Q8W (Table 2) according to institutional standards. The ipilimumab dose is 1 mg/kg administered as a 30-minute (± 5 minutes) IV infusion (not including time required to flush the IV lines), and will occur after the completion of the nivolumab infusion. Ipilimumab may be diluted in 0.9% sodium chloride solution or 5% dextrose solution.

Antiemetic premedications should not be routinely administered prior to dosing of ipilimumab. See Section 6.4.1.5 for premedication recommendations following an ipilimumab-related infusion reaction.

Doses of ipilimumab that are omitted for AEs or any other reason should not be made up.

If nivolumab is permanently discontinued for any reason, ipilimumab must also be permanently discontinued.

6.4 Dose Modifications

6.4.1 Nivolumab and Ipilimumab Modifications

6.4.1.1 Dose Reductions

Dose reductions are not permitted for nivolumab and ipilimumab.

6.4.1.2 Dose Interruptions or Delays

Nivolumab and ipilimumab administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, study drug-related AE, with the exception of fatigue
- Any Grade ≥ 2 study drug-related creatinine, AST, ALT and/or total bilirubin abnormalities
- Any Grade 3 skin, study drug-related AE
- Any Grade 3 study drug-related laboratory abnormality, with the following exceptions:
    - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay
    - Grade ≥ 3 AST, ALT, and/or total bilirubin will require dose discontinuation
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study drug.

Participants who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when re-treatment criteria are met.

Management algorithms for nivolumab- and ipilimumab-related AEs are provided in Appendix 4 for suspected gastrointestinal, renal, pulmonary, hepatic, endocrinopathy, skin, and neurologic toxicities.

6.4.1.3 Criteria to Resume Nivolumab and Ipilimumab

Patients may resume treatment with study drug when the study drug-related AE(s) resolve to Grade ≤ 1 or baseline value, with the following exceptions:

- Patients may resume treatment in the presence of Grade 2 fatigue.
- Patients who have not experienced a Grade 3 study drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- For patients with Grade 2 AST/ALT and/or total bilirubin, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Patients with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 6.4.1.4) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Patients with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the Sponsor Medical Monitor(s).

- Patients with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the Sponsor Medical Monitor(s). Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

If the criterion to resume treatment is met, the patient should restart treatment at the next scheduled time point as per protocol. However, if the treatment is delayed past the next scheduled time point per protocol, the next scheduled time point will be delayed until dosing resumes.

Dose interruption of > 6 weeks in administration of nivolumab or > 18 weeks in administration of ipilimumab will result in permanent discontinuation, except as specified in Section 6.4.1.4.

6.4.1.4 Criteria to Discontinue Nivolumab and Ipilimumab

If nivolumab is permanently discontinued for any reason, ipilimumab must also be permanently discontinued.

Treatment with nivolumab and ipilimumab should be permanently discontinued for the following:

- Any Grade 2 study drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any recurrent Grade 3 non-skin, study drug-related AE
- Any Grade 4 study drug-related AE or laboratory abnormality including, but not limited to creatinine, AST, ALT, or total bilirubin, except for the following events which do not require discontinuation:
    - Grade 4 neutropenia ≤ 7 days
    - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase
    - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of onset.
    - Grade 4 drug-related endocrinopathy AEs, such as hyper- or hypothyroidism or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Sponsor Medical Monitor(s).

- Any event that leads to delay in dosing lasting > 6 weeks from the previous dose for nivolumab or > 18 weeks from the previous dose for ipilimumab requires discontinuation with the following exceptions:
    - Dosing delays to allow for prolonged steroid tapers to manage study drug-related AEs are allowed.
    - Dosing delays lasting > 6 weeks from the previous dose that occur for non-study drug-related reasons may be allowed if approved by the Sponsor Medical Monitor(s).
    - Prior to re-initiating treatment in a patient with a dosing delay lasting > 6 weeks from the previous dose for nivolumab or > 18 weeks from the previous dose for ipilimumab, the Sponsor Medical Monitor(s) must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.
- Any AE, laboratory abnormality, or intercurrent illness that, in the judgment of the Investigator, presents a substantial clinical risk to the patient with continued nivolumab or ipilimumab dosing.

6.4.1.5 Treatment of Nivolumab- or Ipilimumab-related Infusion Reactions

Because nivolumab and ipilimumab contain only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the Sponsor Medical Monitor(s) and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE v4.03 guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as appropriate:

For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated)

Monitor patient until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg at least 30 minutes before additional nivolumab administrations.

For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [e.g., antihistamines, non-steroidal anti-

inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for ≤ 24 hours).

Stop the nivolumab or ipilimumab infusion, begin an IV infusion of normal saline, and treat the patient with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor patient until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor patient closely. If symptoms recur, then no further nivolumab or ipilimumab will be administered at that visit. The amount of study drug infused must be recorded on the eCRF.

The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminphen 325 to 1000 mg should be administered at least 30 minutes before additional nivolumab or ipilimumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms: (Severe reaction, Grade 3: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]). Grade 4: (life-threatening; pressor or ventilatory support indicated).

Immediately discontinue infusion of nivolumab or ipilimumab. Begin an IV infusion of normal saline and treat the patient as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Patient should be monitored until the Investigator is comfortable that the symptoms will not recur. Nivolumab or ipilimumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor patient until recovery from symptoms.

In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

6.4.2 Binimetinib Modifications

Patients will be monitored for AEs at each visit with the NCI CTCAE v4.03 used for all grading. Doses of binimetinib should be adjusted for AEs throughout the study. In general, doses should not be reduced or interrupted for Grade 1 AEs unless the AE is a specific treatment-related ocular AE. Treatment to control symptoms should be provided as appropriate. All dose modifications should be based on the worst preceding toxicity (CTCAE v4.03).

Permitted binimetinib dose reductions due to AE are specified in Table 5.

Table 5: Permitted Binimetinib Dose Reductions due to Adverse Event

Dose Level	Binimetinib Dose	Binimetinib Dose Reduction due to AE
4	45 mg BID	30 mg BID
3	45 mg BID 3W on / 1W off	30 mg BID
2	30 mg BID	no dose reduction permitted
1	30 mg BID 3W on / 1W off	no dose reduction permitted

When the AE that resulted in a dose reduction improves to and remains stable at the patient's Baseline for a minimum of 14 days, the dose can be re-escalated to the next dose level at the discretion of the Investigator, provided there are no other concomitant binimetinib-related toxicities that would prevent drug re-escalation. Following a dose reduction due to toxicity, an individual patient's dose may be re-escalated only one time; however, no dose re-escalation is allowed after a dose reduction due to LVEF dysfunction or prolonged QTcF > 500 msec.

A dose reduction below 30 mg BID is not permitted. Patients requiring additional reductions must be discontinued from study treatment. Dose interruptions of more than 28 days are not allowed and will result in permanent discontinuation unless resuming treatment is judged by the Investigator and the Sponsor's Medical Monitor or designee to be in the best interest of the patient.

Eye disorders should be graded according to CTCAE v4.03 as described below in Table 6.

Table 6: CTCAE Grading for Eye Disorders

Grade	Description
1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL

Grade	Description
3	Severe or medically significant but not immediately sight threatening; Hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL
4	Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye

ADL= activities of daily living

Retinal detachment should be graded according to the CTCAE v4.03 as described below in Table 7.

Table 7: CTCAE Grading for Retinal Detachment

Grade	Description
1	Asymptomatic
2	Exudative and visual acuity 20/40* or better
3	Rhegmatogenous or exudative detachment; operative intervention indicated; decline in vision (worse than 20/40*but better than 20/200*)
4	Blindness (20/200* or worse) in the affected eye

* Please refer to the Snellen Equivalence Chart (Visual Acuity Conversion Chart) (Appendix 5).

Missed/skipped doses will not be made up (i.e. the patient should not double their dose if the previous dose was missed).

Dose reduction/interruption/discontinuation decisions should be based on the CTCAE grade of the toxicity and the guidelines provided below. All AEs should be followed weekly or as clinically appropriate until stabilization or resolution.

Note: In the event that nivolumab (and, if applicable, ipilimumab) is permanently discontinued, binimetinib single agent should not be administered for more than 28 days, at which time it will be permanently discontinued.

Table 8 presents dose adjustment recommendations for binimetinib-induced toxicities.

Table 8: Binimetinib – Recommended Dose Modifications Associated with Treatment-Related Adverse Events

Severity of Adverse Reaction (CTCAE v4.03)	Binimetinib
Cutaneous Reactions (see also Appendix 2)	

Severity of Adverse Reaction (CTCAE v4.03)	**Binimetinib**
• Grade 1	Maintain dose level of binimetinib Initiate Initial Rash Treatment Regimen if it was not already started and rash should be closely monitored
• Grade 2	1st occurrence: • Maintain dose level of binimetinib • Initiate Initial Rash Treatment Regimen if it was not already started and rash should be closely monitored • Reassess within ≤ 14 days. If rash worsens or does not improve, interrupt dosing of binimetinib until resolved to Grade ≤ 1. Then resume treatment at current dose level binimetinib. 2nd occurrence: • Reassess within ≤ 14 days. If rash worsens or does not improve, interrupt dosing of binimetinib until resolved to Grade ≤ 1. Then resume treatment at a reduced dose level of binimetinib.
• Grade 3	1st occurrence: • Interrupt dosing of binimetinib until resolved to Grade ≤ 1. Reassess weekly. Then resume treatment at current dose level of binimetinib. • Consider referral to dermatologist and manage rash per dermatologist's recommendation. 2nd occurrence: • Interrupt dosing of binimetinib until resolved to Grade ≤ 1. Then resume treatment at 1 reduced dose level of binimetinib. Consider referral to dermatologist and manage rash per dermatologist's recommendation.
• Grade 4	Permanently discontinue binimetinib.
Ocular Events: **-** Retinal Events (including serous detachment of the retina) Note: Results and images of ocular coherence tomography (OCT) must be made available upon request. Any visual acuity impairment at screening should be documented and should be considered as baseline.	
• Grade 1	Maintain dose levels of binimetinib and repeat ophthalmic monitoring including visual acuity assessment and OCT within 10 days • If patient remains asymptomatic (Grade 1), maintain dose level of binimetinib and continue the schedule of visual assessments established per protocol • If patient becomes symptomatic (blurred vision, photophobia, etc.) or visual acuity assessment shows Grade 2, follow Grade 2 dose guidelines below
• Grade 2	Interrupt dosing of binimetinib and repeat ophthalmic monitoring

Severity of Adverse Reaction (CTCAE v4.03)	**Binimetinib**
	including visual acuity assessment and OCT within 10 days • If resolved to baseline or Grade ≤ 1, resume treatment at current dose level of binimetinib and continue the schedule of visual assessments established per protocol • If not resolved to baseline or Grade ≤ 1, resume treatment at 1 reduced dose level of binimetinib and continue the schedule of visual assessments established per protocol
• Grade 3	Interrupt dosing of binimetinib and repeat ophthalmic monitoring including visual acuity assessment and OCT within 10 days: • If resolved to baseline or Grade ≤ 2, resume treatment at 1 reduced dose level of binimetinib and continue the schedule of visual assessments established per protocol • If not resolved to baseline or Grade ≤ 2, continue the interruption and repeat the ophthalmic assessment in 10 days. o If resolved to baseline or Grade ≤ 2, resume treatment at 1 reduced dose level of binimetinib and continue the schedule of visual assessments established per protocol • If remains Grade 3, permanently discontinue binimetinib
• Grade 4	Permanently discontinue binimetinib and immediate follow-up with ophthalmic monitoring
Ocular Events: Retinal Vein Occlusion of Any Grade	Permanently discontinue binimetinib and immediately follow-up with ophthalmic monitoring.
Ocular Events: Non-retinal Events	
• Grade 1-2	Maintain dose level of binimetinib and increase frequency of ophthalmic monitoring to at least every 14 days until stabilization or resolution
• Grade 3	Interrupt dosing of binimetinib and refer patient to ophthalmologist within 7 days: • If resolved to Grade ≤ 1 in ≤ 21 days, resume treatment at 1 reduced dose level of binimetinib • If not resolved to Grade ≤ 1 in ≤ 21 days, permanently discontinue binimetinib and close follow-up with ophthalmic monitoring until stabilization or resolution
• Grade 4	Permanently discontinue binimetinib and immediate follow-up with ophthalmic monitoring until stabilization or resolution

Severity of Adverse Reaction (CTCAE v4.03)	**Binimetinib**
Cardiac	
• Symptomatic or Asymptomatic, absolute decrease in LVEF of greater than 10% from baseline that is below the lower limit of normal (LLN)	Withhold binimetinib and evaluate LVEF every 2 weeks. Resume binimetinib at a reduced dose if all of the following are present within 21 days: • LVEF is at or above the lower limit of normal • Absolute decrease from baseline is 10% or less • Patient is asymptomatic If the LVEF does not recover within ≤ 21 days or if patient is symptomatic, permanently discontinue binimetinib
• Symptomatic congestive heart failure	Permanently discontinue binimetinib.
Interstitial Lung Disease/Pneumonitis (see also Appendix 3)	
• Grade 1	• Maintain dose level of binimetinib and monitor weekly • If not resolved within 3 weeks, permanently discontinue binimetinib
• Grade 2	• Withhold binimetinib for up to 3 weeks. If improved to Grade 0 or 1, resume treatment at 1 reduced level.
• Grade 3-4	• Permanently discontinue binimetinib
Venous Thromboembolism	
• Uncomplicated DVT or PE	Withhold binimetinib for up to 3 weeks. • If improved to Grade 0 or 1, resume at reduced dose. • If not improved, permanently discontinue.
• Life threatening PE	Permanently discontinue binimetinib.
Liver Laboratory Abnormalities and Hepatotoxicity	
AST or ALT	
• Grade 2	Maintain binimetinib dose. • If no improvement within 2 weeks, withhold binimetinib until improved to Grade 0 or 1 or to pretreatment/baseline levels and then resume at the same dose.
• Grade 3 or 4	See *Other*
Rhabdomyolysis/Creatine Phosphokinase (CPK) elevation	
• Grade 1-2	Maintain dose of binimetinib. Ensure patient is adequately hydrated. Closely monitor CK and serum creatinine

Severity of Adverse Reaction (CTCAE v4.03)	**Binimetinib**
	• If total CK ≥ 3 × ULN, measure CK isoenzymes and myoglobin in blood or urine
• Grade 3 > 5.0 - 10.0 x ULN **without** renal impairment (i.e., serum creatinine < 1.5 × ULN or 1.5 × baseline)	If asymptomatic, maintain dosing of binimetinib. Ensure patient is adequately hydrated. Monitor and measure isoenzymes and myoglobin in blood or urine and serum creatinine. If symptomatic (muscle pain/spasms/muscle weakness), interrupt dosing of binimetinib until resolved to CTCAE Grade ≤ 1 and monitor closely, then: • If resolved in ≤ 21 days, resume treatment at 1 reduced dose level of binimetinib • If not resolved in ≤ 21 days, permanently discontinue binimetinib
• Grade 4 **without** renal impairment (i.e., serum creatinine < 1.5 × ULN or 1.5 × baseline)	If asymptomatic, interrupt dosing of binimetinib. Ensure patient is adequately hydrated. Monitor and measure isoenzymes and myoglobin in blood or urine and serum creatinine • If resolved in ≤ 21 days, resume treatment at 1 reduced dose level of binimetinib • If not resolved in ≤ 21 days, permanently discontinue binimetinib If symptomatic (muscle pain/spasms/muscle weakness), permanently discontinue binimetinib
• Grade 3 or 4 **with** renal impairment (i.e., serum creatinine ≥ 1.5 × ULN or 1.5 × baseline)	Interrupt dosing of binimetinib until resolved to CTCAE Grade < 1 or baseline level. Ensure patient is adequately hydrated. Monitor closely and measure isoenzymes and myoglobin in blood or urine and serum creatinine, then: • If resolved in ≤ 21 days, consider resuming treatment at 1 reduced dose level of binimetinib • If not resolved in ≤ 21 days, permanently discontinue binimetinib 2nd occurrence: • Permanently discontinue binimetinib
All Other Adverse Events (Suspected To Be Related To Binimetinib)	
• Grade 1-2	• If the event is a persistent Grade 2 AE not responsive to a specific therapy, consider interruption or reduction of binimetinib
• Grade 3	• Interrupt dosing of binimetinib until resolved to Grade ≤1 or to pretreatment/baseline level. If the event resolves ≤ 21 days, then study drug may be resumed at 1 reduced dose level based upon the Investigator's discretion.

Severity of Adverse Reaction (CTCAE v4.03)	Binimetinib
• Grade 4	• Permanently discontinue binimetinib

Abbreviations: AE = adverse event; DVT = deep vein thrombosis; LLN = lower limit of normal; PE = pulmonary embolism.

6.5 Concomitant Medications/Therapies

6.5.1 Permitted Concomitant Medications/Therapies

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient is permitted, unless otherwise specified. For additional information regarding concomitant medications/therapies, please refer to the IB and/or the locally approved prescribing information for binimetinib, nivolumab, and ipilimumab (as applicable).

Patients receiving medications outlined below must be carefully monitored for potentiating of toxicity due to any individual concomitant medication and may require dose titration of the drug substance. Investigators should use caution when prescribing concomitant medications, as clinical experience with these compounds in patients with cancer is often limited. Investigators should contact the Sponsor when they are unsure whether a drug should be prescribed to a patient in the clinical study. All concomitant medications/therapies, transfusions, procedures and dietary supplements must be documented on the eCRF. Refer to Appendix 6 for a list of medications to be used with caution as mentioned above.

6.5.1.1 Antidiarrheals

Patients should be treated for diarrhea as per institutional guidelines, and/or as indicated in the locally approved prescribing information, or for patients receiving binimetinib, per the supportive care recommended guidelines for the management of binimetinib-induced diarrhea (Appendix 1).

6.5.1.2 Antiemetics

Prophylactic antiemetics should be started only once the patient experiences nausea or vomiting and at the discretion of the Investigator. It is recommended that patients use drugs that do not cause QT prolongation.

6.5.2 Permitted Concomitant Therapy Requiring Caution and/or Action

6.5.2.1 UGT Substrates and Inhibitors

Binimetinib has been identified to be primarily metabolized by glucuronidation. It is advised that inhibitors and inducers of UGT1A1 should be taken with caution when co-administered with binimetinib (Appendix 6).

Patients should be closely monitored for the occurrence of AEs.

6.5.2.2 Transporter Substrates and Inhibitors

In vitro data showed that binimetinib is a substrate of the transporter P-gp. Binimetinib is also a substrate of BCRP. Thus, drugs that are known to inhibit or induce P-gp or BCRP (Appendix 6) should be used with caution.

6.5.3 Prohibited Concomitant Therapy

6.5.3.1 Anticancer Therapy

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 drug.

6.5.3.2 Other Prohibited Therapies

The following therapies are prohibited during the study (unless otherwise noted or utilized to treat AEs):

- Investigational drugs and devices
- Radiation therapy (not including palliative radiotherapy at focal sites that covers ≤ 10% of the bone marrow reserve)
- Herbal preparations/medications. Patients should stop using herbal medications 7 days prior to first dose of study treatment.
- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 6.4.1.4 and 6.4.1.5)
- Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of treatment assignment are excluded. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

6.6 Study Drug Supply

6.6.1 Manufacturing, Formulation, Packaging and Labeling

Binimetinib is supplied by the Sponsor as film-coated tablets for PO administration in a dosage strength of 15 mg and packaged into high-density polyethylene (HDPE) bottles with an induction seal and child-resistant cap. Binimetinib film-coated tablets consist of binimetinib drug substance; colloidal silicon dioxide/silica colloidal anhydrous; croscarmellose sodium; lactose monohydrate; magnesium stearate; microcrystalline cellulose/cellulose, microcrystalline; and a commercial film coating. The capsule-shaped tablets are yellow to dark yellow.

For binimetinib, each bottle will be labeled, at a minimum, with a unique identifier (medication number), the lot number, contents (number of tablets), dosage strength, storage conditions and the name and address of the Sponsor.

Nivolumab is manufactured by Bristol-Myers Squibb Company and supplied as a solution at 10 mg/mL in a 100 mg/10 mL single-dose vial.

Ipilimumab is manufactured by Bristol-Myers Squibb Company and supplied as a solution at 5 mg/mL, either as a 50 mg/10 mL single-use vial or a 200 mg/40 mL single-use vial.

All drug labels will be in the local language and comply with the regulatory requirements of each country, as applicable. Responsible site personnel will identify the study treatment bottle/bag to dispense to the patient. Site personnel will add the patient number to the label.

6.6.2 Shipping, Storage and Handling

Labeled, packaged study drug will be shipped to each site by the Sponsor or designee, as described in the Pharmacy Manual. The Investigator or an approved representative (e.g., registered pharmacist) will ensure that all study drug is stored as outlined in the Pharmacy Manual and in accordance with applicable regulatory requirements. The drug storage area at the site must be secure, with access limited to authorized personnel.

Binimetinib film-coated tablets should not be stored above 25°C and should be protected from light. Storage conditions will be described on the medication label.

Stability studies to support drug storage conditions have been conducted by the Manufacturer or an affiliate. The Manufacturer will continue to monitor the stability of binimetinib and the Sponsor will alert the site if a lot is nearing the end of its anticipated shelf life.

Detailed instructions for storage and handling of binimetinib will be provided in the Pharmacy Manual.

Store nivolumab under refrigeration at 2ºC to 8ºC (36ºF to 46ºF). Protect from light by storing in the original package until time to use. Do not freeze or shake.

Store ipilimumab under refrigeration at 2ºC to 8ºC (36ºF to 46ºF). Do not freeze. Protect vials from light.

6.6.3 Accountability and Return of Study Drug Supply

The Investigator or an approved representative (e.g., pharmacist) must maintain accurate records of dates and quantities of study drug received, to whom study drug is dispensed (patient-by-patient accounting), and accounts of any study drug accidentally or deliberately destroyed. The Investigator must retain all unused or expired study drug supplies until the study monitor has confirmed the accountability records. If site policy prohibits holding study drug supplies for monitor review, then a copy of the standard operating procedure (SOP) for processing drug returns must be provided to the Sponsor.

To ensure adequate records, all study drugs (nivolumab, binimetinib, ipilimumab) will be accounted for on a drug accountability inventory form as instructed by the Sponsor. Refer to the Pharmacy Manual for details on how to process all unused or expired study supplies.

6.7 Treatment Compliance

All patients will receive binimetinib and should be instructed to bring their study drug supply and bottles, if applicable, to the site at each study visit. Compliance will be evaluated at each visit by review of patient diary entries, an accounting of returned study drug and patient interviews.

Nivolumab and ipilimumab will be administered per protocol in the clinic by study personnel. Information regarding individual study drug infusions is to be documented as described in Section 6.4.1.4 and Section 6.4.1.5, respectively. Treatment compliance will be monitored by drug accountability (Section 6.6.3) and the patient's medical record and eCRF.

7.0 STUDY PROCEDURES AND ASSESSMENTS

The procedures and assessments that will be conducted during this study are described in this section in narrative form and are presented by study visit in Section 7.5.2 and summarized in Table 11 (Prescreening and Screening Phases), Table 12 (Phase 1b Arm 1A), Table 13 (Phase 1b Arm 1B), Table 14 (Phase 2 Arm 2A) and Table 15 (Phase 2 Arm 2B).

Written informed consent (Prescreening and Screening informed consents) must be granted by each patient prior to the initiation of any study procedure or assessment (other than those considered SOC).

7.1 Prescreening/Screening Assessments and Procedures

7.1.1 MSS and *RAS* Mutation Testing

Patients will be eligible for the study based on identification of MSS and a *RAS* mutation in the tumor as determined by the central or local laboratory as part of Prescreening for the trial or by a local assay result obtained any time prior to Screening (see Table 11). Acceptable local assays are limited to PCR-based assays (including next generation sequencing [NGS]) and IHC showing intact expression of all mismatch repair (MMR) proteins with no loss of MLH1, MSH2, MSH6 or PMS2.

Patients must have central laboratory confirmation of MSS disease and *RAS* mutation within 30 days after initiation of study treatment (i.e., Cycle 1 Day 1) if it was not confirmed during screening. In cases where the central laboratory is not able to confirm presence of MSS or a *RAS* mutation (due to inadequate or poor sample condition or due to a discordant result by the central laboratory) 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 benefit. In such instances, patients must be informed that the MSS and *RAS* mutation status is unconfirmed and must sign a separate ICF that includes this information and describes alternative treatment options.

Central laboratory MSS or *RAS* mutation tests with a definitive result (positive or negative) cannot be repeated to resolve a discordant result. Patients whose sample is determined to be inadequate or who have an indeterminate result on central testing may have samples resubmitted for testing.

Tumor samples previously determined to be MSS or *RAS* mutation-positive by local assessment may be submitted to the central laboratory. In particular, tumors with clinicopathological features of MSS and *RAS* mutations such as right colon tumors; poorly differentiated, mucinous, or signet-ring carcinomas; or tumors metastasized to the peritoneum (Yokota et al. 2011) should be

considered for testing by central laboratory regardless of the results of prior local MSS or *RAS* mutation testing.

7.1.2 Prescreening

The molecular prescreening can be performed at any time prior to Screening (see Section 5.2.1). An informed consent must be signed prior to any prescreening procedure for confirmation of MSS and *RAS* status. If a patient's archival specimen was collected >1 year prior to prescreening, collection of a fresh biopsy (with blood sample) is recommended, if feasible. In patients with documented MSS or *RAS* status determined by local assay prior to the study, when possible, the same tissue source should be submitted to the central laboratory in order to minimize the potential for discordance. Information regarding tissue specimen requirements, sample handling and shipment will be provided in the Laboratory Manual.

Patient numbers will be assigned manually in Phase 1b and Phase 2.

7.1.3 Screening

Patients with documented MSS or *RAS* mutation status determined by a central laboratory during Prescreening or by local assay prior to this study must sign a Screening ICF before additional screening procedures to determine eligibility for participation in the study are performed. A copy of the ICF will be given to the patient or their legal representative. The date that informed consent was obtained must be documented in source documents.

Patient eligibility will be verified against the inclusion and exclusion criteria once all screening procedures are completed. The eligibility check will be embedded in the IWRS system.

7.1.4 Information Collected for Screen Failures

Patients who provide informed consent (i.e., via the Prescreening ICF or the Screening ICF) but are not enrolled/randomized for any reason will be considered screen failures.

Date of informed consent and review of inclusion/exclusion criteria will be collected for screen failures as well as any AEs or SAEs possibly related to a study procedure during the screening period and any medications used to treat those AEs or SAEs (see Section 10.9 for SAE reporting details). For prescreening failures, results of the MSS and *RAS* assay available at Prescreening, AEs or SAEs possibly related to a study procedure will be collected.

7.1.5 Patient Demographics and Other Baseline Characteristics

Demographics, prior medications/therapies/procedures that were administered/conducted within 28 days prior to Day 1, current medications, diagnosis and extent of tumor, baseline tumor

mutation status including site of disease, and details of prior antineoplastic treatments including number of prior metastatic regimens and prior irinotecan will be recorded. Past and present medical history considered by the Investigator to be significant will also be recorded.

7.2 Safety Assessments

7.2.1 Adverse Events

Adverse events will be assessed by direct observation and patient interviews on an ongoing basis. Patients should be questioned using non-leading questions. Definitions and reporting of AEs are described in detail in Section 10.0.

7.2.2 Clinical Laboratory Tests

Laboratory parameters to be assessed are listed in Table 9. During the course of the study, blood sampling for safety monitoring will be consistent with standard-of-care.

Details regarding the collection of blood and urine samples will be outlined in the Laboratory Manual.

Additional clinical laboratory tests may be obtained at any time during the study at the Investigator's discretion.

Table 9: Summary of Clinical Laboratory Tests

Hematology	Chemistry	Urinalysis	Coagulation
Basophils Eosinophils Hematocrit Hemoglobin Lymphocytes Monocytes Neutrophils/ANC Platelets RBC WBC	ALT Amylase AST Albumin Alkaline phosphatase Bicarbonate (CO_2) Bilirubin (total and direct)[a] BNP BUN/urea CA 19-9 Calcium Chloride CK[b] CEA Creatinine Glucose LDH Lipase Magnesium Potassium Sodium Total protein Troponin I Uric acid	Blood Glucose Ketones Leukocytes pH Protein	PT/INR aPTT
Thyroid Panel			**Others**
TSH T3, free T4, free			At Screening only: • Hepatitis B surface antigen • Hepatitis C antibody • HIV, as applicable • CRP If applicable: • Serum pregnancy test • LH, FSH and/or estradiol • Serum CK isoenzymes[b] • Myoglobin

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BNP = brain natriuretic peptide; BUN = blood urea nitrogen; CA 19-9 = cancer antigen 19-9; CEA = carcinoembryonic antigen; CK = creatine kinase; CRP = C-reactive protein; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; INR = International Normalized Ratio; LDH = lactate dehydrogenase; LH = luteinizing hormone; pH = hydrogen ion concentration; PT = prothrombin time; aPPT = activated partial thromboplastin time; RBC = red blood cell(s); T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WBC = white blood cell(s).

[a] Direct bilirubin will be measured at screening only if total bilirubin values are abnormal; the result will be used to calculate indirect bilirubin level for purposes of determining eligibility to participate in the study.

[b] For Grade 2 total CK that is also $\geq 3 \times$ ULN or asymptomatic Grade 3 total CK: measure CK, CK isoenzymes and myoglobin in blood or urine weekly for 3 weeks. If total CK remains above the grade that led to the increased monitoring, continue to assess CK, CK isoenzymes and myoglobin, along with regularly scheduled clinical chemistry assessments, until normalization or improvement to Grade 1. When CK is elevated, ensure patient is adequately hydrated.

7.2.2.1 Hematology, Coagulation and Clinical Chemistry

Blood samples for the hematology, coagulation and chemistry laboratory tests listed in Table 9 will be collected at the time points specified in Table 11 (Prescreening and Screening Phases), Table 12 (Phase 1b Arm 1A), Table 13 (Phase 1b Arm 1B), Table 14 (Phase 2 Arm 2A) and Table 15 (Phase 2 Arm 2B).

Blood sample collections occurring on dosing days must be performed prior to study drug administration. Laboratory test results required to make decisions regarding potential dose modifications (as specified in Section 6.4) should be reviewed prior to study treatment administration.

When assessing renal function, a single method (calculated creatinine clearance using the Cockroft Gault formula or estimated glomerular filtration rate using the MDRD Study formula) should be used consistently for a given patient throughout the study.

7.2.2.2 Urinalysis

Urine samples for the laboratory tests listed in Table 9 will be collected at the time points specified in Table 11 (Prescreening and Screening Phases), Table 12 (Phase 1b Arm 1A), Table 13 (Phase 1b Arm 1B), Table 14 (Phase 2 Arm 2A) and Table 15 (Phase 2 Arm 2B).

All urine collections occurring on dosing days must be performed prior to study treatment administration.

7.2.2.3 Pregnancy and Assessments of Fertility

All females of childbearing potential are required to undergo a serum pregnancy assessment at Screening and serum or urine pregnancy assessments at subsequent time points specified in Table 11 (Prescreening and Screening Phases), Table 12 (Phase 1b Arm 1A), Table 13 (Phase 1b Arm 1B), Table 14 (Phase 2 Arm 2A) and Table 15 (Phase 2 Arm 2B). Female patients of nonchildbearing potential (as defined in Section 5.3) do not require pregnancy tests. Any positive pregnancy test will result in immediate cessation of study treatment administration.

Female patients who have undergone female sterilization using oophorectomy alone will have a blood sample for measurement of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and/or estradiol as described in Section 5.3.

All urine collections for pregnancy tests occurring on dosing days must be performed and assessed prior to study treatment administration.

7.2.3 Vital Signs

Vital signs (blood pressure, pulse and temperature) will be measured per institutional standards at the time points specified in Table 11 (Prescreening and Screening Phases), Table 12 (Phase 1b Arm 1A), Table 13 (Phase 1b Arm 1B), Table 14 (Phase 2 Arm 2A) and Table 15 (Phase 2 Arm 2B).

All vital sign measurements occurring on dosing days must be performed prior to study treatment administration. Any treatment-emergent abnormal findings will be recorded as AEs.

7.2.4 Physical Examination

Physical examinations will be performed by trained medical personnel at the time points specified in Table 11 (Prescreening and Screening Phases), Table 12 (Phase 1b Arm 1A), Table 13 (Phase 1b Arm 1B), Table 14 (Phase 2 Arm 2A) and Table 15 (Phase 2 Arm 2B).

At Screening in both phases, full physical examinations should include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast and pelvic examinations will be performed. Full physical examinations are required throughout Phase 1b, but in Phase 2 for subsequent visits, the physical examinations should be targeted as clinically indicated.

Body weight will be measured as part of the physical examination. Height will be measured only at Screening. All physical examinations occurring on dosing days must be performed prior to study treatment administration. Any treatment-emergent abnormal findings will be recorded as AEs.

7.2.5 Ophthalmic Assessments

7.2.5.1 Routine Testing

Full ophthalmic examination, including best corrected visual acuity for distance testing, slit lamp examination, intraocular pressure and dilated fundoscopy with attention to retinal abnormalities, especially RPED, serous detachment of the retina and RVO (or associated symptoms), will be performed by an ophthalmologist at the time points specified in Table 11 (Prescreening and Screening Phases), Table 12 (Phase 1b Arm 1A), Table 13 (Phase 1b Arm 1B), Table 14 (Phase 2 Arm 2A) and Table 15 (Phase 2 Arm 2B). Visual field testing will be performed for patients only when clinically indicated. For visual field testing only, an optometrist may also perform the assessment. For all patients, ophthalmic assessments may be performed more frequently per standard of care or if clinically indicated for evaluation of any visual signs or symptoms.

7.2.5.2 Additional Testing

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

- For non-vascular abnormalities: OCT of the macula (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) should be sent to the study site and be maintained in the patient's source document file. These images/results may be requested to be sent to the Sponsor or designee.

7.2.6 Dermatologic Evaluations

Immune-mediated rash can occur with nivolumab and immune-mediated dermatitis can occur with ipilumumab treatment. Patients should be monitored for rash, and signs and symptoms of dermatitis, such as rash and pruritus (Opdivo US PI 2017; Yervoy US PI 2017). Dermatologic evaluations will be performed at the time points specified in Table 11 (Prescreening and Screening Phases), Table 12 (Phase 1b Arm 1A), Table 13 (Phase 1b Arm 1B), Table 14 (Phase 2 Arm 2A) and Table 15 (Phase 2 Arm 2B). Dermatologic evaluations should be performed by a dermatologist as clinically indicated.

7.2.7 Electrocardiograms

Standard single 12-lead ECGs will be performed at the time points specified in Table 11 (Prescreening and Screening Phases), Table 12 (Phase 1b Arm 1A), Table 13 (Phase 1b Arm 1B), Table 14 (Phase 2 Arm 2A) and Table 15 (Phase 2 Arm 2B). A triplicate ECG (3 serial ECGs conducted within approximately 5 to 10 minutes total time) will only be performed predose on Cycle 1 Day 1.

Prior to performing the 12-lead ECG, patients should rest in the supine position for at least 5 minutes. The ECG measurement performed at the Screening Visit will be used to determine eligibility. The mean of the triplicate ECG measurements recorded pre-morning dose on Cycle 1 Day 1 will serve as the patient's Baseline value for all postdose comparisons. The ECG measurement at any time point should be used for AE grading and recommended dose modifications.

The Investigator will be responsible for verifying the accuracy of the electronic QTc interval recording using Fridericia's correction formula:

QTcF = QT ÷ cube root of the RR interval

In calculations of QTc, QT is measured in milliseconds, and RR, the duration of the entire cardiac cycle, is measured in seconds.

When an ECG is to be performed at the same time point as a blood collection, the ECG is to be performed first.

Interpretation of the tracing should be made by a qualified physician and documented in the eCRF. Clinically significant abnormalities present when the patient signed the Screening informed consent should be reported in the eCRF. New or worsened clinically significant findings occurring after the Screening informed consent must be recorded in the eCRF.

7.2.8 Echocardiogram/Multi-gated Acquisition Scans

Cardiac ejection fraction will be assessed by transthoracic ECHO or MUGA scans at the time points specified in Table 11 (Prescreening and Screening Phases), Table 12 (Phase 1b Arm 1A), Table 13 (Phase 1b Arm 1B), Table 14 (Phase 2 Arm 2A) and Table 15 (Phase 2 Arm 2B). 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 measurement by ECHO or MUGA.

7.2.9 ECOG Performance Status

Assessment of ECOG PS (Table 10) will be performed at the time points specified in Table 11 (Prescreening and Screening Phases), Table 12 (Phase 1b Arm 1A), Table 13 (Phase 1b Arm 1B), Table 14 (Phase 2 Arm 2A) and Table 15 (Phase 2 Arm 2B).

ECOG PS should be obtained on the scheduled day, even if study treatment is being held.

Table 10: Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

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

7.3 Pharmacokinetic Assessments

Peripheral blood samples (~3 mL each) will be collected at the following time points: 1.5 hours ± 15 minutes post-binimetinib dose on C1D1, predose and 1.5 hours ± 15 minutes post-binimetinib dose on C1D15, and predose on D15 during cycles 2-5. Predose samples should be collected before the patient takes the morning dose of binimetinib. Binimetinib and its active metabolite, AR00426032, will be quantified using a validated bioanalytical method.

Study visits for PK sampling should be scheduled in the morning so that predose and postdose PK blood samples can be collected. On the PK visit days, the morning dose of binimetinib should be taken at the study site, only after collecting the predose PK sample for plasma. Predose sampling information should include the dose amount taken and the date and approximate time of the most recent previous dose of binimetinib. Postdose sampling information should include the date and approximate time of the morning dose, including the dose amount taken, and the time of the PK samples. 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 oral study drug administration on the day of PK sampling, no additional study treatment should be taken in an effort to replace the material that has been vomited. On Cycle 1 Day 1 and Cycle 1 Day 15, whenever possible, the exact time (using the 24-hours clock) of vomiting within the first 4 hours post-dose should be recorded in a separate section of the eCRF. In addition, for Cycles 1-5 Day 15, whenever possible, the exact time of vomiting within the first 4 hours post-dose during the last day prior to the PK day should be recorded in a separate section of the eCRF.

If a patient receiving any of the treatments defined in this protocol experiences an AE that results in an unscheduled visit or meets the criteria for an SAE (Section 10.0), a blood sample for measurement of plasma concentrations of drug-related analytes should be collected, if feasible, if less than 24 hours have elapsed since the last dose of study drug.

Blood should be collected in accordance with institutional guidelines. Any sampling problems should 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.

Plasma concentration data will be summarized and population PK analysis will be performed, as appropriate. CCI [redacted]

7.4 Biomarker Assessments

7.4.1 C-reactive Protein

A blood sample (up to ~10 mL) for analysis of C-reactive protein (CRP) will be collected at the time points specified in Table 11 (Prescreening and Screening Phases), Table 12 (Phase 1b Arm 1A), Table 13 (Phase 1b Arm 1B), Table 14 (Phase 2 Arm 2A) and Table 15 (Phase 2 Arm 2B).

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

7.4.2 Tumor Markers (CEA and CA 19-9)

Blood samples (up to ~10 mL) for analysis of tumor markers carcinoembryonic antigen (CEA) and cancer antigen 19-9 (CA 19-9) will be collected at the time points specified in Table 11 (Prescreening and Screening Phases), Table 12 (Phase 1b Arm 1A), Table 13 (Phase 1b Arm 1B), Table 14 (Phase 2 Arm 2A) and Table 15 (Phase 2 Arm 2B).

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

CCI

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

Further exploratory biomarker research may be conducted on collected blood (including PK) samples. These studies would extend the search for other potential biomarkers relevant to the effects of the drugs given in combination in this study, and/or prediction of these effects, and/or resistance to the treatment, and/or safety, and these additional investigations would be dependent upon clinical outcome, reagent and sample availability.

7.4.4 Optional Tumor Sample Collection at Disease Progression

Patients will be offered the option to have fresh tumor samples collected at the time of progression. Patients will be asked to sign a separate ICF prior to the procedure. These optional biopsy collections should be offered to patients with accessible lesions. Accessible lesions are defined as tumor lesions which are easily biopsied. Lesions with the greatest change in dimensional size are the recommended lesions to be excised at the time of progressive disease (PD). Whenever possible, biopsies at progression should be performed within 3 days of study drug discontinuation. The tissue from these biopsies will be used for potential pharmacodynamic biomarker assessments and to determine possible mechanisms of resistance. Possible pharmacodynamic biomarkers that would be investigated include phosphorylated ERK (pERK), p27, DUSP6, CyclinD1, and the cell proliferation marker Ki67 among possible others. Resistance mechanisms to be explored could include the acquisition of genetic alterations that result in the activation of MAPK pathway signaling or cause the activation of compensatory growth pathways (e.g., the loss of PTEN, or activating mutations in PIK3a) as well as changes in immune markers or gene expression profile of the tumor. Methods to examine possible epigenetic causes of resistance (e.g., increased expression of specific kinases that allow MAPK bypass) could also be explored.

7.4.5 Retention of Samples for Future Analysis

If the patient agrees, and in accordance with local laws, any tumor (archival or fresh) samples remaining after determination of MSS and *RAS* status may be stored for up to 2 years after the completion of the study. The samples may be further analyzed to address scientific questions and/or development of biological tests related to administration of nivolumab and binimetinib with or without ipilimumab and/or cancer. The decision to perform such exploratory biomarker research studies would be based on outcome data from this study or from new scientific findings related to the drug class or disease, as well as reagent and assay availability.

The Sponsor and Bristol-Myers Squibb Company will be the exclusive owners of any data and discoveries resulting from this study.

7.5 Efficacy Assessments

7.5.1 Tumor Response

Tumor response will be evaluated locally by the Investigator according to RECIST, v1.1 (Appendix 7) [redacted]

All potential sites of tumor lesions will be assessed at the time points specified in Table 11 (Prescreening and Screening Phases), Table 12 (Phase 1b Arm 1A), Table 13 (Phase 1b Arm 1B), Table 14 (Phase 2 Arm 2A) and Table 15 (Phase 2 Arm 2B).

At screening, the following should be performed:

- A CT scan with IV contrast of chest, abdomen and pelvis is the preferred technique. If there is concern about radiation exposure, an MRI may be used instead of a CT.
- In patients with a history of asymptomatic brain metastases, a brain MRI or CT scan

If a CT scan or MRI was previously performed within 6 weeks of C1D1, the procedure does not need to be repeated at screening.

Every effort must be made to assess each lesion that is measured at screening by the same method throughout the study so that the comparison is consistent.

All post-screening assessments should be performed every 8 weeks (±7 days) from C1D1 through Week 24, then every 12 weeks (±7 days) thereafter until disease progression, withdrawal of consent, initiation of subsequent anticancer therapy, patient is lost to follow-up, death or defined end of study (Section 4.3). Regardless of whether study treatment is discontinued, the following should be performed:

- Chest, abdomen, and pelvis CT (or MRI) scans
- Brain MRI or CT scan, if metastases were documented at baseline
- Additional imaging evaluations may be performed if there is symptomatic evidence suggesting the possibility of disease progression based on clinical symptoms or physical examination at any time.

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.

If a patient has disease progression during the first 12 weeks of study treatment, that patient's best objective response (BOR) is PD. The BOR in patients who have been participating in the

study for at least 6 weeks and who have not experienced a CR or PR per RECIST will be stable disease (SD).

All CT scans should 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. A CT scan of the brain, preferably with IV contrast, may be performed if MRI is contra-indicated.

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

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

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

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

7.5.2 Survival

Patients will be followed for survival at the time points specified in Table 12 (Phase 1b Arm 1A), Table 13 (Phase 1b Arm 1B), Table 14 (Phase 2 Arm 2A), and Table 15 (Phase 2 Arm 2B). Patients will be contacted via telephone every 12 weeks ± 2 weeks after treatment discontinuation until the End of Study (see Section 4.3) or until withdrawal of consent for such follow up, lost to follow up, or death. Patients may be contacted at additional time points to obtain survival status prior to planned data analyses. Survival assessment of patients who withdraw consent for such follow up or are lost to follow up will be conducted via public records.

8.0 SCHEDULE OF PROCEDURES AND ASSESSMENTS

The procedures and assessments that will be conducted during this study are described in this section by study visit, described in narrative form in Section 7.0, and presented in separate tables for: Table 11 (Prescreening and Screening Phases), Table 12 (Phase 1b Arm 1A), Table 13 (Phase 1b Arm 1B), Table 14 (Phase 2 Arm 2A) and Table 15 (Phase 2 Arm 2B).

For all visits except C1D1, there is a general ±3-day window on assessments to take into account scheduling over public or religious holidays, if not explicitly specified otherwise. For PK sampling, the samples may be obtained ±1 day from the scheduled date (except for PK sampling on C1D1). For imaging assessments, a ±7-day window is allowed.

Table 11: Schedule of Events: Prescreening and Screening (All arms and phases)

Procedure/ Assessment	Prescreening	Screening	
	Prior to Day -28	Day -28 to -1	Day -14 to -1
Prescreening informed consent	X		
Prescreening inclusion/exclusion criteria	X		
Tumor sample (archival or fresh) to confirm *RAS* and MSS status	X		
Blood collection if fresh biopsy collected	X		
RAS mutation assessment (central or local test is acceptable for eligibility determination)	X		
MSS testing by PCR or IHC (central or local test is acceptable for eligibility determination)	X		
Primary informed consent		X	
Central *RAS* and MSS confirmation		X	
2 blood samples (up to 10 mL each) collected for biomarker analyses		X	
Blood sample for tumor markers (CEA, CA 19-9)		X	
Demography		X	
Verify inclusion/exclusion criteria		X	X
Medical history		X	
Cancer diagnosis and extent of disease		X	
Prior systemic cancer therapies, radiation, surgery		X	
Tumor burden assessment (RECIST CCI		X	
Body weight/height			X
Vital signs			X
Physical examination			X
ECOG PS			X
Ophthalmic examination[a]		X	
Dermatologic examination		X	

Procedure/ Assessment	Prescreening	Screening	
	Prior to Day -28	Day -28 to -1	Day -14 to -1
ECHO/MUGA			X
Single 12-lead ECG			X
Serum pregnancy test for women of childbearing potential			X[b]
LH, FSH, and/or estradiol test for post-menopausal women and women surgically sterile by oophorectomy alone			X
HBV and HCV serology testing and HIV where applicable			X
Hematology			X
Clinical chemistry including BNP and troponin I			X
Coagulation			X
Cardiac/muscle enzymes			X
Thyroid panel			X
C-reactive protein level			X
Urinalysis (central lab)		X	
CT or MRI of chest, abdomen/pelvis, and brain (only in patients with a history of asymptomatic brain metastases)[c]		X	
Concomitant medications/therapies		X	
Phase 1b and Phase 2: Manual assignment of patient number	X		
Phase 2 only: Register in IWRS for randomization			X

Abbreviations: BNP=brain natriuretic peptide; CA 19-9=cancer antigen 19-9; CEA=carcinoembryonic antigen; CT=computed tomography; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; FSH=follicle-stimulating hormone; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IHC=immunohistochemistry; CCI [redacted] IWRS= interactive web response system; LH=luteinizing hormone; MRI=magnetic resonance imaging; MSS= microsatellite stable; MUGA=multigated acquisition; PCR=polymerase chain reaction; PS=performance status; RECIST= Response Evaluation Criteria in Solid Tumors.

[a] Full ophthalmic examination, including best corrected visual acuity for distance testing, slit lamp examination, intraocular pressure and dilated fundoscopy with attention to retinal abnormalities, especially RPED, serous detachment of the retina and RVO (or associated symptoms), will be performed. Optical coherence tomography (OCT) and fluorescein angiography performed for any non-vascular/vascular abnormality, respectively. Visual field testing will only be performed when clinically indicated.

[b] Performed within 24 hours prior to Day 1.

[c] If a CT scan or MRI was previously performed within 6 weeks of C1D1, the procedure does not need to be repeated at screening

Table 12: Schedule of Events: Phase 1b Arm 1A (Nivolumab + Binimetinib)

Procedure/ Assessment (± 3-day window for all visits except for C1D1 [no window] and 100-day follow up [± 7 days] and 150-day follow-up [+7 days])	Treatment Phase							Follow-up Phase			
	Cycle 1			Cycle 2		Subsequent Cycles		End of Treatment[a]	30-Day Follow up[b]	100-Day Follow up[b]	150-Day Follow up[b]
	Day 1	Day 15	Day 22	Day 1	Day 15	Day 1	Day 15				
Verify inclusion/exclusion criteria pre-treatment	X										
Body weight	X			X		X	X	X	X		
Vital signs	X	X		X	X	X	X	X	X		
Physical examination	X			X		X	X	X	X		
ECOG PS	X			X		X	X	X	X		
Ophthalmic examination[c]				X		X[d]		X	X[e]		
Dermatologic examination	X					X[f]		X	X		
ECHO/MUGA				X		X[g]		X			
Triplicate 12-lead ECG[h]	X[i]										
Single 12-lead ECG[h]	X[j]			X[k]		X[l]		X			
Pregnancy test	X[m]			X[n]		X[n]		X[n]	X[n]		
Hematology	X	X	X	X		X		X	X		
Clinical chemistry incl. BNP and troponin I	X	X		X		X		X	X		
Coagulation	X			X		X		X	X		
Cardiac/muscle enzymes[o]	X	X	X	X	X	X		X			
Thyroid panel	X			X		X		X	X		
Urinalysis[p]	X			X		X					
PK blood sample	X[q]	X[q,r]			X[r]		X[r,s]				
Tumor biopsy (optional)				X				X			
Blood sample (if optional biopsy performed)				X				X			
Blood sample for biomarkers	X			X		X		X			
Blood sample for tumor markers (CEA, CA19-9)	X			X		X		X			
Blood sample for genomic profiling	X										

Procedure/ Assessment (± 3-day window for all visits except for C1D1 [no window] and 100-day follow up [± 7 days] and 150-day follow-up [+7 days])	Treatment Phase							Follow-up Phase			
	Cycle 1			Cycle 2		Subsequent Cycles		End of Treatment[a]	30-Day Follow up[b]	100-Day Follow up[b]	150-Day Follow up[b]
	Day 1	Day 15	Day 22	Day 1	Day 15	Day 1	Day 15				
CT scan or MRI of chest, abdomen/pelvis, and brain (only if positive during screening)	Every 8 weeks (±7 days) from C1D1 through Week 24, then every 12 weeks (±7 days)										
Nivolumab (480 mg infusion Q4W)	X			X		X[t]					
Binimetinib dispensing plus diary (15 mg tablets BID; total dose based on cohort)	X			X		X					
Assess binimetinib compliance				X		X		X			
Adverse events	Assess continuously									X	X[v]
Concomitant medications/therapies	Assess continuously									X	X
Survival Follow up									X[u]	X[u]	X[u]

Abbreviations: BID=twice daily; BNP=brain natriuretic peptide; CA 19-9=cancer antigen 19-9; CEA=carcinoembryonic antigen; CT=computed tomography; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; IV=intravenous; MRI=magnetic resonance imaging; MUGA=multigated acquisition; PK=pharmacokinetic; PS=performance status; Q4W=every 4 weeks.

[a] Within 2 weeks of coming off study and before the 30-day safety follow up.
[b] Document subsequent anticancer therapy and progressive disease after subsequent anticancer therapy.
[c] Optical coherence tomography (OCT) and fluorescein angiography performed for any non-vascular/vascular abnormality, respectively. Visual field testing will only be performed when clinically indicated.
[d] Performed at C4D1 and then Q8W thereafter (i.e., C6D1, C8D1, C10D1, etc.).
[e] Only required if there was a clinically significant abnormality noted at the End of Treatment Visit.
[f] Performed at C3D1 and then Q8W thereafter (i.e., C5D1, C7D1, etc.).
[g] Performed at C5D1 and then Q12W thereafter (i.e., C8D1, C11D1, etc.).
[h] Electrocardiograms should be performed prior to PK and biomarker blood collection.
[i] Triplicate 12-lead ECG performed pre-binimetinib administration (within 5-10 mins total time).
[j] Single 12-lead ECG performed 1 hour (± 15 min) after binimetinib administration.
[k] Performed pre-binimetinib administration and at 1 hour (± 15 min) after binimetinib administration.
[l] Performed predose (all study drugs).
[m] For women of childbearing potential only: If not performed within 24 hours prior to Day 1 dosing, perform a predose serum pregnancy test.
[n] Serum or urine.
[o] If creatine kinase ≥ 3 × upper limit of normal (ULN), follow with isoenzymes serum creatinine and myoglobin in blood or urine weekly and troponin in blood as applicable.
[p] Performed locally; however, if abnormal, send to the central lab.
[q] To be collected 1.5 hours (± 15 minutes) post-binimetinib dose.
[r] To be collected pre-binimetinib dose.
[s] Collected only through Cycle 5.
[t] Administered at C3D1 and Q4W thereafter (i.e., C4D1, C5D1, etc.).

[u] Patients to be contacted via telephone every 12 weeks ± 2 weeks after treatment discontinuation until the End of Study (see Section 4.3) or until withdrawal of consent for such follow up, lost to follow up, or death.
[v] Only SAEs will be assessed.

Table 13: Schedule of Events: Phase 1b Arm 1B (Nivolumab + Ipilimumab + Binimetinib)

Procedure/ Assessment (± 3-day window for all visits except for C1D1 [no window] and 100-day follow up [± 7 days] and 150-day follow-up [+7days])	Treatment Phase							Follow-up Phase			
	Cycle 1			Cycle 2		Subsequent Cycles		End of Treatment[a]	30-Day Follow up[b]	100-Day Follow up[b]	150-Day Follow up[b]
	Day 1	Day 15	Day 22	Day 1	Day 15	Day 1	Day 15				
Verify inclusion/exclusion criteria pre-treatment	X										
Body weight	X	X		X	X	X	X	X	X		
Vital signs	X	X		X	X	X	X	X	X		
Physical examination	X	X		X	X	X	X	X	X		
ECOG PS	X	X		X	X	X	X	X	X		
Ophthalmic examination[c]				X		X[d]		X	X[e]		
Dermatologic examination	X					X[f]		X	X		
ECHO/MUGA				X		X[g]		X			
Triplicate 12-lead ECG[h]	X[i]										
Single 12-lead ECG[h]	X[j]			X[k]		X[l]		X			
Pregnancy test	X[m]			X[n]		X[n]		X[n]	X[n]		
Hematology	X	X	X	X		X		X	X		
Clinical chemistry incl. BNP and troponin I	X	X		X		X		X	X		
Coagulation	X	X		X		X		X	X		
Cardiac/muscle enzymes[o]	X	X	X	X	X	X		X			
Thyroid panel	X			X		X		X	X		
Urinalysis[p]	X			X		X					
PK blood sample	X[q]	X[q,r]			X[r]		X[r,s]				
Tumor biopsy (optional)				X				X			
Blood sample (if optional biopsy performed)				X				X			
Blood sample for biomarkers	X			X		X		X			
Blood sample for tumor markers (CEA, CA19-9)	X			X		X		X			
Blood sample for genomic profiling	X										
CT scan or MRI of chest, abdomen/pelvis, and brain (only if positive during screening)	Every 8 weeks (±7 days) from C1D1 through Week 24, then every 12 weeks (±7 days)										

Procedure/ Assessment (± 3-day window for all visits except for C1D1 [no window] and 100-day follow up [± 7 days] and 150-day follow-up [+7days])	Treatment Phase							Follow-up Phase			
	Cycle 1			Cycle 2		Subsequent Cycles		End of Treatment[a]	30-Day Follow up[b]	100-Day Follow up[b]	150-Day Follow up[b]
	Day 1	Day 15	Day 22	Day 1	Day 15	Day 1	Day 15				
Nivolumab (480 mg infusion Q4W)	X			X		X[t]					
Binimetinib dispensing plus diary (15 mg tablets BID; total dose based on cohort)	X			X		X					
Assess binimetinib compliance				X		X		X			
Ipilimumab (1 mg/kg Q8W)	X					X[u]					
Adverse events	Assess continuously									X	X[w]
Concomitant medications/therapies	Assess continuously									X	X
Survival Follow up									X[v]	X[v]	X[v]

Abbreviations: BID=twice daily; BNP=brain natriuretic peptide; CA 19-9=cancer antigen 19-9; CEA=carcinoembryonic antigen; CT=computed tomography; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; IV=intravenous; MRI=magnetic resonance imaging; MUGA=multigated acquisition; PK=pharmacokinetic; PS=performance status; Q4W=every 4 weeks; Q8W=every 8 weeks.

[a] Within 2 weeks of coming off study and before the 30-day safety follow up.
[b] Document subsequent anticancer therapy and progressive disease after subsequent anticancer therapy.
[c] Optical coherence tomography (OCT) and fluorescein angiography performed for any non-vascular/vascular abnormality, respectively. Visual field testing will only be performed when clinically indicated.
[d] Performed at C4D1 and then Q8W thereafter (i.e., C6D1, C8D1, C10D1, etc.).
[e] Only required if there was a clinically significant abnormality noted at the End of Treatment Visit.
[f] Performed at C3D1 and then Q8W thereafter (i.e., C5D1, C7D1, etc.).
[g] Performed at C5D1 and then Q12W thereafter (i.e., C8D1, C11D1, etc.).
[h] Electrocardiograms should be performed prior to PK and biomarker blood collection.
[i] Triplicate 12-lead ECG performed pre-binimetinib administration (within 5-10 mins total time).
[j] Single 12-lead ECG performed 1 hour (± 15 min) after binimetinib administration.
[k] Performed pre-binimetinib administration and at 1 hour (± 15 min) after binimetinib administration.
[l] Performed predose (all study drugs).
[m] For women of childbearing potential only: If not performed within 24 hours prior to Day 1 dosing, perform a predose serum pregnancy test.
[n] Serum or urine.
[o] If creatine kinase ≥ 3 x upper limit of normal (ULN), follow with isoenzymes serum creatinine and myoglobin in blood or urine weekly and troponin in blood as applicable.
[p] Performed locally; however, if abnormal, send to the central lab.
[q] To be collected 1.5 hours (± 15 minutes) post-binimetinib dose and before the beginning of the ipilimumab infusion on C1D1.
[r] To be collected pre-binimetinib dose.
[s] Collected only through Cycle 5.
[t] Administered at C3D1 and Q4W thereafter (i.e., C4D1, C5D1,C6D1, etc.).
[u] Administered at C3D1 and Q8W thereafter (i.e., C5D1, C7D1, C9D1, etc.).

[v] Patients to be contacted via telephone every 12 weeks ± 2 weeks after treatment discontinuation until the End of Study (see Section 4.3) or until withdrawal of consent for such follow up, lost to follow up, or death

[w] Only SAEs will be assessed.

Table 14: Schedule of Events: Phase 2 Arm 2A (Nivolumab + Binimetinib)

Procedure/ Assessment (± 3-day window for all visits except for C1D1 [no window] and 100-day follow up [± 7 days] and 150-day follow-up [+7days])	Treatment Phase							Follow-up Phase			
	Cycle 1			Cycle 2		Subsequent Cycles		End of Treatment[a]	30-Day Follow up[b]	100-Day Follow up[b]	150-Day Follow up[b]
	Day 1	Day 15	Day 22	Day 1	Day 15	Day 1	Day 15				
Verify inclusion/exclusion criteria pre-treatment	X										
Body weight	X			X		X	X	X	X		
Vital signs	X	X		X	X	X	X	X	X		
Physical examination	X			X		X	X	X	X		
ECOG PS	X			X		X	X	X	X		
Ophthalmic examination[c]				X		X[d]		X	X[e]		
Dermatologic examination	X					X[f]		X	X		
ECHO/MUGA				X		X[g]		X			
Triplicate 12-lead ECG[h]	X[i]										
Single 12-lead ECG[h]	X[j]			X[k]		X[l]		X			
Pregnancy test	X[m]			X[n]		X[n]		X[n]	X[n]		
Hematology	X	X	X	X		X		X	X		
Clinical chemistry incl. BNP and troponin I	X	X		X		X		X	X		
Coagulation	X			X		X		X	X		
Cardiac/muscle enzymes[o]	X	X	X	X	X	X		X			
Thyroid panel	X			X		X		X	X		
Urinalysis[p]	X			X		X					
PK blood sample	X[q]	X[q,r]			X[r]		X[r,s]				
Tumor biopsy (optional)				X				X			
Blood sample (if optional biopsy performed)				X				X			
Blood sample for biomarkers	X			X		X		X			
Blood sample for tumor markers	X			X		X		X			
Blood sample for genomic profiling	X										
CT scan or MRI of chest, abdomen/pelvis, and brain (only if positive during screening)	Every 8 weeks (±7 days) from C1D1 through Week 24, then every 12 weeks (±7 days)										

Procedure/ Assessment (± 3-day window for all visits except for C1D1 [no window] and 100-day follow up [± 7 days] and 150-day follow-up [+7days])	Treatment Phase							Follow-up Phase			
	Cycle 1			Cycle 2		Subsequent Cycles		End of Treatment[a]	30-Day Follow up[b]	100-Day Follow up[b]	150-Day Follow up[b]
	Day 1	Day 15	Day 22	Day 1	Day 15	Day 1	Day 15				
Nivolumab (480 mg infusion)	X			X		X[t]					
Binimetinib dispensing plus diary (15 mg tablets BID at the RP2D)	X			X		X					
Assess binimetinib compliance				X		X		X			
Adverse events	Assess continuously									X	X[v]
Concomitant medications/therapies	Assess continuously									X	X
Survival Follow up									X[u]	X[u]	X[u]

Abbreviations: BID=twice daily; BNP=brain natriuretic peptide; CA 19-9=cancer antigen 19-9; CEA=carcinoembryonic antigen; CT=computed tomography; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; IV=intravenous; MRI=magnetic resonance imaging; MUGA=multigated acquisition; PK=pharmacokinetic; PS=performance status; Q4W=every 4 weeks; RP2D=recommended Phase 2 dose.

[a] Within 2 weeks of coming off study and before the 30-day safety follow up.
[b] Document subsequent anticancer therapy and progressive disease after subsequent anticancer therapy.
[c] Optical coherence tomography (OCT) and fluorescein angiography performed for any non-vascular/vascular abnormality, respectively. Visual field testing will only be performed when clinically indicated.
[d] Performed at C4D1 and then Q8W thereafter (i.e., C6D1, C8D1, C10D1, etc.).
[e] Only required if there was a clinically significant abnormality noted at the End of Treatment Visit.
[f] Performed at C3D1 and then Q8W thereafter (i.e., C5D1, C7D1, etc.).
[g] Performed at C5D1 and then Q12W thereafter (i.e., C8D1, C11D1, etc.).
[h] Electrocardiograms should be performed prior to PK and biomarker blood collection.
[i] Triplicate 12-lead ECG performed pre-binimetinib administration (within 5-10 mins total time).
[j] Single 12-lead ECG performed 1 hours (± 15 min) after binimetinib administration.
[k] Performed pre-binimetinib administration and at 1 hour (± 15 min) after binimetinib administration.
[l] Performed predose (all study drugs).
[m] For women of childbearing potential only: If not performed within 24 hours prior to Day 1 dosing, perform a predose serum pregnancy test.
[n] Serum or urine.
[o] If creatine kinase ≥ 3 x upper limit of normal (ULN), follow with isoenzymes serum creatinine and myoglobin in blood or urine weekly and troponin in blood as applicable.
[p] Performed locally; however, if abnormal, send to the central lab.
[q] To be collected 1.5 hours (± 15 minutes) post-binimetinib dose
[r] To be collected pre-binimetinib dose.
[s] Collected only through Cycle 5.
[t] Administered at C3D1 and Q4W thereafter (i.e., C4D1, C5D1, C6D1, etc.).
[u] Patients to be contacted via telephone every 12 weeks ± 2 weeks after treatment discontinuation until the End of Study (see Section 4.3) or until withdrawal of consent for such follow up, lost to follow up, or death.
[v] Only SAEs will be assessed.

Table 15: Schedule of Events: Phase 2 Arm 2B (Nivolumab + Ipilimumab + Binimetinib)

Procedure/ Assessment (± 3-day window for all visits except for C1D1 [no window] and 100-day follow up [± 7 days] and 150-day follow-up [+7days])	Treatment Phase							Follow-up Phase			
	Cycle 1			Cycle 2		Subsequent Cycles		End of Treatment[a]	30-Day Follow up[b]	100-Day Follow Up[b]	150-Day Follow Up[b]
	Day 1	Day 15	Day 22	Day 1	Day 15	Day 1	Day 15				
Verify inclusion/exclusion criteria pre-treatment	X										
Body weight	X	X		X	X	X	X	X	X		
Vital signs	X	X		X	X	X	X	X	X		
Physical examination	X	X		X	X	X	X	X	X		
ECOG PS	X	X		X	X	X	X	X	X		
Ophthalmic examination[c]				X		X[d]		X	X[e]		
Dermatologic examination	X					X[f]		X	X		
ECHO/MUGA				X		X[g]		X			
Triplicate 12-lead ECG[h]	X[i]										
Single 12-lead ECG[h]	X[j]			X[k]		X[l]		X			
Pregnancy test	X[m]			X[n]		X[n]		X[n]	X[n]		
Hematology	X	X	X	X		X		X	X		
Clinical chemistry incl. BNP and troponin I	X	X		X		X		X	X		
Coagulation	X	X		X		X		X	X		
Cardiac/muscle enzymes[o]	X	X	X	X	X	X		X			
Thyroid panel	X			X		X		X	X		
Urinalysis[p]	X			X		X					
PK blood sample	X[q]	X[q,r]			X[r]		X[r,s]				
Tumor biopsy (optional)				X				X			
Blood sample (if optional biopsy performed)				X				X			
Blood sample for biomarkers	X			X		X		X			
Blood sample for tumor markers (CEA and CA 19-9)	X			X		X		X			
Blood sample for genomic profiling	X										
CT scan or MRI of chest, abdomen/pelvis, and brain (only if positive during screening)	Every 8 weeks (±7 days) from C1D1 through Week 24, then every 12 weeks (±7 days)										
Nivolumab (480 mg infusion Q4W)	X			X		X[t]					

Procedure/ Assessment (± 3-day window for all visits except for C1D1 [no window] and 100-day follow up [± 7 days] and 150-day follow-up [+7days])	Treatment Phase							Follow-up Phase			
	Cycle 1			Cycle 2		Subsequent Cycles		End of Treatment[a]	30-Day Follow up[b]	100-Day Follow Up[b]	150-Day Follow Up[b]
	Day 1	Day 15	Day 22	Day 1	Day 15	Day 1	Day 15				
Binimetinib dispensing plus diary (15 mg tablets BID at the RP2D)	X			X		X					
Assess binimetinib compliance				X		X		X			
Ipilimumab (1 mg/kg Q8W)	X					X[u]					
Adverse events	Assess continuously									X	X[w]
Concomitant medications/therapies	Assess continuously									X	X
Survival Follow up									X[v]	X[v]	X[v]

Abbreviations: BID=twice daily; BNP=brain natriuretic peptide; CA 19-9=cancer antigen 19-9; CEA=carcinoembryonic antigen; CT=computed tomography; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; IV=intravenous; MRI=magnetic resonance imaging; MUGA=multigated acquisition; PK=pharmacokinetic; PS=performance status; Q4W=every 4 weeks; Q8W=every 8 weeks; RP2D=recommended Phase 2 dose.

[a] Within 2 weeks of coming off study and before the 30-day safety follow up.
[b] Document subsequent anticancer therapy and progressive disease after subsequent anticancer therapy.
[c] Optical coherence tomography (OCT) and fluorescein angiography performed for any non-vascular/vascular abnormality, respectively. Visual field testing will only be performed when clinically indicated.
[d] Performed at C4D1 and then (Q8W thereafter (i.e., C6D1, C8D1, C10D1, etc.).
[e] Only required if there was a clinically significant abnormality noted at the End of Treatment Visit.
[f] Performed at C3D1 and then Q8W thereafter (i.e., C5D1, C7D1, etc.).
[g] Performed at C5D1 and then Q12W thereafter (i.e., C8D1, C11D1, etc.).
[h] Electrocardiograms should be performed prior to PK and biomarker blood collection.
[i] Triplicate 12-lead ECG performed pre-binimetinib administration (within 5-10 minutes total time).
[j] Single 12-lead ECG performed 1 hour (± 15 min) after binimetinib administration.
[k] Performed pre-binimetinib administration and at 1 hours (± 15 min) after binimetinib administration.
[l] Performed predose (all study drugs).
[m] For women of childbearing potential only: If not performed within 24 hours prior to Day 1 dosing, perform a predose serum pregnancy test.
[n] Serum or urine.
[o] If creatine kinase ≥ 3 x upper limit of normal (ULN), follow with isoenzymes serum creatinine and myoglobin in blood or urine weekly and troponin in blood as applicable.
[p] Performed locally; however, if abnormal, send to the central lab.
[q] To be collected 1.5 hours (± 15 minutes) post-binimetinib dose and before the beginning of the ipilimumab infusion on C1D1. To be collected pre-binimetinib dose.
[r] To be collected pre-binimetinib dose.
[s] Collected only through Cycle 5.
[t] Administered at C3D1 and Q4W thereafter (i.e., C4D1, C5D1, C6D1, etc.).
[u] Administered at C3D1 and Q8W thereafter (i.e., C5D1, C7D1, C9D1, etc.).
[v] Patients to be contacted via telephone every 12 weeks ± 2 weeks after treatment discontinuation until the End of Study (see Section 4.3) or until withdrawal of consent for such follow up, lost to follow up, or death.
[w] Only SAEs will be assessed.

8.1 Prescreening (All Arms and Phases)

Patient may undergo molecular prescreening at any time prior to randomization based on eligibility criteria described in Section 5.2.1.

- Obtain written informed consent for molecular testing
- Verify all prescreening inclusion/exclusion criteria
- Manually assign a patient study number
- If tumor has previously been determined to be MSS and *RAS* mutant by local assay, confirm testing was done using PCR, IHC or NGS
- Obtain and send archival or fresh tumor specimen to the central laboratory, as soon as possible following the signing of the Prescreening informed consent for confirmation of MSS and *RAS* status (see Section 7.1.1). If an adequate archival tumor sample (tumor block or minimum of 6 slides; optimally up to 15 slides) is not available, a tumor biopsy is required. If a patient's archival specimen was collected >1 year prior to prescreening, collection of a fresh biopsy is recommended, if feasible. The same tumor sample will be used for the *RAS* and MSI testing. If the central laboratory determines that the sample is inadequate for analysis, a second sample may be submitted.
- If a fresh biopsy is collected, collect a blood sample at the time of biopsy

8.2 Screening (All Arms and Phases)

All screening procedures to determine eligibility for study participation must be performed within specific time windows before the first dose of study treatment. Eligibility is determined using results of screening assessments performed before the first dose of study treatment and up to and including Day 1. Patients may be re-screened once at the discretion of the Investigator and/or individual assessments may be repeated, as appropriate. If a particular assessment is repeated, the results obtained closest to the first dose of study treatment should be used to assess eligibility.

At the site, the Investigator will maintain a log for all screened patients (including patients who fail screening after providing written informed consent) and all enrolled patients. If the patient has not been molecularly prescreened, obtain written informed consent for molecular testing.

Screening: Within 28 days prior to Day 1

- Obtain Screening informed consent (must be obtained prior to performance of any study-specific tests or evaluations that are not considered SOC)
- Confirm MSS and *RAS* status using a central laboratory if not performed previously

- Collect 2 blood samples (up to 10 mL each) for biomarker analyses
- Record demographic information (age, race, ethnicity).
- Record current and past medical history
- Document cancer diagnosis and extent of disease
- Document prior systemic cancer therapies, radiation, surgery
- Record all medications/treatments that were administered/conducted within 28 days prior to Day 1
- Obtain full ophthalmic examination
- Obtain full dermatologic examination
- Obtain urine sample for urinalysis
- CT or MRI of chest, abdomen/pelvis, and brain (only in patients with a history of asymptomatic brain metastases
- Complete tumor burden assessments according to RECIST CCI
- Verify all Screening inclusion/exclusion criteria

Screening: Within 14 days prior to Day 1

- Measure body weight and height
- Assess vital signs (blood pressure, pulse, and temperature)
- Complete physical examination
- Assess ECOG PS
- Perform ECHO/MUGA scan
- Single ECG
- Collection of blood samples for the following:
    - Hematology, coagulation, chemistry including brain natriuretic peptide (BNP) and troponin I
    - Serum pregnancy test (females of childbearing potential only)
    - LH, FSH and/or estradiol (only for females who are post-menopausal and females surgically sterile by oophorectomy alone)
    - Hepatitis B surface antigen
    - Hepatitis C antibody
    - HIV, where applicable

- CRP
- Cardiac/muscle enzymes
- Thyroid panel

- Verify all Screening inclusion/exclusion criteria
- **Phase 2 only:** Register patient in IWRS for randomization

8.3 Phase 1b Arm 1A and Phase 2 Arm 2A (nivolumab + binimetinib): Cycle 1

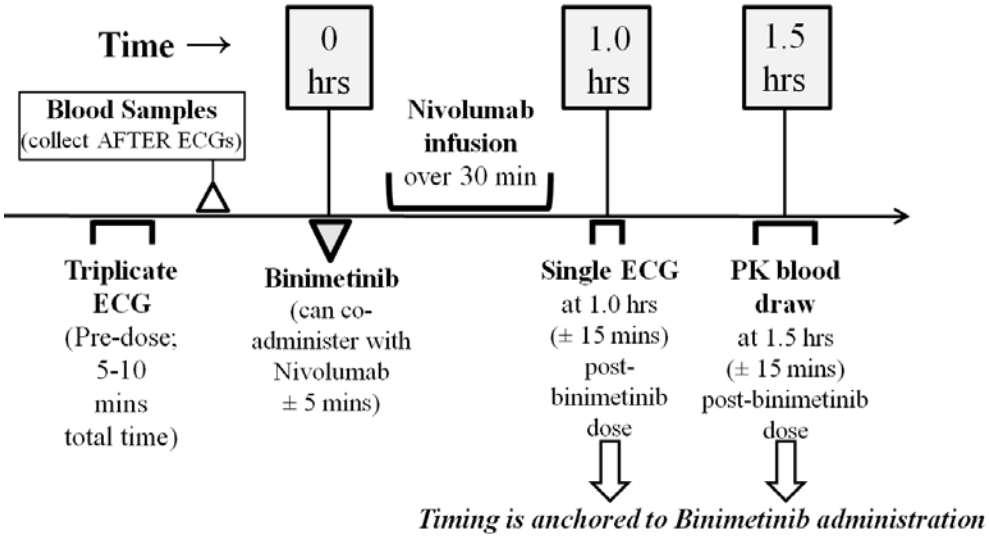
8.3.1 Phase 1b Arm 1A and Phase 2 Arm 2A (nivolumab + binimetinib): Cycle 1 Day 1

Note: Critical procedures and activities that occur closely together around the time of study drug administration on Cycle 1 Day 1 are represented in Figure 3 in order to assist with the timing of each activity. The figure does not include all required procedures and activities occurring on Cycle 1 Day 1.

- Verify all Screening inclusion/exclusion criteria pretreatment
- Measure body weight
- Assess vital signs (blood pressure, pulse, and temperature)
- Complete physical examination
- Assess ECOG PS
- Obtain full dermatologic examination
- Triplicate 12-lead ECG performed pre-binimetinib administration (within 5-10 minutes total time), then a single ECG 1 hour (± 15 minutes) after binimetinib administration
- Collection of blood samples for the following:
  - Hematology, coagulation, chemistry including BNP and troponin I
  - If not performed within 24 hours prior to Day 1 dosing, predose serum pregnancy test (females of childbearing potential only)
  - Cardiac/muscle enzymes
  - Thyroid panel
  - Biomarker analysis
  - CCI
- Obtain urine sample for urinalysis
- CT or MRI of chest, abdomen/pelvis, and brain (only if positive during screening)
- Administer binimetinib

- Administer nivolumab
- Collect a PK blood sample 1.5 hours (± 15 minutes) post binimetinib dosing
- Dispense a 4-week supply of binimetinib along with a monthly diary. Review dosing instructions with patient.
- Assess AEs
- Assess concomitant medications/therapies

Figure 3: Arm 1A/Arm 2A: Timing of ECGs and Blood Collections in Relation to Study Drug Administration on Cycle 1 Day 1



8.3.2 Phase 1b Arm 1A and Phase 2 Arm 2A (nivolumab + binimetinib): Cycle 1 Day 15

- Assess vital signs (blood pressure, pulse, and temperature)
- Collection of blood samples for the following:
    - Hematology, chemistry including BNP and troponin I
    - Cardiac/muscle enzymes
    - PK analysis (collected prior to morning dose of binimetinib)
- Administer binimetinib
- Collect a PK blood sample 1.5 hours (± 15 minutes) post binimetinib dosing
- Assess AEs
- Assess concomitant medications/therapies

8.3.3 Phase 1b Arm 1A and Phase 2 Arm 2A (nivolumab + binimetinib): Cycle 1 Day 22

- Collection of blood samples for the following:
    - Hematology
    - Cardiac/muscle enzymes
- Assess AEs
- Assess concomitant medications/therapies

8.4 Phase 1b Arm 1A and Phase 2 Arm 2A (nivolumab + binimetinib): Cycle 2

8.4.1 Phase 1b Arm 1A and Phase 2 Arm 2A (nivolumab + binimetinib): Cycle 2 Day 1

- Measure body weight
- Assess vital signs (blood pressure, pulse, and temperature)
- Complete physical examination
- Assess ECOG PS
- Obtain full ophthalmic examination
- Perform ECHO/MUGA scan
- Single 12-lead ECG performed pre-binimetinib administration, then 1 hour (± 15 minutes) after binimetinib administration
- Collection of blood samples for the following:
    - Hematology, coagulation, chemistry including BNP and troponin I
    - Serum (or urine) pregnancy test (females of childbearing potential only)
    - Cardiac/muscle enzymes
    - Thyroid panel
    - Biomarker analysis
- Obtain urine sample for urinalysis
- Perform optional tumor biopsy and if performed, collect a blood sample at the time of biopsy
- Administer binimetinib
- Administer nivolumab
- Assess binimetinib compliance and dispense a 4-week supply along with a monthly diary. Review dosing instructions with patient.
- Assess AEs
- Assess concomitant medications/therapies

8.4.2 Phase 1b Arm 1A and Phase 2 Arm 2A (nivolumab + binimetinib): Cycle 2 Day 15

- Assess vital signs (blood pressure, pulse, and temperature)
- Collection of blood samples for the following:
    - Cardiac/muscle enzymes
    - PK analysis (collected prior to morning dose of binimetinib)
- Assess AEs
- Assess concomitant medications/therapies

8.5 Phase 1b Arm 1A and Phase 2 Arm 2A (nivolumab + binimetinib): Subsequent Cycles

8.5.1 Phase 1b Arm 1A and Phase 2 Arm 2A (nivolumab + binimetinib): Subsequent Cycles Day 1

- Measure body weight
- Assess vital signs (blood pressure, pulse, and temperature)
- Complete physical examination
- Assess ECOG PS
- **Cycle 3 Day 1, Cycle 5 Day 1 and Cycle 7 Day 1 and then Q12W:** (±7 days)**:** CT or MRI of chest, abdomen/pelvis, and brain (only if positive during screening)
- **Cycle 3 Day 1:** Obtain full dermatologic examination - performed Q8W thereafter (i.e., C5D1, C7D1, etc.)
- **Cycle 4 Day 1:** Obtain full ophthalmic examination - performed Q8W thereafter (i.e., C6D1, C8D1, etc.).
- **Cycle 5 Day 1 and then Q12W:** Perform ECHO/MUGA scan
- Single 12-lead ECG performed predose (all study drugs)
- Collection of blood samples for the following:
    - Hematology, coagulation, chemistry including BNP and troponin I
    - Serum (or urine) pregnancy test (females of childbearing potential only)
    - Cardiac/muscle enzymes
    - Thyroid panel
    - Biomarker analysis
- Obtain urine sample for urinalysis
- Administer binimetinib

- Administer nivolumab – then Q4W thereafter
- Assess binimetinib compliance and dispense a 4-week supply along with a monthly diary. Review dosing instructions with patient.
- Assess AEs
- Assess concomitant medications/therapies

8.5.2 Phase 1b Arm 1A and Phase 2 Arm 2A (nivolumab + binimetinib): Subsequent Cycles Day 15

- Measure body weight
- Assess vital signs (blood pressure, pulse, and temperature)
- Complete physical examination
- Assess ECOG PS
- **Cycles 3 through 5:** Collect blood samples for PK analysis prior to morning dose of binimetinib
- Assess AEs
- Assess concomitant medications/therapies

8.6 Phase 1b Arm 1B and Phase 2 Arm 2B (nivolumab + binimetinib + ipilimumab): Cycle 1

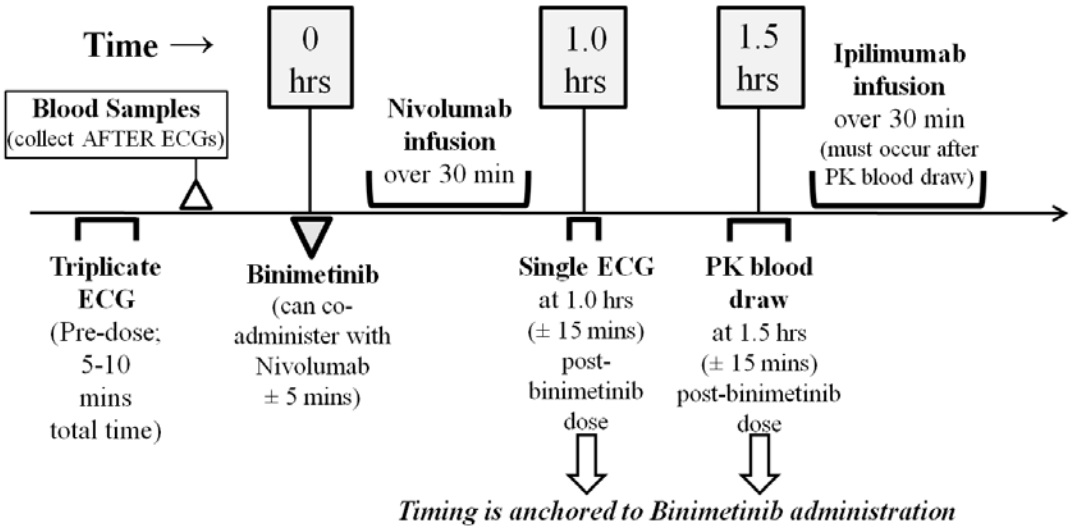
8.6.1 Phase 1b Arm 1B and Phase 2 Arm 2B (nivolumab + binimetinib + ipilimumab): Cycle 1 Day 1

Note: Critical procedures and activities that occur closely together around the time of study drug administration on Cycle 1 Day 1 are represented in Figure 4 in order to assist with the timing of each activity. The figure does not include all required procedures and activities occurring on Cycle 1 Day 1.

- Verify all Screening inclusion/exclusion criteria pretreatment
- **Phase 2 only:** Register patient in IWRS for randomization
- Measure body weight
- Assess vital signs (blood pressure, pulse, and temperature)
- Complete physical examination
- Assess ECOG PS
- Obtain full ophthalmic examination
- Obtain full dermatologic examination

- Triplicate 12-lead ECG performed pre-binimetinib administration (within 5-10 minutes total time), then a single ECG 1 hour (± 15 minutes) after binimetinib administration
- Collection of blood samples for the following:
    - Hematology, coagulation, chemistry including BNP and troponin I
    - If not performed within 24 hours prior to Day 1 dosing, predose serum pregnancy test (females of childbearing potential only)
    - Cardiac/muscle enzymes
    - Thyroid panel
    - Biomarker analysis
    - CCI
- Obtain urine sample for urinalysis
- CT or MRI of chest, abdomen/pelvis, and brain (only if positive during screening)
- Administer binimetinib
- Administer nivolumab
- Collect a PK blood sample 1.5 hours (± 15 minutes) post binimetinib dosing
- Administer ipilimumab after PK blood sample is collected
- Dispense a 4-week supply of binimetinib along with a monthly diary. Review dosing instructions with patient.
- Assess AEs
- Assess concomitant medications/therapies

Figure 4: Arm 1B/Arm 2B: Timing of ECGs and Blood Collections in Relation to Study Drug Administration on Cycle 1 Day 1



8.6.2 Phase 1b Arm 1B and Phase 2 Arm 2B (nivolumab + binimetinib + ipilimumab): Cycle 1 Day 15

- Measure body weight
- Assess vital signs (blood pressure, pulse, and temperature)
- Complete physical examination
- Assess ECOG PS
- Collection of blood samples for the following:
    - Hematology, coagulation, chemistry including BNP and troponin I
    - Cardiac/muscle enzymes
    - PK analysis (collected prior to morning dose of binimetinib)
- Administer binimetinib
- Collect a PK blood sample 1.5 hours (± 15 minutes) post binimetinib dosing
- Assess AEs
- Assess concomitant medications/therapies

8.6.3 Phase 1b Arm 1B and Phase 2 Arm 2B (nivolumab + binimetinib + ipilimumab): Cycle 1 Day 22

- Collection of blood samples for the following:

- Hematology
- Cardiac/muscle enzymes

- Assess AEs
- Assess concomitant medications/therapies

8.7 Phase 1b Arm 1B and Phase 2 Arm 2B (nivolumab + binimetinib + ipilimumab): Cycle 2

8.7.1 Phase 1b Arm 1B and Phase 2 Arm 2B (nivolumab + binimetinib + ipilimumab): Cycle 2 Day 1

- Measure body weight
- Assess vital signs (blood pressure, pulse, and temperature)
- Complete physical examination
- Assess ECOG PS
- Obtain full ophthalmic examination
- Perform ECHO/MUGA scan
- Single 12-lead ECG performed pre-binimetinib administration, then 1 hour (± 15 minutes) after binimetinib administration
- Collection of blood samples for the following:
  - Hematology, coagulation, chemistry including BNP and troponin I
  - Serum (or urine) pregnancy test (females of childbearing potential only)
  - Cardiac/muscle enzymes
  - Thyroid panel
  - Biomarker analysis
- Obtain urine sample for urinalysis
- Perform optional tumor biopsy and if performed, collect a blood sample at the time of biopsy
- Administer binimetinib
- Administer nivolumab
- Assess binimetinib compliance and dispense a 4-week supply along with a monthly diary. Review dosing instructions with patient.
- Assess AEs
- Assess concomitant medications/therapies

8.7.2 Phase 1b Arm 1B and Phase 2 Arm 2B (nivolumab + binimetinib + ipilimumab): Cycle 2 Day 15

- Measure body weight
- Assess vital signs (blood pressure, pulse, and temperature)
- Complete physical examination
- Assess ECOG PS
- Collection of blood samples for the following:
    - Cardiac/muscle enzymes
    - PK analysis (collected prior to morning dose of binimetinib)
- Assess AEs
- Assess concomitant medications/therapies

8.8 Phase 1b Arm 1B and Phase 2 Arm 2B (nivolumab + binimetinib + ipilimumab): Subsequent Cycles

8.8.1 Phase 1b Arm 1B and Phase 2 Arm 2B (nivolumab + binimetinib + ipilimumab): Subsequent Cycles Day 1

- Measure body weight
- Assess vital signs (blood pressure, pulse, and temperature)
- Complete physical examination
- Assess ECOG PS
- **Cycle 3 Day 1, Cycle 5 Day 1 and Cycle 7 Day 1 and then Q12W:** (±7 days)**:** CT or MRI of chest, abdomen/pelvis, and brain (only if positive during screening)
- **Cycle 4 Day 1:** Obtain full ophthalmic examination - performed Q8W thereafter (i.e., C6D1, C8D1, etc.)
- Obtain full dermatologic examination - performed Q8W thereafter
- Perform ECHO/MUGA scan then **Q12W** thereafter
- Single 12-lead ECG performed predose (all study drugs)
- Collection of blood samples for the following:
    - Hematology, coagulation, chemistry including BNP and troponin I
    - Serum (or urine) pregnancy test (females of childbearing potential only)
    - Cardiac/muscle enzymes
    - Thyroid panel

- Biomarker analysis

- Obtain urine sample for urinalysis
- Administer binimetinib
- Administer nivolumab
- Administer ipilimumab - administered Q8W thereafter
- Assess binimetinib compliance and dispense a 4-week supply along with a monthly diary. Review dosing instructions with patient.
- Assess AEs
- Assess concomitant medications/therapies

8.8.2 Phase 1b Arm 1B and Phase 2 Arm 2B (nivolumab + binimetinib + ipilimumab): Subsequent Cycles Day 15

- Measure body weight
- Assess vital signs (blood pressure, pulse, and temperature)
- Complete physical examination
- Assess ECOG PS
- **Cycles 3 through 5:** Collect blood samples for PK analysis prior to morning dose of binimetinib
- Assess AEs
- Assess concomitant medications/therapies

8.9 Follow-up Visits (All Arms and Phases)

8.9.1 End of Treatment Visit

- Measure body weight
- Assess vital signs (blood pressure, pulse, and temperature)
- Complete physical examination
- Assess ECOG PS
- Obtain full ophthalmic examination
- Obtain full dermatologic examination
- Perform ECHO/MUGA scan
- Single 12-lead ECG
- Collection of blood samples for the following:

  - Hematology, coagulation, chemistry including BNP and troponin I
  - Serum (or urine) pregnancy test (females of childbearing potential only)
  - Cardiac/muscle enzymes
  - Thyroid panel
  - Biomarker analysis
- Perform optional tumor biopsy and if performed, collect a blood sample at the time of biopsy
- Assess binimetinib compliance
- Assess AEs
- Assess concomitant medications/therapies

8.9.2 30-Day Safety Follow-up Visit

All patients will return for a 30-Day Safety Follow-up Visit approximately 30 days (± 3 days) after the last dose of study drug. Information related to AEs (including concomitant medication taken for ongoing AEs) and ongoing antineoplastic treatments will be collected (see Section 10.9).

- Measure body weight
- Assess vital signs (blood pressure, pulse, and temperature)
- Complete physical examination
- Assess ECOG PS
- Obtain full dermatologic examination
- Collection of blood samples for the following:
  - Hematology, coagulation, chemistry including BNP and troponin I
  - Serum (or urine) pregnancy test (females of childbearing potential only)
  - Thyroid panel
- Assess AEs
- Assess concomitant medications/therapies
- If applicable, document subsequent anticancer therapy and progressive disease after subsequent anticancer therapy

8.9.3 100-Day Safety Follow-Up Visit

All patients will return for a 100-Day Safety Follow-Up visit which occurs 100 days (± 7 days) after last dose of study drug. Information related to AEs and SAEs (including concomitant

medication taken for ongoing AEs/SAEs) and ongoing antineoplastic treatments will be collected (see Section 10.9).

- Assess all AEs and SAEs
- Assess concomitant medications/therapies administered for all AEs and SAEs
- If applicable, document subsequent anticancer therapy and progressive disease after subsequent anticancer therapy

8.9.4 150-Day Safety Follow-Up Assessment (Phone Call)

All patients will be contacted via telephone 150 days (+ 7 days) after last dose of study drug to obtain information on SAEs (including concomitant medications taken for ongoing SAEs) and survival as available. Ongoing antineoplastic treatments will be collected if available (see Section 10.9).

8.9.5 Tumor Assessment Follow-up Visits

All tumor assessments should be performed every 8 weeks (±7 days) from C1D1 through Week 24, then every 12 weeks (±7 days) thereafter until disease progression, withdrawal of consent, initiation of subsequent anticancer therapy, patient is lost to follow-up, death or defined end of study (Section 4.3).

- CT or MRI of chest, abdomen/pelvis, and brain (only if positive during screening).

8.9.6 Survival Follow-up

Contact patients or medical caregiver via telephone every 12 weeks ± 2 weeks after treatment discontinuation for survival status until the End of Study (see Section 4.3) or until withdrawal of consent for such follow up, lost to follow up, or death.

- If applicable, document subsequent anticancer therapy and progressive disease after subsequent anticancer therapy.

8.10 Collection of Data for Ongoing Patients Following Database Lock

If the primary objective of the study has been met or the Sponsor decides to stop the study early, the database may be locked for the purpose of analyzing and reporting data. Patients may continue to receive study treatment per protocol beyond database lock if the Investigator and the Sponsor agree that patients' best interests are served by continuing to receive study treatment.

In such cases, appropriate safety information will continue to be captured per protocol and submitted to the Sponsor. The information to be collected may include treatment-related AEs and SAEs, laboratory results of special interest, study drug administration, patient status and date and reason(s) for study withdrawal.

9.0 STUDY DISCONTINUATION

9.1 Termination of the Study by the Sponsor

This study may be discontinued at any time due to safety concerns, failure to meet expected enrollment goals, administrative reasons or at the discretion of the Sponsor. Should the study be terminated prematurely, the Sponsor will provide written notification to all Investigators and regulatory authorities and will specify the reason(s) for early termination. The Investigator must inform the Institutional Review Board (IRB) promptly and provide the reason(s) for the termination.

9.2 Treatment Discontinuation for Individual Patients

Patients may withdraw their consent to participate in the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. Upon withdrawal of consent, patients should be asked if they are willing to be contacted by telephone for monitoring of survival. If a patient withdraws consent, the date, stated reason for and level of consent withdrawal should be documented. Patient data collected up to the date of consent withdrawal will be included in the analyses. Any blood or tissue samples collected up to the date of withdrawal of consent will be analyzed.

Wherever possible, the tests and evaluations listed for the End of Treatment visit should be carried out and an effort should be made to continue follow-up. The Sponsor should be notified of all study withdrawals through the designated eCRFs in a timely manner.

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

- Withdrawal of consent (no further participation)
- Patient decision to discontinue study treatment (but request agreement to return for end of treatment assessments, safety follow-up assessments and/or survival follow-up)
- Unacceptable AEs or failure to tolerate study drug
- Dose interruption of > 28 consecutive days in administration of binimetinib or > 6 weeks in administration of nivolumab or > 18 weeks in administration of ipilimumab, unless judged by the Investigator and the Sponsor's Medical Monitor or designee to be in the best interest of the patient to continue treatment
- Changes in the patient's condition or development of an intercurrent illness which renders the patient unacceptable for further treatment in the judgment of the Investigator
- Disease progression as defined by RECIST, v1.1 (continuation of treatment beyond progression permitted in special circumstances as defined in Section 4.2)

- Clinical progression, per the discretion of the Investigator
- Receipt of non-protocol-specified anticancer therapy for study indication (chemotherapy, biological therapy or radiation therapy that includes > 30% of the bone marrow reserve)
- Patient becomes pregnant or begins breastfeeding
- Significant protocol deviation that, in the opinion of the Investigator and/or Sponsor, renders the patient unsuitable for further study drug administration
- Lost to follow-up
- Death
- Termination of the study by the Sponsor (described in Section 9.1).

Patients meeting any of the following criteria may, at the discretion of the Investigator, be discontinued from study drug treatment:

- Is found not to have met eligibility criteria; the patient would be discontinued if the investigator determines that the patient would not benefit from participation in the study due to eligibility deviation.
- Is noncompliant with study procedures or study drug administration in the opinion of the investigator (see Section 6.7).

9.3 Study Discontinuation for Individual Patients

The patient may be considered discontinued from the study for the following reasons:

- Withdrawal of consent for survival follow-up
- Lost to follow-up
- Death
- Termination of the study by the Sponsor (described in Section 9.1).

9.4 Replacement of Patients

In Phase 1b of the study, patients who terminate participation in the study for any reason other than an AE or abnormal laboratory value unrelated to disease, disease progression, intercurrent illness or concomitant medications/therapies before completing at least 75% dose intensity (administered dose in mg/planned dose in mg) of the binimetinib doses in Cycle 1 will be considered ineligible for the safety assessment required for MTD determination.

In the Phase 2 part of the study, randomized patients who discontinue prior to study completion will not be replaced.

10.0 SAFETY MONITORING: DEFINITIONS AND REPORTING

10.1 Adverse Event

An AE is defined as any untoward medical occurrence, including the exacerbation of a pre-existing condition, in a patient administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

10.2 Immune-Mediated Adverse Events

Every AE must be assessed by the investigator with regard to whether it is considered immune-mediated. Immune-mediated AEs are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (e.g., infection or tumor progression) have been ruled out and that require the use of corticosteroids. Immune-mediated AEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. For events which are potentially immune-mediated, additional information will be collected on the eCRF.

10.3 Events Related to Progression of Disease

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors) will be designated as progression of disease in the eCRF and should not be reported as an AE or SAE unless a causal relationship to study drug is suspected.

10.4 Clinical Laboratory Abnormalities

An abnormal laboratory value that is not associated with an already reported AE is to be recorded as an AE only if an action on the study drug is made as a result of the abnormality, if intervention for management of the abnormality is required, or at the discretion of the Investigator.

Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or baseline, or per Investigator discretion.

10.5 Overdose

An overdose of study drug (whether symptomatic or asymptomatic) will be reported as an AE.

10.6 Assessment of Severity

The severity rating of an AE refers to its intensity. The severity of each AE will be determined by the Investigator using the NCI CTCAE v4.03. For any term that is not specifically listed in the CTCAE scale, severity should be assigned a Grade of 1 through 5 using the following CTCAE guidelines:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Fatal

10.7 Assessment of Causality

An assessment of causal relationship of each study drug to each AE must be performed by the Investigator. Medical judgment should be used to determine the cause of the AE, considering all relevant factors such as (but not limited to) the underlying study indication, coexisting disease, concomitant medication, relevant history, pattern of the AE, temporal relationship to the study medication and de-challenge or re-challenge.

Yes (possibly, probably or definitely related): there is a reasonable possibility that the study drug caused the event; one or more of the following criteria apply:

- The event follows a reasonable temporal sequence from administration of study drug.
- The event could not be reasonably attributed to the known characteristics of the patient's clinical state, environmental or toxic factors or other modes of therapy administered to the patient.
- The event follows a known pattern of response to study drug.
- The event disappears or decreases on cessation or reduction in dose of the study drug. (It should be noted that in some situations an AE will not disappear or decrease in intensity upon discontinuation of study drug despite other clear indications of relatedness).

- The event reappears or worsens when the study drug is re-administered.

No (unlikely, probably not related or definitely not related): there is no reasonable possibility that the study drug caused the event; one or more of the following criteria apply:

- The event does not follow a reasonable temporal sequence from administration of study drug.
- The event could be reasonably attributed to the known characteristics of the patient's clinical state, concurrent illness, environment or toxic factors or other modes of therapy administered to the patient.
- The event does not follow a known pattern of response to study drug.
- The event does not disappear or decrease on cessation or reduction in dose of the study drug, and it does not reappear or worsen when the study drug is re-administered.

10.8 Assessment of Seriousness

An AE is considered "serious" if it results in any of the following outcomes:

- Results in death.

  Note: Death is an outcome of an SAE and not an SAE in itself. Death should only be reported as an SAE term when no additional information is known about a fatal event. When death is an outcome, the event(s) resulting in death should be reported (e.g., "pulmonary embolism" with a fatal outcome) and assigned severity Grade 5.

- Is immediately life-threatening (its occurrence places the patient at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization.

  Note: Hospitalization includes any hospital admission, even if for less than 24 hours. The following do not meet hospitalization serious criteria:

  - A visit to the emergency room, or outpatient observation that does not result in admission
  - Elective surgery, planned prior to signing consent
  - Routine health assessment requiring admission
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital anomaly/birth defect.

- Based upon appropriate medical judgment, represents an important medical event that may jeopardize the patient or may require intervention to prevent one of the outcomes described above.

10.9 Reporting of Serious and Nonserious Adverse Events

All AEs, serious and nonserious (including the exacerbation of a pre-existing condition) and regardless of causality to study drug, will be fully recorded on the appropriate eCRF. For each AE, the Investigator must provide its duration (start and end dates or ongoing), severity (intensity), assessment of causality, whether specific action or therapy was required, and whether action was taken with regard to study drug treatment.

Any AE that occurs from the signing of the ICF until the first dose of study drug is to be recorded on the AE eCRF page only if the event was related to a study procedure. All other AEs/findings prior to the first dose of study drug should be recorded on the medical history eCRF. All AEs occurring from the first dose of study drug until 100 days after the last dose of study drug must be recorded on the AE eCRF, regardless of causal relationship to the investigational product. After 100 days, SAEs only are to be reported until 150 days after the last dose of study drug, regardless of causal relationship to investigational product. SAEs occurring greater than 150 days after the last dose of study drug should be reported only if considered related to investigational product.

In addition to recording SAEs on the AE eCRF, all SAEs must be reported to the Sponsor within 24 hours of the Investigator's knowledge by faxing the completed SAE form to the Sponsor at the number provided on the SAE form or fax cover sheet. If new information becomes available for a previously reported SAE, a follow-up SAE report should be sent within 24 hours.

Investigators must follow patients with AEs/SAEs until the event has resolved, the condition has stabilized, withdrawal of consent, the patient is lost to follow up, or death OR until 150 days after the last dose of study drug, whichever occurs first. Ongoing treatment-related SAEs may be followed beyond this time period if clinically indicated.

10.10 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

Suspected unexpected serious adverse reactions (SUSARs) will be collected and reported by the Sponsor and/or designee to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

10.11 Pregnancy or Drug Exposure during Pregnancy

If a patient becomes pregnant during the study, administration of study drug is to be discontinued immediately.

Pregnancies (both those of female patients and female partners of male patients) must be reported to the Sponsor or designee within 24 hours of the Investigator's knowledge using the Investigational Product Pregnancy Report. All pregnancies will be followed through to outcome and the outcome must be reported to the Sponsor or designee using the Investigational Product Pregnancy Outcome Report.

Pregnancies themselves are not considered AEs or SAEs. However, any AEs or SAEs occurring during pregnancy are to be reported following AE and SAE reporting guidelines.

11.0 STATISTICAL METHODS

11.1 Sample Size

For the dose-finding period of this study (Phase 1b), the primary objective is to determine the RP2D of binimetinib in combination with nivolumab with or without ipilimumab. The total number of patients enrolled in the dose-finding period will depend on the number of dose levels tested and the number of patients treated in each cohort before the RP2D has been determined.

Approximately 90 patients are planned. A maximum of approximately 42 patients will be enrolled in Phase 1b and a minimum of approximately 48 patients will be enrolled in Phase 2.

In Phase 1b, a maximum of approximately 21 patients will be treated in each arm, with a target of 9 patients at the MTD. In the Phase 2 period of the study, a minimum of approximately 24 patients will be treated in each arm. Randomization into Phase 2 will continue until at least 33 patients have received the doublet and the triplet, respectively, at the RP2D (Phase 1b and Phase 2 combined).

The primary analysis of the response rate and efficacy endpoints will include all Phase 2 patients plus those treated at the same dose/schedule in Phase 1b; thus, it is expected that a minimum of 33 patients in each arm will be available for the primary efficacy evaluation.

In the doublet arm, a response rate of 5% or less will be considered unacceptably low. Hence, in, the null hypothesis that the response rate is at most 5% will be tested against the alternative hypothesis that the response rate is greater than 5%. The targeted response rate is 20%. With these assumptions, and a two-tailed alpha = 0.10 significance level, 33 patients will provide approximately 86% power.

In the triplet arm, a response rate of 10% or less will be considered unacceptably low. Hence, the null hypothesis that the response rate is at most 10% will be tested against the alternative hypothesis that the response rate is greater than 10%. The targeted response rate is 30%. With these assumptions, and a two-tailed alpha = 0.10 significance level, 33 patients will provide approximately 91% power

The study is not adequately powered to compare the response rate between treatment arms; these comparisons will be descriptive only.

11.2 Analysis Sets

11.2.1 Full Analysis Set

The Full Analysis Set (FAS) will consist of all patients who receive at least one dose of study drug.

11.2.2 Safety Set

The Safety Set (SS) will consist of all patients who receive at least one dose of study drug.

11.2.3 Dose-Determining Set

The Dose-Determining Set (DDS) includes all patients from Phase 1b who either experience a DLT or receive at least 75% of the planned binimetinib dose intensity during the first cycle of treatment.

Patients in the DDS who do not experience DLT during the first cycle will be considered to have sufficient safety evaluations if they have been observed for ≥ 28 days following the first dose and are considered by both the Sponsor and Investigators to have enough safety data to conclude that a DLT did not occur.

11.2.4 Per Protocol Set

The Per-Protocol Set (PPS) will consist of all patients in the FAS who are sufficiently compliant with the protocol requirements. A precise definition of the criteria required for inclusion in the PPS will be provided in the statistical analysis plan (SAP).

11.2.5 Pharmacokinetic Set

The PK Analysis Set (PAS) will consist of all patients who receive at least one dose of binimetinib and have at least one evaluable bioanalytical result.

11.3 Statistical Analyses and Methods

11.3.1 General 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 or key secondary endpoint definition or analysis will also be described in a protocol amendment.

Data analyses from this study will be performed by the Sponsor or designee.

11.3.2 Patient Characteristics

The following baseline patient characteristics will be summarized descriptively by treatment group: ECOG PS, demographics (age, gender and race); prior anticancer agents (chemotherapy,

biologics, targeted small molecules); prior chemotherapy; best response to prior chemotherapy; prior radiotherapy, prior surgery; medical history; concomitant medication usage; various genes' mutation status.

11.3.3 Efficacy Analyses

Unless otherwise stated, efficacy analyses will be conducted using the FAS. A supportive analysis of the primary efficacy endpoint from Phase 2 will be conducted using the PPS.

Additional details for methodology for endpoints not listed below will be provided in the SAP.

11.3.3.1 Objective Response Rate

The overall best response (i.e., CR or partial response [PR]) as assessed by the Investigator per RECIST v1.1 will be determined for each patient. The ORR will be calculated within each treatment arm, where ORR is defined as the number of patients achieving an overall best response of CR or PR divided by the total number of patients in that treatment arm. The ORR with exact (Clopper-Pearson) 95% confidence intervals (CIs) will be provided.

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

A similar analysis will be provided for the rate of CR.

CCI [redacted]

11.3.4 Safety Analyses

Descriptive statistics will be used to summarize safety data. AEs, ECG and laboratory data will be reviewed and summarized on an ongoing basis during the study. All AE, ECG and safety laboratory abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively by dose group, time, and cohort where appropriate. Absolute value data and change from baseline data will be summarized as appropriate.

All AEs will be coded by body system using the Medical Dictionary for Regulatory Activities (MedDRA®), and summary tables for all AEs will be generated. Incidence rates will be summarized for each preferred term and body system. Additional summary tables will be generated for the following subsets of patients: patients with SAEs, patients with study drug related AEs, patients who died, and patients who discontinued due to AEs. Severity of events will also be summarized.

11.3.5 Pharmacokinetic Analysis

Non-compartmental pharmacokinetic parameters will not be estimated due to sparse sampling in this trial. Pharmacokinetic parameters will be determined for binimetinib and/or AR00426032 using a model-based approach to determine appropriate model-based PK parameters and their respective variability, if deemed appropriate. PK data may be analyzed in at least 2 ways:

- Data from this study will be analyzed alone based on the previously described population PK model. The structure of the model will remain similar but parameters (fixed and random effects) will be estimated based on the current population.
- If needed, prior knowledge from other studies with intensive sampling may be introduced in the analysis by either fixing the population parameters to the value estimated previously or by adding data from the previous studies to the dataset to estimate population parameters and derive Empirical Bayes Estimates of PK parameters for patients in this study.

Details of these analyses and of the incorporation of prior information will be provided in a specific standalone modeling plan. Analysis will be provided in a specific report as appropriate.

CCI [redacted] PK exposure will be derived from the population PK model in order to obtain actual daily exposure.

CCI [redacted]

11.4 Operating Characteristics

Dose-escalation and de-escalation decisions will be based on the methodology outlined in the mTPI-2 paper (Guo et al. 2017). The dose levels in Arm 1A are ranked based on dose intensity, as outlined in Table 16 (higher ranks imply higher dose intensity).

Table 16: Dose Levels

Arm	Dose Level (*Starting Dose Level)	Binimetinib	Nivolumab	Ipilimumab
1A (Doublet)	4*	45 mg BID	480 mg Q4W	N/A
	3	45 mg BID 3W on / 1W off		
	2	30 mg BID		
	1	30 mg BID 3W on / 1W off		
1B (Triplet)[a]	4	45 mg BID	480 mg Q4W	1 mg/kg Q8W
	3	45 mg BID 3W on / 1W off		
	2	30 mg BID		
	1	30 mg BID 3W on / 1W off		

[a] The starting Dose Level of Arm 1B (Triplet) will be the RP2D of binimetinib from Arm 1A. If tolerated, the RP2D of binimetinib from Arm 1A will be considered the RP2D for Arm 1B. If not tolerated, any dose level below the RP2D for Arm 1B may be explored.

Modifying the mTPI-2 to allow for a maximum of 9 patients at a dose level modifies the operating characteristics of the standard mTPI-2. Results of simulations based on these modifications are provided below for various true DLT rates.

Simulations are generated with the following additional assumptions: Max sample size of 21, target probability of DLT = 30%, equivalence interval = (25%, 35%), cohort size = 3, number of simulations per scenario = 1000.

Table 17: Dose-limiting Toxicities Probability Scenarios

Dose Level				
Rank based on dose intensity	**1**	**2**	**3**	**4**
Binimetinib dose/schedule	30 mg BID Q3/4w	30 mg BID	45 mg BID Q3/4w	45 mg BID
Scenario 1				
True DLT rate	10%	15%	20%	35%
Probability selected as MTD*	.005	.097	.165	.732
Average total sample size	11.5			
% of patients experiencing a DLT	30.1%			
Scenario 2				
True DLT rate	5%	10%	20%	25%
Probability selected as MTD*	.004	.039	.074	.882
Average total sample size	10.2			
% of patients experiencing a DLT	23.1%			

*In cases where rows do not add up to 100%, the model concluded that no dose level was acceptable.

12.0 DATA RECORDING, RETENTION AND MONITORING

12.1 Data Management

Data will be collected using an electronic data capture system (EDC) at the clinical site. The Investigator or designee will record data specified in the protocol using eCRFs. 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.

It is the Investigator's responsibility to ensure eCRFs are complete and accurate. 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 portable document format (PDF) file of the eCRFs will be provided to the site after all data have been monitored and reconciled. An electronic copy will be archived at the site.

12.2 Data Monitoring

This study will be closely monitored by representatives of the Sponsor throughout its duration. 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. It is the monitor's responsibility to inspect eCRFs at regular intervals throughout the study to verify the completeness, accuracy and consistency of the data and to confirm adherence to the study protocol and to Good Clinical Practice (GCP) guidelines. The Investigator agrees to cooperate with the monitor to ensure that any problems detected during the course of this study are resolved promptly. The Investigator and site will permit study-related monitoring, audits, EC review and regulatory inspection, including direct access to source documents.

It is understood that study monitors and any other personnel authorized by the Sponsor may contact and visit the Investigator and will be permitted to inspect all study records (including eCRFs and other pertinent data) on request, provided that patient confidentiality is maintained and that the inspection is conducted in accordance with local regulations.

Every effort will be made to maintain the anonymity and confidentiality of patients during this study. However, because of the experimental nature of this treatment, the Investigator agrees to allow representatives of the Sponsor, the development partner of the Sponsor, as well as authorized representatives of regulatory authorities to inspect the facilities used in the conduct of this study and to inspect, for purposes of verification, the hospital or clinic records of all patients enrolled in the study.

12.3 Quality Control and Quality Assurance

Quality control procedures will be conducted according to the Sponsor's internal procedures. The study site may be audited by a quality assurance representative of the Sponsor. All necessary data and documents will be made available for inspection.

13.0 REGULATORY, ETHICAL AND LEGAL OBLIGATIONS

13.1 Good Clinical Practice

The study will be performed in accordance with the protocol, guidelines for GCP established by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and applicable local regulatory requirements and laws and in accordance with European Clinical Trials Directive.

13.2 Ethics Committee Approval

The Investigator must inform and obtain approval from the EC for the conduct of the study at named sites, the protocol, informed consent documents and any other written information that will be provided to the patients and any advertisements that will be used. Written approval must be obtained prior to recruitment of patients into the study and shipment of study drug.

Proposed amendments to the protocol and aforementioned documents must be submitted to the Sponsor for review and approval, then to the EC. Amendments may be implemented only after a copy of the approval letter from the EC has been transmitted to the Sponsor. Amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented prior to receiving Sponsor or EC approval. However, in this case, approval must be obtained as soon as possible after implementation.

Per GCP guidelines, the Investigator will be responsible for ensuring that an annual update is provided to the EC to facilitate continuing review of the study and that the EC is informed about the end of the study. Copies of the update, subsequent approvals and final letter must be sent to the Sponsor.

13.3 Regulatory Authority Approval

The study will be performed in accordance with the requirements of each country's regulatory authorities (e.g., FDA, European Medicines Agency (EMA) and Health Canada) and will also meet all of the requirements of ICH GCP guidance. Amendments to the protocol will be submitted to the relevant authorities (e.g., FDA, EMA or Health Canada) for approval prior to implementation in accordance with applicable regulations.

13.4 Other Required Approvals

In addition to EC 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.

13.5 Informed Consent

Informed consent is a process that is initiated prior to the patient's agreeing to participate in the study and continues throughout the patient's study participation. 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. Each patient should be given a copy of the informed consent document and associated materials. The original copy of the signed and dated informed consent document must be retained at the site and is subject to inspection by representatives of the Sponsor or regulatory authorities. If any amendments occur throughout the course of the study that affect the ICF (i.e., when new study procedures or assessments have been added), all active patients should be reconsented using the same process for the initial consent.

13.6 Patient Confidentiality

The Investigator must ensure that the patient's privacy is maintained. On the eCRF or other documents submitted to the Sponsor, patients will be identified by a patient number only. Documents that are not submitted to the Sponsor (e.g., signed informed consent documents) should be kept in a confidential file by the Principal Investigator.

The Investigator shall 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. As part of the required content of informed consent documents, the patient must be informed that his/her records will be reviewed in this manner.

13.7 Disclosure of Information

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

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

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

13.8 Publication of Study Data

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

14.0 ADHERENCE TO THE PROTOCOL

Investigators must apply due diligence to avoid protocol deviations, 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. Protocol deviations will be recorded.

14.1 Amendments to the Protocol

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 EC must be sought, and the Investigator should inform the Sponsor and the full EC within 5 working days after the emergency occurred. All amendments that have an impact on patient risk or the study objectives or require revision of the informed consent document must receive approval from the EC prior to implementation.

APPENDICES

APPENDIX 1: RECOMMENDED GUIDELINES FOR THE MANAGEMENT OF BINIMETINIB-INDUCED DIARRHEA

Proactively Investigate for Occurrence of Diarrhea and Educate Patient:

1. Remind patients at each visit to contact the Investigator immediately upon the first sign of loose stool or symptoms of abdominal pain. Additionally, at each study visit, each patient should be asked regarding occurrence of diarrhea or diarrhea-related symptoms. If the patient has had symptoms, the patient should be asked regarding the actions taken for these symptoms and re-instruct if indicated.
2. Patients should be instructed on dietary modification and early warning signs of diarrhea and potentially life-threatening illnesses (e.g., severe cramping might be a sign of severe diarrhea; fever with diarrhea might be a sign of infection; fever and dizziness on standing might be a sign of shock).
3. Patients should be educated about what to report to the Investigator (i.e., number of stools, stool composition, stool volume).

Anti-diarrhea Therapy:

In order to effectively manage diarrhea and mitigate the escalation in severity or duration of diarrhea, patient education as outlined above, as well as proper management of diarrhea is important.

Management of diarrhea should be instituted at the first sign of abdominal cramping, loose stools or overt diarrhea. All concomitant therapies /used for treatment of diarrhea must be recorded on the eCRF. It is recommended that patients be provided loperamide tablets and be instructed on the use of loperamide on the first day of binimetinib dosing. In addition to the binimetinib-induced diarrhea dosing guidelines provided in Section 6.4.2 of the protocol, these instructions should be provided at each visit and the site should ensure that the patient understood the instructions.

See Section 6.4.2 in the protocol to explain the frequency of diarrhea and its relationship to NCI CTCAE v.4.03 grading and to determine if diarrhea is complicated or uncomplicated.

Rule out Other or Concomitant Causes:

These may include:

- Infection with *Candida*, *Salmonella*, *Clostridium difficile*, *Campylobacter*. *Giardia*, *Entamoeba* or *Cryptosporidium* species, which can lead to severe infections in immunosuppressed patients.
- Medication-induced diarrhea.
- Malabsorption/lactose intolerance.
- Fecal impaction, partial bowel obstruction.

For Uncomplicated Grade 1/2 Diarrhea:

- Stop all lactose-containing products and alcohol, and eat frequent small meals that include bananas, rice, applesauce or toast.
- Stop laxatives, bulk fiber (e.g., Metamucil®), and stool softeners (e.g., docusate sodium, Colace®).
- Stop high-osmolar food supplements (e.g., Ensure® Plus, Jevity® Plus [with fiber]).
- Drink 8 to 10 large glasses of clear liquids per day (e.g., water, Pedialyte®, Gatorade®, broth).
- Consider administration of a standard dose of loperamide: initial administration 4 mg, then 2 mg every 4 hours (maximum of 16 mg/day) or after each unformed stool.
- Discontinue loperamide after 12-hours diarrhea-free (Grade 0) interval.
- Consider temporary interruption of binimetinib until resolved to Grade ≤ 1. Re-treatment may then be resumed at current dose level.
- If uncomplicated Grade 1 to Grade 2 diarrhea persists for more than 24 hours, escalate to high-dose loperamide: 2 mg every 2 hours (maximum of 16 mg/day) or after each unformed stool.

Note: Oral antibiotics may be started as prophylaxis for infections under the discretion of the physician.

- If uncomplicated Grade 1 to Grade 2 diarrhea persists after 48 hours of treatment with loperamide, discontinue loperamide and begin a second-line agent which can be an opiate (opium tincture or paregoric), octreotide acetate or steroid (budesonide).

For Complicated Grade 1/2 Diarrhea or Any Grade 3/4 Diarrhea:

- The patient must call the Investigator immediately.

- Temporarily interrupt binimetinib treatment until resolved to Grade ≤ 1. Restart binimetinib at a reduced dose level.
- If loperamide has not been intitiated, initiate loperamide immediately. Initial administration 4 mg, then 2 mg every 4 hours (maximum of 16 mg/day) or after each unformed stool.
- Administer IV fluids and electrolytes as needed. In case of severe hydration, replace loperamide with octreotide acetate.
- Monitor/continue IV fluids and antibiotics as needed. Intervention should be continued until the patient is diarrhea-free for at least 24 hours.
- Hospitalization may need to be considered.

APPENDIX 2: RECOMMENDED GUIDELINES FOR THE MANAGEMENT OF BINIMETINIB-INDUCED CUTANEOUS REACTIONS

Clinical judgment and experience of the treating physician should guide the management plan of each patient. In addition to the binimetinib-induced cutaneous reaction dosing guidelines provided in Section 6.4.2 of the protocol, these instructions should be provided at each visit and the site should ensure that the patient understood the instructions.

The Initial Rash Treatment Regimen may be initiated as prophylactic treatment 24 hours prior to the first treatment, or later as needed to treat mild rash (CTCAE Grade 1).

Initial Rash Treatment Regimen:

- Application of topical agents to the most commonly affected skin areas such as face, scalp, neck, upper chest and upper back. Topical agents include the following:
    - Non-oily sunscreen (PABA-free, SPF ≥ 30, UVA/UVB protection);
    - Topical steroids, preferably mometasone cream (e.g., Elocon®);
    - Topical erythromycin (e.g., Eryaknen®);
    - Topical pimocrolimus.

Note: Topical agents should be applied on a daily basis starting on Day 1 of study treatment or 24 hours prior to first treatment, and more often as needed.

- Possibly oral doxycycline (100 mg daily) for the first 2 to 3 weeks of study drug administration.

Other effective medications are antihistamines, other topical corticosteroids, other topical antibiotics and low-dose systemic corticosteroids.

The treatment algorithm based on CTCAE grade is as follows:

Mild Rash (CTCAE Grade 1) Treatment Regimen:

- Initiate Initial Rash Treatment Regimen, if not already started.
- Use of topical corticosteroid (e.g., mometasone cream) and/or topical antibiotic (e.g., erythromycin 2%) is recommended.
- The patient should be reassessed within a maximum of 2 weeks, or as per Investigator opinion.

Moderate Rash (CTCAE Grade 2) Treatment Regimen:

- Use of topical erythromycin or clindamycin (1%) plus topical mometasone or topical pimecrolimus (1% cream) plus oral antibiotics, such as lymecycline (408 mg QD), doxycycline (100 mg BID) or minocycline (50 to 100 mg BID).
- Although there has been no evidence of phototoxicity or photosensitivity in patients treated with binimetinib, doxycycline (or minocycline as second line) should be used with thorough UV protection (i.e., avoidance of direct exposure to sunlight, use of sunscreen and sunglasses, etc.).
- Use of acitretin is not recommended.

Severe Rash (CTCAE Grade 3-4) Treatment Regimen:

CTCAE Grade 3:

- In addition to the interventions recommended for moderate rash, consider oral prednisolone at a dose of 0.5 mg/kg. Upon improvement, taper the dose in a stepwise manner (25 mg for 7 days, subsequently decreasing the dose by 5 mg/day every day).
- Alternatively, in addition to the interventions recommended for moderate rash, consider oral isotretinoin (low dose, i.e., 0.3 to 0.5 mg/kg) (Lacouture et al. 2011).
- Use of acitretin is not recommended.

CTCAE Grade 4 Treatment Regimen:

- Immediately discontinue the patient from study drug and treat the patient with oral or topical medications (see recommendation CTCAE Grade 3).

Symptomatic Treatment Regimen:

It is strongly recommended that patients who develop rash/skin toxicities receive symptomatic treatment:

- For pruritic lesions: use cool compresses and oral antihistamine agents.
- For fissuring: use Monsel's solution, silver nitrate or zinc oxide cream. If not sufficient, use mild corticosteroid ointments or ointments containing a combination of corticosteroid and antibiotic such as Fucicort®.
- For desquamation: use emollients that are mild pH 5/neutral (recommended to contain 10% urea).

- For paronychia: use antiseptic bath and local potent corticosteroids, use oral antibiotics, and, if no improvement is seen, refer to a dermatologist or surgeon.
- For infected lesions: obtain bacterial and fungal cultures and treat with topical or systemic antibiotics, if indicated, based on sensitivity of culture.

References:

Lacouture ME, Anadkat MJ, Bensadoun RJ et al. Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. Support Care Cancer 2011;19:1079–95.

APPENDIX 3: RECOMMENDED GUIDELINES FOR THE MANAGEMENT OF BINIMETINIB-ASSOCIATED INTERSTITIAL LUNG DISEASE

Clinical judgment and experience of the treating physician should guide the management plan of each patient. In addition to the binimetinib-associated interstitial lung disease (ILD) dosing guidelines provided in Section 6.4.2 of the protocol, these instructions should be provided at each visit and the site should ensure that the patient understood the instructions.

Drug-associated ILD or pneumonitis is a clinical diagnosis based on clinical signs and symptoms, radiological changes, pulmonary function tests (PFT) and exclusion of other possible etiologies of parenchymal lung disease. The most common symptoms of ILD are nonspecific and include dyspnea, dry cough, fever, fatigue, hypoxia, and occasional hemoptysis. The CTCAE v.4.03 criteria for ILD (pneumonitis) are provided below.

CTCAE v. 4.03 Criteria for Pneumonitis

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death

Definition: A disorder characterized by inflammation or diffusely affecting the lung parenchyma.

All patients should be instructed to immediately report new or worsening respiratory symptoms. Diagnostic procedures include PFT and high-resolution CT scans. The principal management of ILD consists of drug interruption and/or dose reduction and treatment with steroids as specified below. Empirical antibiotics directed at likely pathogens should also be considered while the results of diagnostic procedures and cultures are pending.

- Prednisolone 40 mg oral, daily
    - Reduce dose by 10 mg every 2 weeks × 2 (until dose reduced to 20 mg oral, daily)
    - Reduce dose by 5 mg weekly × 4 weeks
- Combine with empirical antimicrobial therapy while awaiting results of diagnostic procedures

References:

Shah R. Tyrosine kinase inhibitor-induced interstitial lung disease: Clinical features, diagnostic challenges, and therapeutic dilemmas. Drug Saf 2016;39:1073-1091.

APPENDIX 4: RECOMMENDED MANAGEMENT ALGORITHMS FOR GASTROINTESTINAL, RENAL, PULMONARY, HEPATIC, ENDOCRINOPATHY, SKIN, AND NEUROLOGIC ADVERSE EVENTS FROM NIVOLUMAB OR IPILIMUMAB TREATMENT

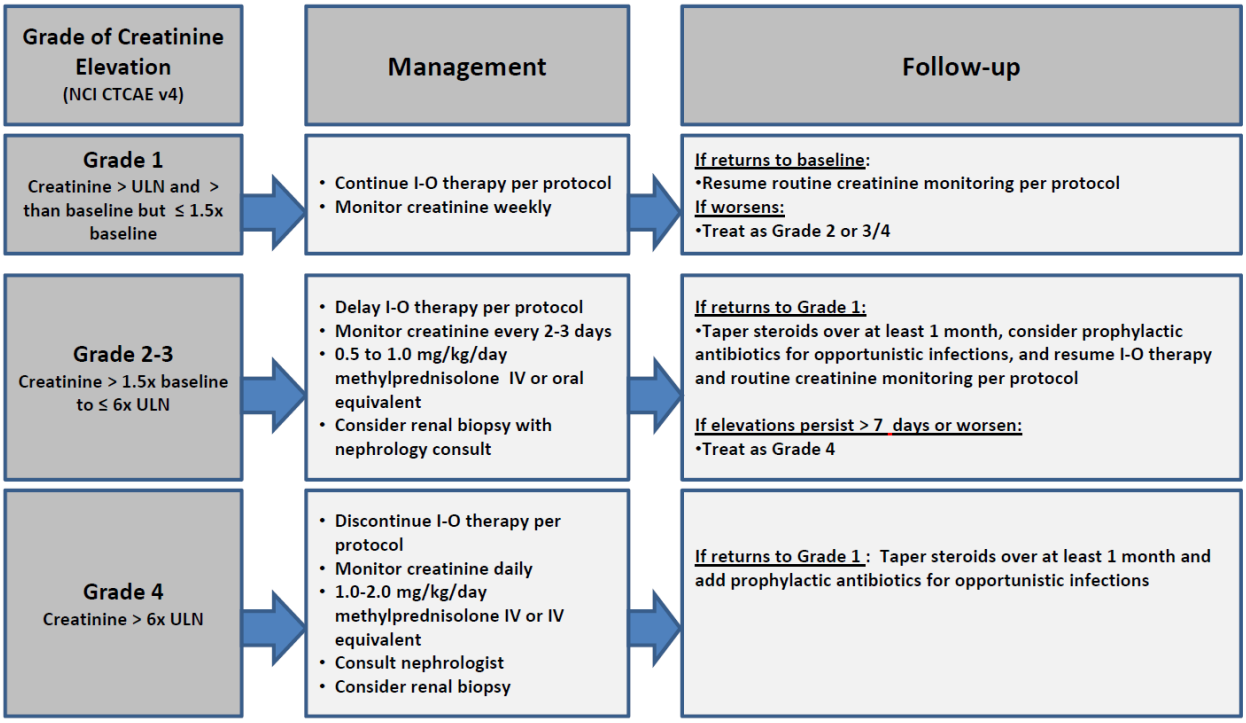
Figure A: GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

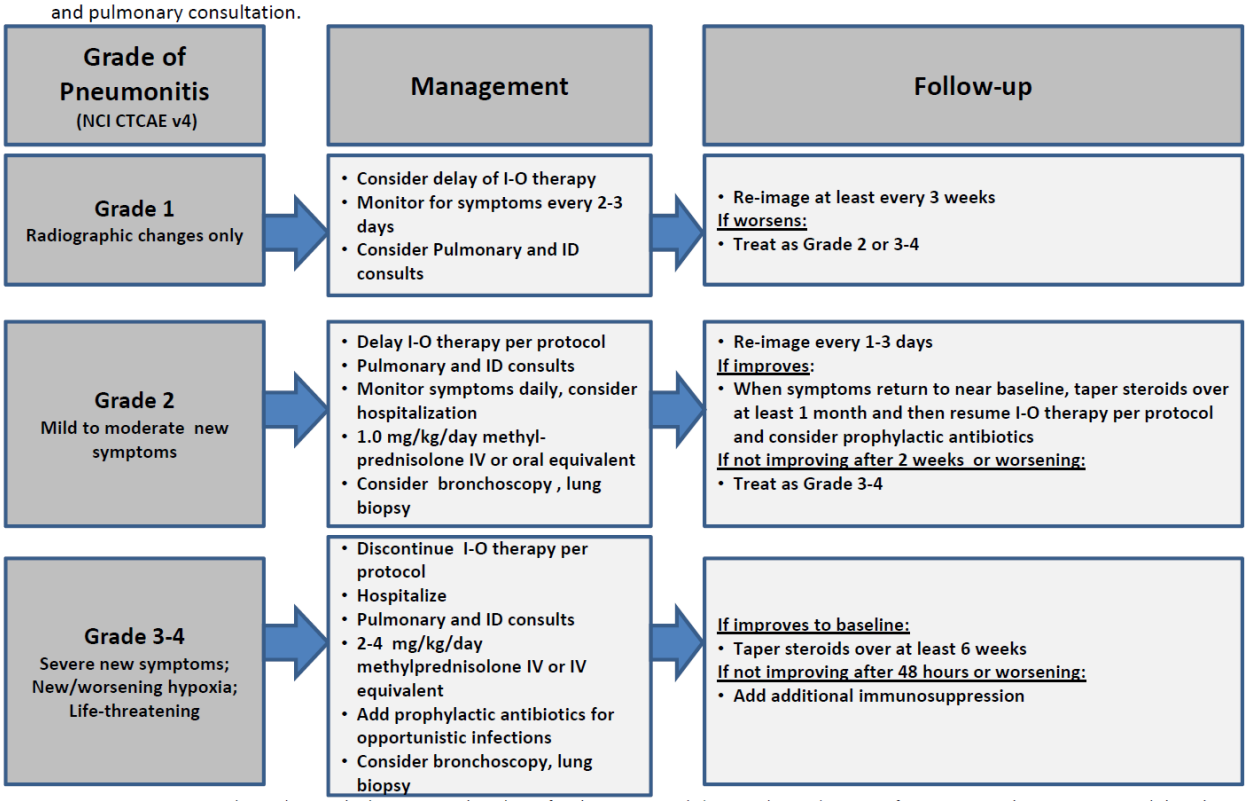
Figure B: Renal Adverse Event Management Algorithm



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Figure C: Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

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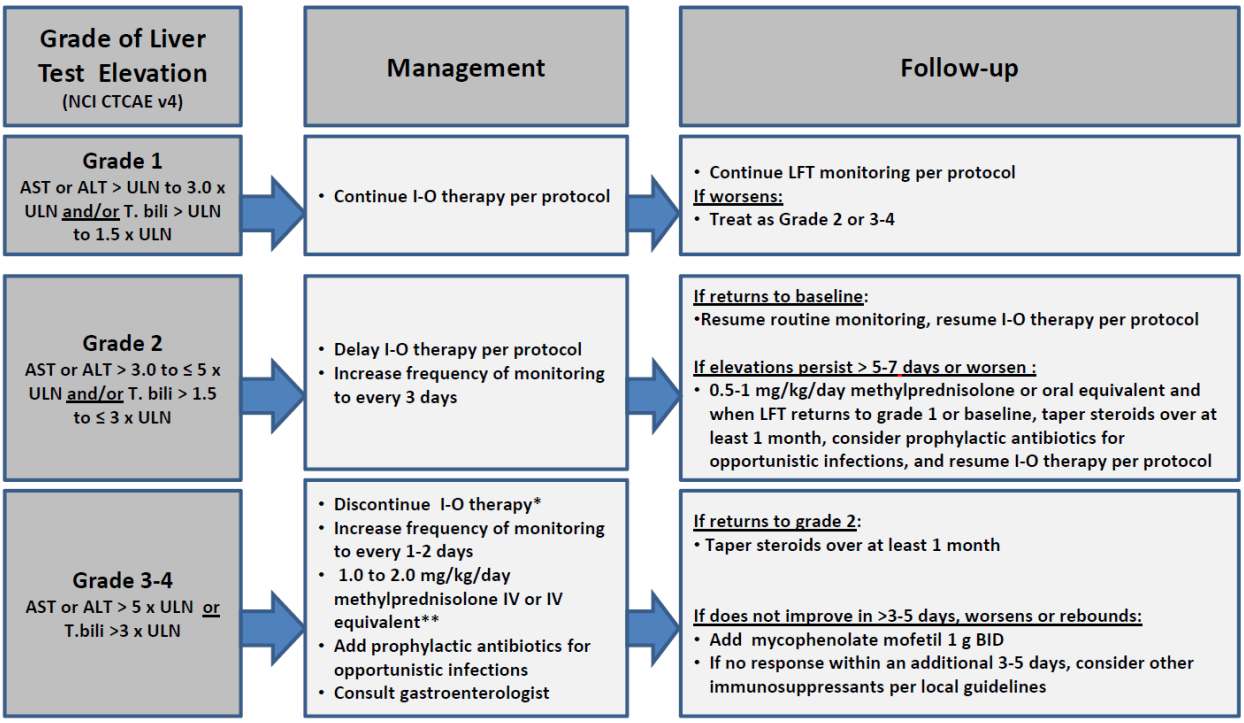
Figure D: Hepatic Adverse Event Management Algorithm

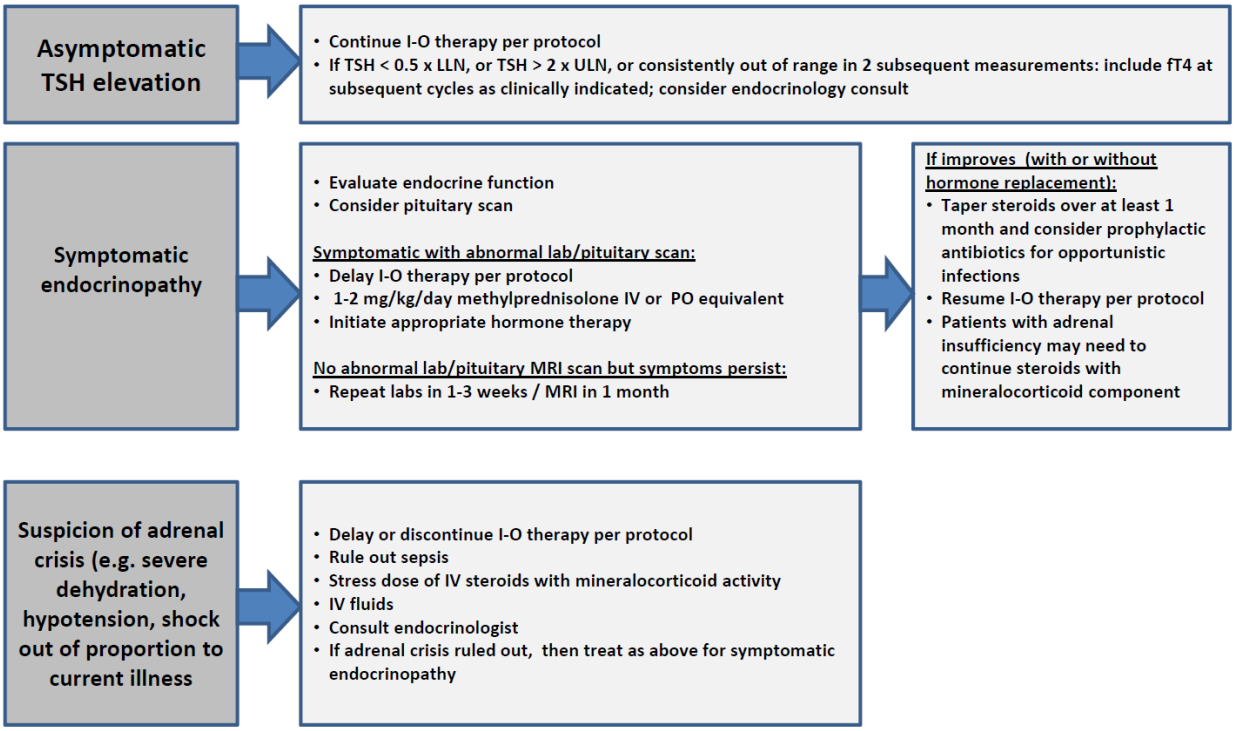
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**
**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Figure E: Endocrinopathy Management Algorithm

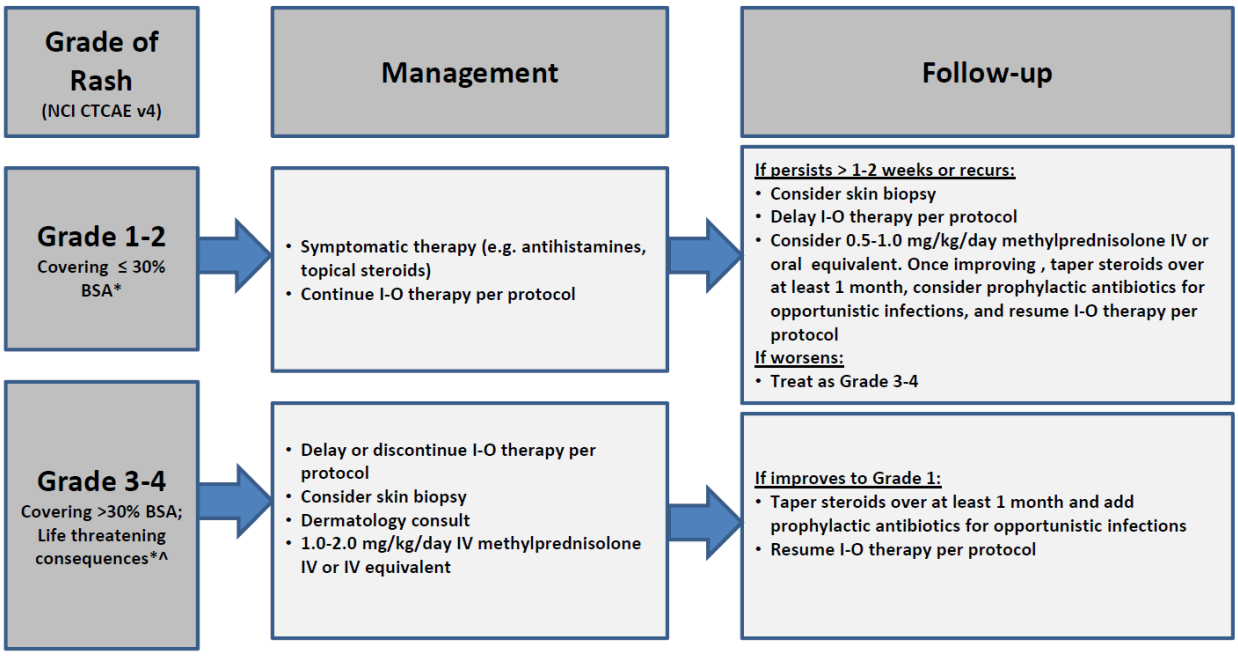
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Figure F: Skin Adverse Event Management Algorithm

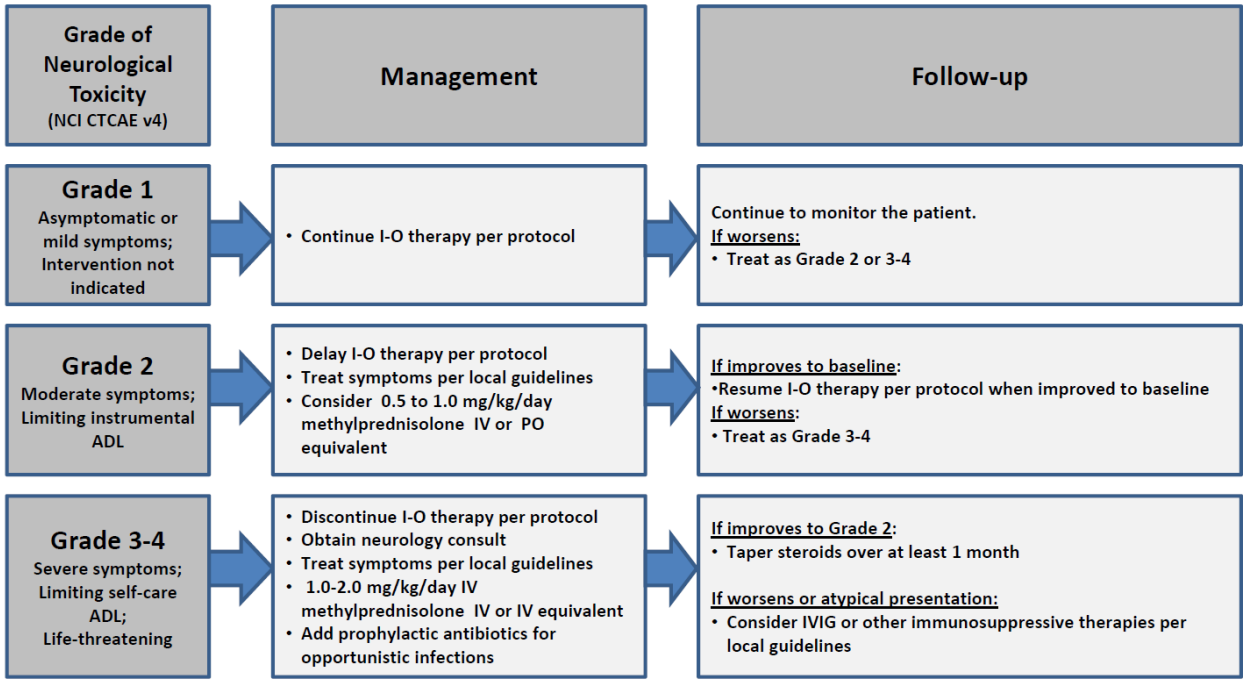
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.
^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

Figure G: Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

APPENDIX 5: SNELLEN EQUIVALENCE (VISUAL ACUITY CONVERSION CHART)

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

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

References:

Holladay JT. Visual acuity measurements. J Cataract Refract Surg. 2004;30:287-90.

APPENDIX 6: LIST OF CONCOMITANT MEDICATIONS

Table A: P-gp and BCRP Inhibitors/Inducers to Be Used with Caution

Transporter	Gene	Inhibitor [1]	Inducer [2]
P-gp	ABCB1	Alogliptin, amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, daclatasvir, diltiazem, dronedarone, eliglustat, erythromycin, felodipine, flibanserin, fluvoxamine, indinavir, indinavir and ritonavir, itraconazole, ivacaftor, ketoconazole, lapatinib, lopinavir and ritonavir, nelfinavir, paroxetine, propafenone, quercetin, quinidine, quinine, ranolazine, rifampin, ritonavir, rolapitant, saquinavir and ritonavir, simeprevir, St. John's Wort, suvorexant, telaprevir, ticagrelor, tipranavir and ritonavir, velpatasvir, verapamil, vorapaxar	Avasimibe, carbamazepine, danshen (Salvia miltiorrhiza), efavirenz, phenytoin, rifampin, St. John's wort, tipranavir/ritonavir
BCRP	ABCG2	Cyclosporine, elacridar (GF120918), eltrombopag, gefitinib	Not known

Based on University of Washington Database (https://didb.druginteractioninfo.org/resources/list-of-substrates-inhibitors-and-inducers/?Oid=1130) and the FDA draft guidance for drug-drug interaction studies (https://www.fda.gov/downloads/drugs/guidances/ucm292362.pdf)

[1] Inhibitors listed for P-gp are those that showed > 25% increase in digoxin or fexofenadine area under the concentration-time curve (AUC).

[2] Inducers listed for P-gp are those that showed > 20% decrease in digoxin or fexofenadine AUC.

Table B: List of Inhibitors and Inducers of UGT1A1 to Be Used with Caution

Inhibitors of UGT1A1	Inducers of UGT1A1
Atazanavir, erlotinib, flunitrazepam, gemfibrozil, indinavir, ketoconazole, nilotinib, pazopanib, propofol, regorafenib, sorafenib	Carbamazepine, nicotine, rifampicin, testosterone propionate

APPENDIX 7: RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST), VERSION 1.1

1.0 MEASURABILITY OF TUMOR AT BASELINE

1.1 Definitions

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

1.1.1 Measurable

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

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

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

1.1.2 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, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

1.1.3 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 mestastases 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:

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

1.2 Specifications by Methods of Measurements

1.2.1 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.

1.2.2 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 tumor 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.

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

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

or stable disease in order to differentiate between response (or stable disease) and progressive disease.

2.0 TUMOR RESPONSE EVALUATION

2.1 Assessment of Overall Tumor Burden and Measurable Disease

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

2.2 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 tumor. As previously noted, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the *short* axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, 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 tumor regression in the measurable dimension of the disease.

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

2.3 Response Criteria

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

2.3.1 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.

2.3.2 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'.

2.3.3 Evaluation of Non-Target Lesion

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

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

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor 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.

2.3.4 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 tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression *solely* on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the 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 tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the 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.

2.3.5 New Lesions

The appearance of new malignant lesions denotes disease progression. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion

should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor. This is particularly important when the 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:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion. A 'positive' FDG-PET scan lesion is one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up:

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

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

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

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'.

2.4.1 Time Point Response

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

Table C: 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**

CR=complete response, PR=partial response, SD=stable disease, PD=progressive disease, NE=inevaluable

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

Table D: 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.

2.4.2 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 are made at an assessment, usually the case is also considered NE at that time point, unless convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

2.4.3 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.

2.4.4 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.

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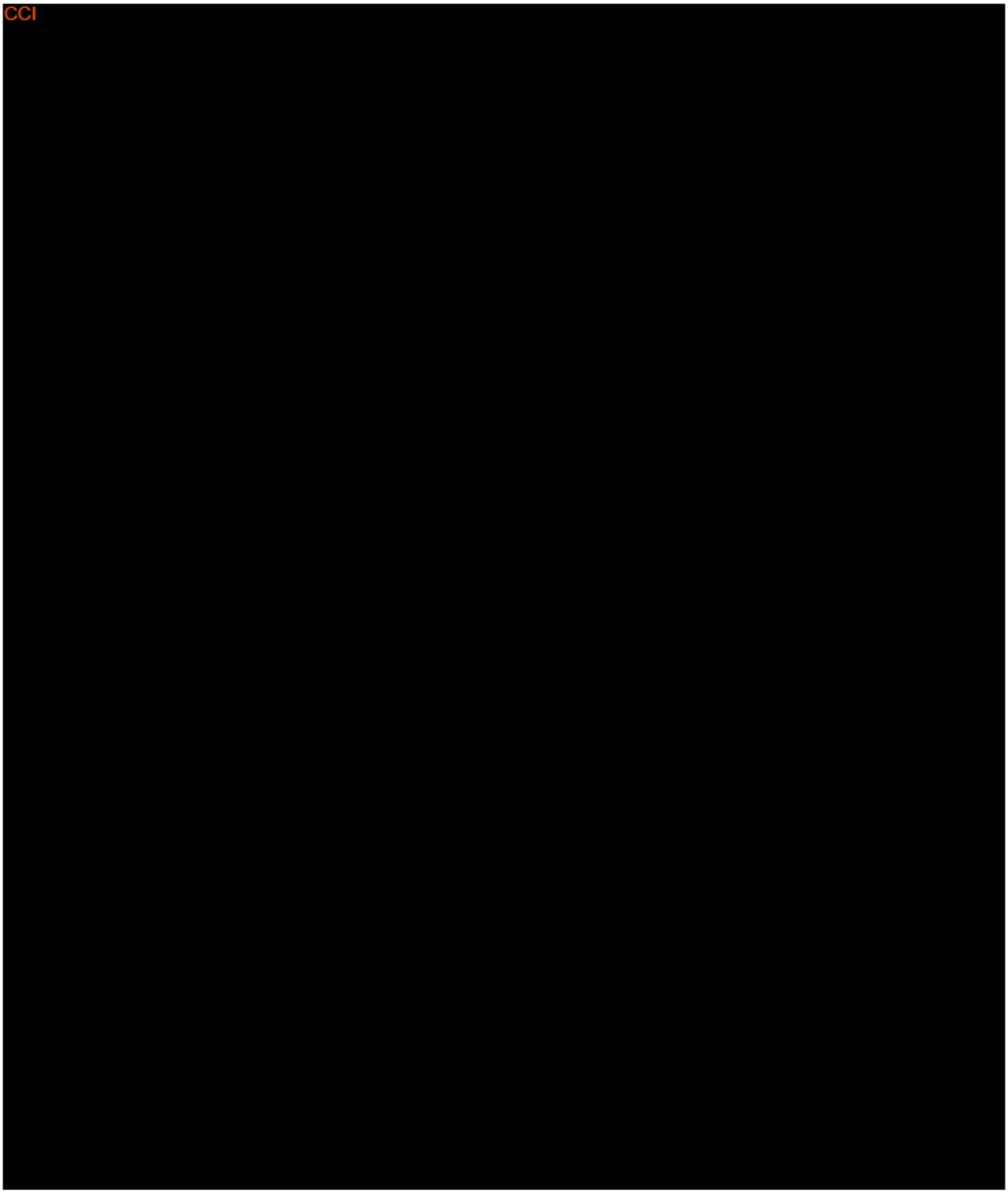


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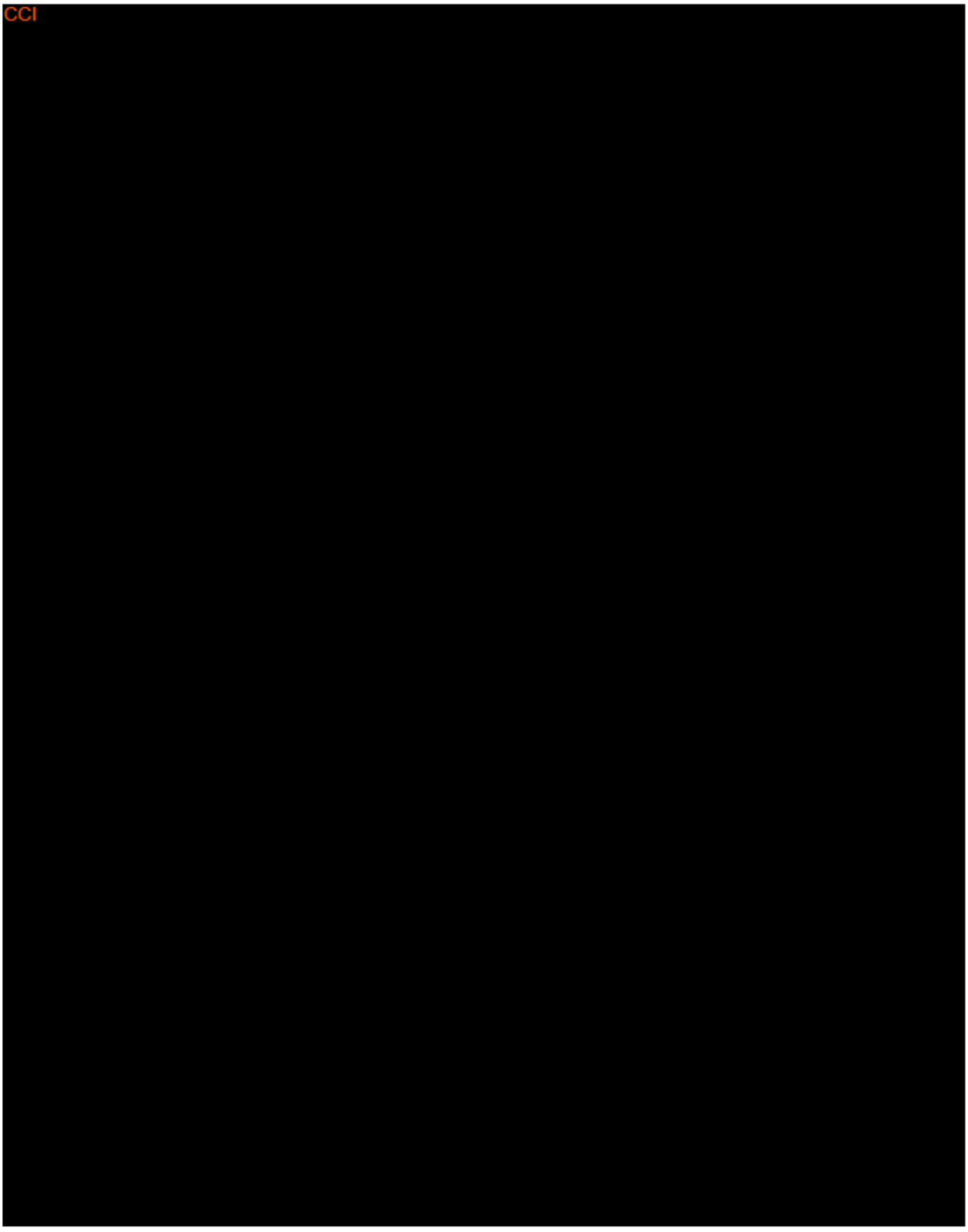
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