Phase II study of pembrolizumab in combination with binimetinib and bevacizumab in patients with refractory colorectal cancer

Principal Investigator: Christopher H. Lieu, MD

NCT03475004

December 30, 2021

Phase II study of pembrolizumab in combination with binimetinib and bevacizumab in patients with refractory colorectal cancer

COMIRB / Protocol Number:	17-0466
Principal Investigator:	Christopher H. Lieu, MD
Coordinating Center:	University of Colorado
Medical Monitor:	University of Colorado
IND Sponsor:	Christopher H. Lieu, MD
IND Number:	138244
Funded by:	Merck & Co, Inc., Pfizer, Inc.
Version Date:	December 30, 2021

STATEMENT OF COMPLIANCE

This is an investigator-initiated study. The Principal Investigator (PI), **Christopher H. Lieu, MD**, is conducting the study and acting as the sponsor. As the sponsor-investigator, both the legal/ethical obligations of a PI and those of a sponsor will be followed.

The trial will be carried out in accordance with Good Clinical Practice (GCP) as required by applicable United States (US) laws and applications, including but not limited to United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

The PI will assure that no changes to the protocol will take place without documented approval from the Institutional Review Board (IRB). All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Sponsor-Lead Principal Investigator: Christopher H. Lieu, MD

Signed: _____ **Date:** _____

LIST OF ABBREVIATIONS

ACRONYM	DESCRIPTION
IIT	Investigator-Initiated Trial
ALP	Alkaline phosphatase
BID	Bis in die or Twice a day
CEA	Carcinoembryonic antigen
Cl	Clearance
Cmax	Maximum concentration
Cmin	Minimum concentration
CR	Complete response
CRC	Colorectal cancer
cSCC	cutaneous squamous cell carcinoma
CT	Computed tomography
Ctrough	Target trough concentration
Cyp	Cytochrome P 450
DLT	Dose limiting toxicity
DOR	Duration of response
EC	Ethics committee
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	Electronic data capture
ERK	Extracellular signal regulated kinase
FFPE	Formalin-fixed, paraffin-embedded
FOLFIRI	Leucovorin plus Fluorouracil plus irinotecan
GEJ	Gastroesophageal junction
HBcAb	Hepatitis B core antibody
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocelluclar Carcinoma
HCV	Hepatitis C virus
HIPAA	Health insurance portability and Accountability Act
HNSCC	Head and Neck Squamous Cell Carcinoma
HNSTD	Highest non-severely Toxic Dose
HR	Hazard Ratio
IARC	International Agency for Research on Cancer
ICH	International conference on Harmonization
IMP	Investigational medicinal product
IND	Investigational new drug
IRB	Institutional Review Board
Iv	Intravenous

ACRONYM	DESCRIPTION
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody
MAPK	Mitogen-activated protein kinase
mCRC	Metastatic colorectal cancer
MHC	Major histocompatibility complex
MRI	Magnetic resonance imaging
MSI	Microsatellite
MSI-H	Microsatellite instability-high
MTD	Maximum-tolerated dose
MUGA	Multigated acquisition
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	Next generation Sequencing
NOEL	No observed Effect level
NSCLC	Non-small cell Lung cancer
OHRP	Office for Human Research Protections
ORR	Overall response rate
OS	Overall survival
PBPK	Physiologically-based PK
PCR	Polymerase chain reaction
PD-1	Programmed death-1
PD-L1	Programmed death ligand-1
PFS	Progression free survival
PMCBCL	Primary Mediastinal Large B-cell Lymphoma
PO	Per Os
PR	Partial response
Q2w	Every 2 weeks
Q3w	Every 3 weeks
QD	Once per day
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SCLC	Small Cell Lung Cancer
SD	Stable disease
TIL	Tumor-infiltrating lymphocyte
TMB-H	Tumor Mutation Burden-High
TNF-α	Tumor necrosis factor-α
TSH	Thyroid-stimulating hormone
UAP	Unanticipated Problems
UC	Urotheliel Carcinoma
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor

PROTOCOL SUMMARY / SYNOPSIS

Protocol Title: *Phase II study of pembrolizumab in combination with binimetinib and bevacizumab in patients with refractory colorectal cancer*

Objectives:

- ***Primary Objective:***
  To determine the effect of pembrolizumab, binimetinib, and bevacizumab on response rate using RECIST v1.1 in patients with colorectal cancer who have progressed on at least two lines of standard therapy

- ***Secondary Objectives:***
  1. *To determine the progression-free survival (PFS) of combination therapy with pembrolizumab, binimetinib, and bevacizumab*
  2. *To determine the effect of combination therapy with pembrolizumab, binimetinib, and bevacizumab on overall survival*
  3. *To evaluate safety and tolerability of combination therapy*

- ***Exploratory Objectives****:*
  1. *Evaluate relationship between PD-L1 tumor expression and mismatch repair status and efficacy of pembrolizumab, binimetinib and bevacizumab.*
  2. *To assess change in PD-L1 and phosphorylated ERK expression in pre-and post-treatment tumor tissue.*
  3. *To compare the response rate determined according to RECIST v1.1 to that identified by Immune Related Response Criteria (irRC).*

Endpoint:

- ***Primary Endpoint:***
  Objective Response rate (ORR per RECIST V1.1)

- ***Secondary Endpoints:***
  Progression Free Survival (PFS)
  Overall Survival (OS)
  Safety and Tolerability

- ***Tertiary/ exploratory:***
  - *Response rate according to pre-treatment PD-L1 tumor expression by IHC*
  - *Change in pre-and post-treatment levels of PD-L1 and phosphorylated ERK expression by IHC.*
  - *Patterns of change in mRNA expression in a panel of immune related genes in tumor tissues prior to treatment*

after binimetinib alone, and after binimetinib, pembrolizumab and bevacizumab.

- *Compare the response rate determined according to RECIST v1.1 to that identified by Immune Related Response Criteria (irRC).*

Population:	• ***Gender*** *Male and Female* • ***Age*** *≥ 18 years* • ***Demographic group*** *refractory metastatic colorectal cancer* • ***General health status*** *ECOG 0-1*
Phase:	*II*
Number of Participating Sites enrolling subjects:	*1*
Description of Study Agent:	*Pembrolizumab 200 mg IV Q3weeks* *Binimetinib 45 mg PO BID continuous* *Bevacizumab 7.5 mg IV Q3weeks*
Study Duration:	*Approximately 12 months*

SCHEMATIC OF STUDY DESIGN

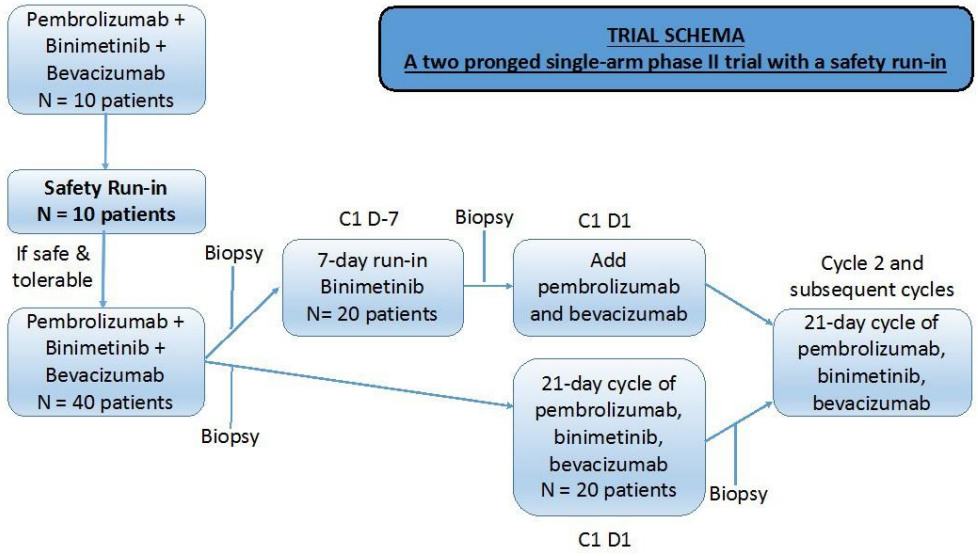

TABLE OF CONTENTS

1 PARTICIPATING SITES

University of Colorado is the participating site in this study. A complete and current listing of investigators, research personnel, research facilities and other study centers (if applicable) participating in this study will be maintained throughout the duration of this study on applicable study required forms such as an *FDA Form 1572*, the *COMIRB Research Personnel Form*, and/or a *UCCC Protocol Contact List*, incorporated herein by reference.

2 INTRODUCTION: BACKGROUND INFORMATION & SCIENTIFIC RATIONALE

2.1 Background Information

Colorectal cancer (CRC) is among the top four causes of cancer in the United States, and the SEER database estimates that 8% of all cancer deaths were secondary to colorectal cancer in 2016. Late stage colorectal cancer has a very low 5-year survival rate, and unfortunately, 20% of patients have metastatic CRC (mCRC) at the time of diagnosis [1]. Approximately 55-60% of patients with mCRC will have a rat sarcoma virus (RAS) proto-oncogene mutation. RAS mutation may comprise of activating mutations in KRAS (exon 2, 3, 4), NRAS (exon 2, 3, 4) or infrequently in HRAS [2]. RAS mutations are an important negative predictive and prognostic biomarker because they correlate with worse outcomes and resistance to anti-EGFR therapies. BRAF mutations are yet another negative prognostic marker for mCRC. Although ongoing research advances have resulted in some improved therapies for advanced CRC in the last decade, it continues to be associated with poor survival [3, 4]. There is a very clear unmet need for effective therapies for patients with advanced CRC.

The initial standard of care for treatment of mCRC, irrespective of RAS status, is systemic 5-FU based chemotherapy. Anti-VEGF therapies are usually used in combination with 5-FU based chemotherapy and/or alone. Median survival for untreated patients with mCRC is less than a year while median overall survival (OS) with standard of care therapy is approximately 30 months. Patients with RAS-wild type tumors have the option of being treated with anti-epidermal growth factor receptor monoclonal antibodies such as cetuximab. An insight into cancer cell biology is integral to developing new targeted therapies. Sustained proliferative signaling such as the MAPK (Mitogen Activated Protein Kinase) signaling cascade, angiogenesis and evasion of immune destruction are some of the critical hallmarks of tumor growth [5]. Understanding these processes is critical and are described below in further detail.

MAPK Signaling Pathway

The mitogen activated protein kinase signaling cascade is a key intracellular signaling network that transduces multiple proliferative and differentiating signals from the extracellular environment to the nucleus of the cells to activate cellular growth and differentiation. The MAPK pathway has also been implicated in the regulation of the tumor immune micro-

environment. MEK inhibition takes advantage of blocking the signaling cascade as well as altering the immunogenicity.

The MAPK signaling cascade is activated by upstream stimuli through activated cell membrane tyrosine kinase receptors. This in turn leads to a series of phosphorylation events and protein interactions involving RAS-RAF-MEK-ERK, which ultimately results in tumor cell proliferation, invasion, migration, angiogenesis and metastases. RAS and RAF mutations activate the MAPK signaling pathway through MEK which has made MEK a highly sought after target in cancer drug development. MEK inhibition alone or in combination is already FDA approved for melanoma [2].

In addition to blocking the signaling cascade, there is growing evidence to suggest that the MAPK pathway influences TIL populations and expression of PD-L1. Kakavand et al showed that there was a significant increase in CD4, CD8 and PD-1 lymphocytes in patients treated with combination therapy of BRAF and MEK inhibitors [6]. Triple negative breast cancers were shown to be associated with improved prognosis if TILs were noted in residual disease post treatment with neoadjuvant chemotherapy. Genetic or transcription alterations that resulted in activation of the RAS-MAPK signaling pathway correlated with lower TILs. Breast cancer mouse models showed enhanced anti-cancer immune response with combined MEK and PD-L1/PD-1 inhibition [7]. Lui et al also showed that a MEK inhibitor alone or in combination with PD-1 inhibitor in vivo led to increased CD4 and CD8 TILs. Their study also indicated improved efficacy with concurrent MEK and PD-1 inhibition or sequential MEK inhibition followed by PD-1 inhibition compared to PD-1 followed by MEK inhibition [8].

The Programmed T-cell Death Ligand Pathway

Cancer development is a multistep multifactorial process. Evasion of immune detection and destruction has been proposed as one of the emerging hallmarks of cancer development. The theory of immune surveillance suggests that the immune system constantly monitors cells in the body and eliminates the majority of nascent cancer cells. People who have suppressed or defective immune systems such as HIV or transplant patients who are pharmacologically immune suppressed have a higher incidence of certain types of cancer [5]. However, healthy immunocompetent individuals are also known to develop cancer. Tumors have shown the ability to create and maintain an immunosuppressive microenvironment that promotes their survival and growth [5, 9]. Programmed Death-Ligand 1(PD-L1/B7-H1/CD274) is expressed by many cancer cells. PD-L1 and PD-L2 are ligands to PD-1, a cell surface receptor that belongs to the immunoglobulain superfamily. Binding of PD-L1 to PD-1 receptors on T cells results in suppression of T-cell migration, proliferation and function. The cancer cell effectively prevents T cell mediated destruction by promoting the PD-L1-PD-1 axis (**Figure 1**)[9-14]. This understanding has led to the development of immune checkpoint inhibitors such as pembrolizumab.

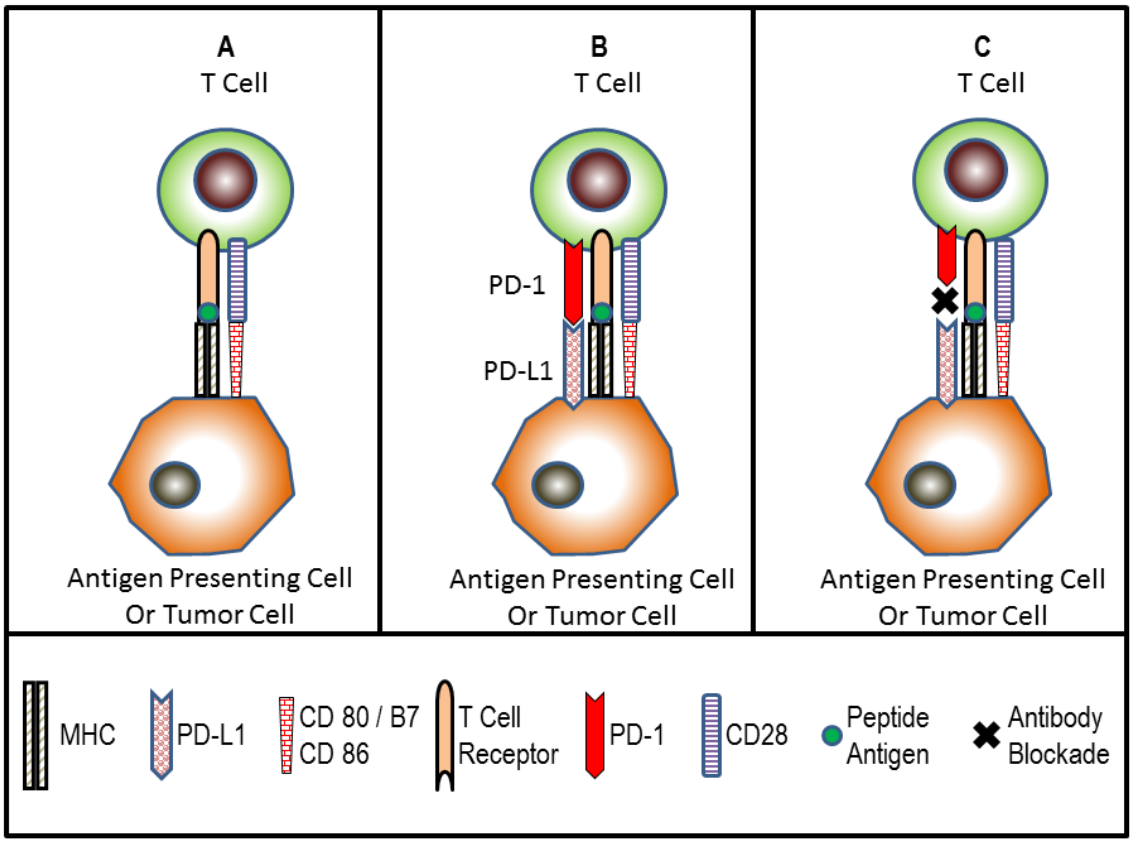

Figure 1. PD-1 mediated T-cell activation (A), exhaustion (B) and blockade (C). (A) APC or tumor cell mediated T-cell activation results in PD-1 expression. (B) PD-L1 binds to PD-1 and "turns off" the T-cell. (C) PD-L1-PD-1 blockade results in persistent activation of the T-cell which then continues to maintain its effector functions. APC, Antigen presenting cell; IFN-γ, Interferon gamma; MHC, major histocompatibility complex; PD-1, Programmed death-1; PD-L1, programmed death ligand 1; TCR, T-cell receptor[11]

The Angiogenesis Signaling Pathway

The hypothesis that angiogenesis, the formation of new blood vessels, is crucial to tumor growth is supported by a large body of scientific data. In the adult, angiogenesis (a continuous process during embryogenesis) is turned on only transiently as part of physiological processes. During tumor progression, an "angiogenic switch" is almost always activated, which leads to continuous production of new vessels that sustain expanding neoplastic growths [5]. Recognition that angiogenesis is crucial to tumor growth has led to the identification of a large number of angiogenic growth factors, including VEGF, which is responsible for stimulating new blood vessel formation.

Angiogenesis is the rate-limiting step for tumor proliferation and thus a target for antitumor therapy. In addition, VEGF has been involved in the inhibition of the immune cell function by tumors [16, 17]. VEGF leads to a functional defect of the dendritic cells, which are potent antigen-presenting cells critical to regulation of the adaptive immune response. VEGF binds to CD34-positive cells (through VEGFR1/Flt-1) and inhibits the activation of the transcription

factor NF-kB, which leads to a defect in the functional maturation of the dendritic cells [17, 18]. The defects in the dendritic cell function are a major component of tumor immune escape and influence vascular endothelial and hematopoietic progenitors that allow tumor immune escape.

Bevacizumab is a recombinant humanized IgG1 mAb that binds VEGF and neutralizes the biological activity of VEGF by preventing the interaction of VEGF with its receptors. Bevacizumab is a commercially available medication (Avastin®) that has a broad development program as it has been evaluated and shown efficacy across several tumor types, including CRC. Bevacizumab is approved for the treatment of mCRC.

Background on Binimetinib

Binimetinib (MEK162/ARRY-438162) is an orally bioavailable, small molecule selective and potent mitogen-activated protein kinase (MEK) 1 and MEK 2 inhibitor. It is currently being investigated as a single agent and in combination with other chemotherapeutic and targeted agents in patients with advanced or metastatic solid tumors.

Summary of non-clinical trials with binimetinib

CRC xenograft tumors in mice showed dose and time dependent inhibition of ERK phosphorylation and tumor growth following administration of binimetinib. Similar efficacy was observed in other xenograft models of NSCLC, pancreatic cancer, ovarian cancer, fibrosarcoma and melanoma. The primary metabolic pathways were glucoronidation, N-demethylation and cleavage of N-O bond. Both fecal and urinary excretion of binimetinib were observed.

Toxicity studies were conducted in rats and monkeys. The most commonly occurring toxicities in rats were skin inflammation and tissue mineralization of multiple organs. The HNSTD (highest non-severely toxic dose) for binimetinib based on 28-day monkey toxicity studies was 3 mg/kg. The 9 month repeat dosing study in monkeys showed GI inflammation and associated secondary changes in blood work and NOEL was identified as 2 mg/kg.

Summary of clinical trials with binimetinib

As of January 2017, a total of 2750 healthy adult subjects and patients have received at least 1 dose of binimetinib, either as a single agent or in combination with targeted inhibitors of PKC, CDK4/6, PI3K, RAF, EGFR or IGF-1R or with the standard chemotherapy agent paclitaxel. These patients constitute the binimetinib safety population, which includes 229 healthy subjects, 164 patients with rheumatoid arthritis, 17 patients with hepatic dysfunction, 6 patient with renal dysfunction and 2334 patients with advanced cancer.

Healthy subjects

220 healthy subjects received at least a single dose of binimetinib across 11 studies. In the ARRY-162-0602 study, the most frequently reported AE were diarrhea, headache, rash and acne. The CMEK162X2108 study reported a total of 14 AE with 3 of those AE being grade 3. The side effect profile was very similar to the ARRY-162-0602 study except for increased

ALT, AST and GGT. Some other studies reported decreased neutrophil count and pre-syncope. None of these studies in healthy subjects reported SAE or deaths.

Advanced cancer patients – monotherapy

2159 advanced cancer patients received at least 1 dose of binimetinib in 20 clinical studies either as a single agent or in combination. The recommended single agent dose of binimetinib has been evaluated in two phase I studies (ARRAY-162-111 and CMEK162X1101) and multiple other phase II and III trials and has been determined to be 45 mg BID.

Advanced cancer patients – combination therapy

Binimetinib has been administered in combination with RAF inhibitors (encorafenib or RAF265), PI3KC/AKT pathway inhibitors (BEZ235, buparlisib, BYL719), PKC-selective inhibitor sotrastaurin, CDK4/6 inhibitor LEE011, IGF-1R monoclonal inhibitor ganitumab, EGFR inhibitor panitumumab, and standard chemotherapy agent paclitaxel in 1275 patients across 13 studies. The RP2D of binimetinib in combination studies is 45 mg BID.

Clinical Pharmacokinetics of Binimetinib

Clinical studies have assessed the pharmacokinetics of binimetinib in healthy subjects to determine the absolute bioavailability and food effect. The food effect study (CMEK162A2103) showed that food delayed but did not affect the amount of absorption of binimetinib into the systemic circulation. Therefore, patients are not required to fast when taking binimetinib. The Clinical study ARRY-162-0602 in healthy subjects identified a median t1/2 of binimetinib for all doses was 7.11 h and the median Tmax was 1 h post dose. The ADME of a single oral dose of 45 mg of 14C-binimetinib was investigated in healthy males in the CMEK162A2102. The metabolism of binimetinib is primarily through direct glucorinidation and estimated to be approximately 61.2%. 62.3% of binimetinib is eliminated in the feces while the rest is eliminated in the urine. There is an ongoing study (CMEK162A2104) investigating the PK of binimetinib in patients with hepatic impairment. Preliminary data indicates that there are no significant PK changes in patients with mild hepatic impairment.

Background on Pembrolizumab

Pembrolizumab (KEYTRUDA, MK-3475) is an intravenous, potent and highly selective humanized monoclonal antibody of the immunoglobulin G4 (IgG4)/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is currently approved for use in advanced or unresectable melanoma, non-small cell lung cancer (NSCLC),head and neck squamous cell cancer (HNSCC), classical Hodgkin's Lymphoma, primary mediastinal large B-cell lymphoma (PMBCL), urothelial carcinoma (UC), microsatellite instability-high (MSI-H) tumors, gastric and gastroesophageal junction (GEJ) adenocarcinoma, cervical cancer, hepatocellular carcinoma (HCC), Merkel cell carcinoma (MCC), and advanced renal cell carcinoma (RCC). [15]

Summary of nonclinical trials

Pembrolizumab has been shown to enhance T-lymphocyte immune responses in cultured blood cells from healthy subjects, cancer patients and cynomolgus monkeys. In vivo, pembrolizumab was shown to enhance human T-cell response to staphylococcus Enterotoxin B. It was also shown to potentiate antigen-specific recall response to the tetanus toxoid antigen.

Pembrolizumab binds to human and cynomolgus monkey PD-1 with comparable affinity and blocks the binding of PD-1 to PD-L1 and PD-L2 with comparable potency. Pembrolizumab did not bind to mouse, dog or rat blood PD-1. These studies have provided the rationale for cynomolgus macaque as the relevant species for preclinical development. Due to lack of cross reactivity of pembrolizumab with PD-1 from rodents, an anti-mouse PD-1 antibody was generated for use in in-vivo studies in syngeneic mouse tumor models. PD-1 blockage demonstrated anti-tumor efficacy in each of these syngeneic tumor models. Anti-PD-1 therapy was also shown to enhance efficacy and regression rates of chemotherapeutic agents such as 5-FU in-vivo. The use of pembrolizumab in combination regimens that included dexamethasone was also assessed. Results showed no impact on efficacy of anti-PD-1 treatment.

Toxicology of pembrolizumab was studied in 1-month and 6-month repeat dose chronic nonclinical toxicity studies. Pembrolizumab was well tolerated at all dose levels. There were no test article related concerning findings. PD-L1 signaling blockade has been noted in murine models of allogeneic pregnancy. Treatment with anti-PD-L1 mAb resulted in increased rates of abortion. There is good evidence to suggest the PD-1/PD-L1 blockade is important in feto-maternal tolerance. Therefore, data suggests that PD-1/PD-L1 blockade will result in increased risk of abortion and /or still births.

Immunogenicity of pembrolizumab was also evaluated as part of the toxicity studies. Anti-pembrolizumab antibodies were detectable but no related toxicities were observed.

Summary of clinical trials

The efficacy of pembrolizumab has been studied in multiple cancers. Currently, pembrolizumab is FDA approved for use in melanoma, NSCLC, SCLC, HNSCC, classical Hodgkin's Lymphoma, PMBCL, UC, MSI-H cancer, gastric and GEJ adenocarcinoma, cervical cancer, HCC, MCC, RCC, endometrial carcinoma, TMB-H cancer, cSCC, and MSI-H CRC.

In melanoma, pembrolizumab has been studied in the phase I setting, in ipilimumab and BRAF inhibitor refractory BRAF–mutant advanced melanoma (KEYNOTE-002) and ipilimumab-naïve unresectable or metastatic melanoma (KEYNOTE-006, Phase III, randomized to IPI vs Pembrolizumab). The KEYNOTE-002 study showed a statistically significant improvement in PFS with a suggestion of benefit in OS. The KEYNOTE-006 showed benefits in OS and PFS. The data from these studies led to the approval of pembrolizumab for patients with unresectable or metastatic melanoma.

In NSCLC, two clinical studies – KEYNOTE-001 and KEYNOTE-010. KEYNOTE-001 was an open label, phase 1 trial while KEYNOTE-010 was a randomized phase 2/3 trial of 7 pembrolizumab vs docetaxel in PD-L1 positive, platinum refractory NSCLC. The

KEYNOTE-010 trial demonstrated clinically significant improvement in OS and PFS. The patients with a PD-L1 tumor proportion score (TPS) ≥ 50% had the greatest benefit. KEYNOTE-012, a phase 1b trial included cohorts of patients who progressed following cetuximab and platinum therapy and subjects who progresses following platinum therapy without cetuximab. 16% of patients experienced tumor response to pembrolizumab and the duration of response was higher than that seen with standard of care treatments.

Pharmacokinetics of Pembrolizumab

PK has been obtained from various pembrolizumab trials including advanced melanoma, NSCLC, HNSCC, urothelial carcinoma, and MSI-H tumors. Pembrolizumab is administered IV and is a 100% bioavailable. PK analysis from studies confirm that pembrolizumab has a low systemic clearance and a limited volume of distribution. Pembrolizumab is eliminated via catabolism with minimal renal excretion. Hence, food and drug-drug interactions are not expected to affect pembrolizumab exposure. The systemic clearance of pembrolizumab is 0.22 L/day and the $t_{1/2}$ is estimated to be ~ 22 days. Steady state of the drug is achieved after ~ 18 weeks of ongoing therapy.

Pembrolizumab exposure occurs in a dose-dependent manner with clearance being independent of time or concentration. PK studies have indicated that the fixed dosing of 200 mg provides the same adequate level of exposure to drug as body weight based dosing. Population PK analysis shows that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distribution of exposures, supporting suitability of 200 mg Q3W. Additionally, pharmacology data shows full target saturation in both systemic circulation (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W.

Studies have shown no significant difference in clearance of pembrolizumab between patients with normal renal function vs mild to moderate renal impairment. Pembrolizumab has not been studied in the setting of severe (GFR <30 and ≥ 15 ml/min/1.73 m^2) renal impairment. Similarly, no important differences have been observed in clearance of pembrolizumab in patients with mild hepatic impairment. However, pembrolizumab has not been studied in moderate to severe hepatic impairment.

Background on Bevacizumab

Bevacizumab has been studied in more than 96,500 patients in Phase I–IV clinical trials in multiple tumor types since the beginning of it clinical development. More than 2 million patients have been treated with bevacizumab as a marketed product worldwide.

The pharmacokinetics of bevacizumab are characterized by a slow CL, long half-life, and a volume of distribution consistent with limited extravascular distribution.
A comprehensive population PK analysis of the pooled data demonstrated that CL was consistent across all studies and tumor types and that overall inter-individual variability in CL was approximately 33%. Post-hoc estimates of bevacizumab PK parameters from various tumor types show that the pharmacokinetics of bevacizumab were accurately estimated across tumor types and a number of the covariates evaluated explain the observed PK variability. Albumin levels, body weight, and sex were found to be significant covariates that explained

some of the inter-individual variability.

The results from drug-drug interaction PK studies showed that there were no interactions between bevacizumab and the anti-cancer agents tested. Co-administration of bevacizumab with other anti-cancer agents resulted in similar values of CL and the volume of central compartment for bevacizumab was not affected by dosing with other anti-cancer agents.

See the Bevacizumab Investigator's Brochure for details on nonclinical and clinical studies.

2.2 Rationale

There is an unmet need for treatment options for patients with refractory metastatic CRC. Patients are currently offered chemotherapy which provides a limited duration of disease control and results in multiple toxicities that impact quality of life. This study proposes combination therapy with three agents that are known to target three key aspects of metastatic CRC cell biology- immune evasion, proliferative signaling and angiogenesis [5]. Clinical and non-clinical data suggests that inhibition of MEK, PD-1 and angiogenesis should result in additive anti-tumor activity.

This study requires a tumor biopsy pre- and post- treatment. Since the advent of the targeted therapy era it has become clear that a better understanding of the intimate biological mechanisms that tailor the cancer cell phenotype would be translated into a better chance of disease control. However, this has been a difficult task due to the complex interaction between the tumor cell, tumor stroma, immune response, and angiogenesis. The animal models do not appropriately represent these intricate interactions, especially for the immune system.

Therefore, tumor biopsies during the clinical study at different time-points present the best opportunity to increase understanding of the anti−tumor immune response as well as to identify biomarkers predictive of response and resistance.

2.3 Potential Risks and Benefits

Despite recent advances, mCRC is commonly an incurable disease and patients eventually succumb to the disease. There has been ongoing research to fulfill this unmet need.

Combination therapy with multiple targeted agents is one of the possible research strategies. Clinical and non-clinical data suggest potential enhancement in anti-tumor activity with combining MEK, PD-1 and angiogenesis inhibitors. Every drug has its own set of side-effects, and the risk in combining multiple agents is an increase in number and intensity of adverse events. The potential risks and benefits of this combination therapy are listed below.

2.3.1 IMPORTANT IDENTIFIED/ POTENTIAL RISKS

Pembrolizumab

Pembrolizumab is generally well tolerated and demonstrates a favorable safety profile in comparison to chemotherapy. Pembrolizumab is an immunomodulatory agent, and based on this mechanism of action, immune- mediated AEs are of primary concern. The important identified risks for pembrolizumab monotherapy are primarily of an immune-mediated nature and included the following in the last IB (Edition 20): pneumonitis; colitis; hepatitis; nephritis; endocrinopathies that include hypophysitis (including hypopituitarism and

secondary adrenal insufficiency), thyroid disorder (hypothyroidism, hyperthyroidism and thyroiditis), and Type I diabetes mellitus; uveitis; myositis; Guillain-Barré syndrome; pancreatitis; myocarditis; myasthenic syndrome/myasthenia gravis (including exacerbation); myelitis; encephalitis; sarcoidosis; severe skin reactions including SJS and TEN, some with fatal outcome; and solid organ transplant rejection following pembrolizumab treatment in donor organ recipients (risk applicable primarily to postmarketing setting only, as such patients are currently excluded from Merck-sponsored clinical studies with pembrolizumab).

Immune-mediated ARs, including severe and fatal cases, have occurred in patients receiving pembrolizumab. Immune-mediated ARs can occur after discontinuation of treatment. Immune-mediated ARs affecting more than one body system can occur simultaneously. In clinical studies, most immune-mediated ARs were reversible and managed with interruptions of pembrolizumab, administration of corticosteroids, and/or supportive care.

The safety profile for pembrolizumab also includes 2 important potential risks – ie, increased risk of severe complications (such as early severe GVHD and veno-occlusive disease) of allogeneic transplant in patients with hematologic malignancies who have previously been treated with PD-1 inhibitors; and GVHD after pembrolizumab administration in patients with a history of allogeneic HSCT.

Safety data from the sponsor's reference safety dataset includes data from KEYNOTE-001, KEYNOTE-002, KEYNOTE-006 and KEYNOTE-010 (n = 2799). 97.4% of patients in this dataset experienced 1 or more AE. 73.7% of patients experienced adverse events which were thought to be drug related by the investigator. The percentage of participants in the safety data set who experienced SAEs was lower. 37.2% of participants experienced 1 or more SAEs; 11.9% of participants discontinued due to an AE; and 10.1% of subjects experienced a drug- related SAE as determined by the investigator.

Most frequently reported (≥5%) AE in decreasing order of frequency thought to be drug related were fatigue, pruritus, rash, diarrhea, nausea, arthralgia, decreased appetite, asthenia, hypothyroidism, vitiligo and myalgias. Of this the 5 most frequently reported AE that are considered drug-related are fatigue (24.2%), pruritus (16.7%), rash (13.8%), diarrhea (12.3%) and nausea (10.9%).

Most frequently reported drug related SAEs (≥0.2%) in decreasing order of frequency were pneumonitis, colitis, diarrhea, pyrexia, autoimmune hepatitis, pneumonia, adrenal insufficiency, hyponatremia, dyspnea, hyperthyroidism, nausea, acute kidney injury, confusional state, hypophysitis, hypopituitarism, hypothyroidism, and vomiting. The 5 most commonly reported SAE that are considered drug-related are pneumonitis (1.6%), colitis (0.9%), diarrhea (0.6%), pyrexia (0.4%) and autoimmune hepatitis (0.3%).

Adverse events of special interest in patients treated with pembrolizumab include hypothyroidism, hyperthyroidism, pneumonitis, infusion reactions, colitis, severe skin reactions, adrenal insufficiency, hepatitis, hypophysitis, thyroiditis, uveitis, myositis, nephritis, pancreatitis, T1DM, Guillain-Barre syndrome, myasthenic syndrome, sarcoidosis, encephalitis.

Binimetinib

Across all oncologic studies, the majority of AEs were reversible and grade 1 or 2 in severity. These adverse events include ocular events (retinal, vascular and other eye), dermatologic events (rash and other), edema, myopathy/rhabdomyolysis (including CK elevation), HTN, liver issues, fatigue/asthenia, pneumonitis, hemorrhage, thrombotic and embolic events. CMEK162X2201 reported 24% of patients had Grade 3 or 4 elevations in blood CK. All other AE have been grade 1 or 2. Reproductive toxicity and QT prolongation are included in the toxicity profile for Binimetinib but this information comes from nonclinical data.

Bevacizumab

The most serious adverse events identified in clinical trials with bevacizumab have been gastrointestinal perforations, hemorrhage (including tumor-associated bleeding and pulmonary hemorrhage/hemoptysis), which is more common in NSCLC patients, and arterial thromboembolic events. Other adverse events observed in patients treated with bevacizumab include fistulae, wound-healing complications, hypertension, arterial and venous thromboembolism, and proteinuria. In addition, congestive heart failure was observed rarely. Analyses of the clinical safety data suggest that the occurrence of hypertension and proteinuria with bevacizumab is likely to be dose dependent.

The most frequently observed adverse events in patients who received bevacizumab have been hypertension, fatigue or asthenia, diarrhea, and abdominal pain. Increased rates of severe neutropenia, febrile neutropenia, or infection with severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab in comparison to chemotherapy alone. There have been rare reports in the post-marketing setting of the development of signs and symptoms that are consistent with posterior reversible encephalopathy syndrome in bevacizumab-treated patients. Very rare cases of hypertensive encephalopathy have also been reported, some of which were fatal.

2.3.2 KNOWN POTENTIAL BENEFITS

The study regimen combines three agents that target three relevant features of cancer cell biology, the so-called hallmarks of cancer: proliferative signaling, angiogenesis, and immune evasion[5]. Furthermore, the nonclinical and clinical data suggest that the inhibition of MEK, PD-L1, and the neo-angiogenesis should lead to a more than additive anti-tumor activity.

Nonclinical data show a negative association between MEK activity and active antigen presentation (MHC-I and II expression) that appears to be coupled to simultaneous PD-L1 expression. These findings link the MAPK pathway activation to the tumor immune-evasion. Consistently, MEK inhibition results in an increased number of tumor-infiltrating CD8-positive T lymphocytes and PD-L1 and MHC expression [7, 19]. These effects are responsible for the enhanced anti-tumor immune response observed with the combination of MEK with PD-L1/PD-1 inhibitors [7]. The Phase I Study KEYNOTE-022 presented at ASCO 2016 which combined pembrolizumab with MAPK pathway inhibition (BRAF-I and MEK-I) in advanced melanoma patients showed a 60% ORR (n = 15)[20]. In the Phase Ib Study GP28363, another MEK-I - cobimetinib was administered with pembrolizumab (immune checkpoint inhibitor) and it has shown promising results in patients with refractory CRC (ORR of 17.4%) (in-house data generated at the University of Colorado). VEGF plays an important role in immune tolerance in the tumor microenvironment through inhibition of dendritic cell differentiation and maturation [17, 21, 22]. Dendritic cells are a relevant component of the immune response that links the adaptive and innate immune systems through the antigen presentation function. In patients with CRC, the inhibition of VEGF with bevacizumab increases the peripheral B and T cell compartments, decreases the Treg compartment, and enhances the functional maturation of dendritic cells [17, 22, 23]. As a result of these effects, bevacizumab increases CD8-positive T cell accumulation in tumors in both nonclinical and clinical biopsies (in-house mouse data; Phase Ib biopsy data with bevacizumab and pembrolizumab).

Based on the potential benefit of the study regimen, the availability of standard therapy in case the disease progresses and the well-defined and tolerable profile of each agent, the Sponsor believes that in this study the potential benefits outweigh its risks.

The risks to subjects are reasonable in relation to the anticipated benefits to subjects and/or society, and in relation to the importance of the knowledge that may reasonably be expected to result, thereby falling in favor of performing the study:

- To Subject: benefit of possible short term and sustained disease response resulting in improvement in both quantity and quality of life.
- To Society: The knowledge gained in terms of toxicity and efficacy will guide treatment for other patients with mCRC.
- Justify the importance of the knowledge gained: The knowledge gained in terms of toxicity and efficacy will help determine direction future research in the area of mCRC.

3 OBJECTIVES AND PURPOSE

Primary objective:

1. To determine the effect of pembrolizumab, binimetinib, and bevacizumab on response rate in this patient population using RECIST v1.1.

Secondary objectives:

1. To determine the progression free survival (PFS) of combination therapy with pembrolizumab, binimetinib, and bevacizumab in patients with advanced CRC refractory to at least two standard lines of therapy.
2. To determine the effect of pembrolizumab, binimetinib, and bevacizumab on overall survival in this patient population.
3. To evaluate the safety and tolerability of pembrolizumab, binimetinib, and bevacizumab.

Exploratory Objectives:

1. To evaluate the relationship between PD-L1 tumor expression and mismatch repair (MSS v MSI) status and efficacy of pembrolizumab, binimetinib, and bevacizumab.

2. To assess for change in PD-L1 and phosphorylated ERK expression in pre- and post- treatment tumor tissue.
3. To compare the response rate determined according to RECIST v1.1 to that identified by Immune Related Response Criteria (irRC).

4 STUDY DESIGN AND ENDPOINTS

4.1 Description of the Study Design

This is an open-label, single-center, single-arm phase II clinical trial evaluating the combination of pembrolizumab, binimetinib, and bevacizumab in patients with metastatic colorectal adenocarcinoma refractory to at least two standard lines of therapy. All patients in the expansion cohorts will require a tumor biopsy prior to treatment and again prior to cycle 1, day 1 (binimetinib run-in cohort) or prior to cycle 2, day 1 (in patients not receiving the binimetinib run-in).

There are 2 stages to this study:

1. Stage 1: safety run-in (n = 10)
2. Stage 2: Dose expansion* (n = 64) with two cohorts – Cohort A (n = 32) and Cohort B (n = 32)

* Up to 32 participants may be enrolled into each cohort to account for attrition and screen fails. However, only 20 total participants are needed per cohort to meet the study objectives.

Stage 1: Safety run-in

Rationale:

Pembrolizumab, binimetinib and bevacizumab have been assessed in clinical trials as monotherapy. Combination therapy of PD-1 inhibition with MEK inhibition has also been studied in the phase I setting. There is an ongoing phase I trial of a PD-L1 inhibitor, MEK-I and bevacizumab but the toxicity data from this trial is not yet available. We are unaware of any studies that have combined pembrolizumab, binimetinib and bevacizumab previously. Therefore, the safety run-in is a measure to mitigate the toxicity risk posed by combining these three agents.

Design:

Ten patients will be accrued to stage 1 and treated with standard doses of pembrolizumab, binimetinib and bevacizumab. If the standard doses are not tolerable and 2 or more patients experience a DLT, then patients would be enrolled in dose level -1 which would comprise of standard doses of pembrolizumab and bevacizumab but binimetinib would be at a dose lower of 30 mg PO BID. If 2 or more patients experience a DLT at dose level -1, then patients will be enrolled in dose level -2 which will comprise of standard doses of pembrolizumab and bevacizumab but a lower dose of binimetinib at 15 mg BID. Upon determination of the safety and tolerability of the treatment regimen, the study will proceed to stage 2.

If any of the following situations occur, then further enrollment and study treatments will be halted immediately until a thorough investigation and safety analysis has been conducted (DLT):

- If any patient experiences death due to an adverse event that is assessed as related to study treatment (by investigator and/or Sponsor), it will lead to temporary hold of study pending review by study team.
- Approximately 3 or more of the 10 patients meet individual stopping rules.

The following are treatment stopping rules for an individual patient and for the safety run-in phase of the study. If any of the following situations of potentially overlapping toxicities occur and are assessed as related to study treatment by the investigator, the study treatment will be halted immediately for the individual patient, and a thorough investigation and safety analysis will be conducted:

- Grade ≥ 3 hypertension (defined as ≥ 180 mmHg systolic or ≥ 110 mmHg diastolic blood pressure) refractory to optimal anti-hypertensive management for > 14 consecutive days
- Grade ≥ 3 hemorrhage (symptoms and transfusion of packed RBCs indicated)
- Grade ≥ 3 pneumonitis (symptomatic, interfering with activities of daily living; oxygen indicated)
- Recurrent Grade 2 pneumonitis (symptomatic; medical intervention indicated; limiting instrumental ADL)
- Grade ≥ 3 left ventricular dysfunction (symptomatic congestive heart failure responsive to intervention)
- Grade ≥ 3 colitis or diarrhea not responsive to anti-diarrheal agents (increase of ≥ 7 stools per day over baseline; incontinence; IV fluids for ≥ 24 hours; hospitalization)

- ALT or AST > 5 × ULN in combination with total bilirubin > 2 × ULN
- Grade ≥ 3 retinopathy or retinal vein occlusion.

Once 10 patients have been enrolled into the study, further accrual to the study will be temporarily halted while the study team reviews the totality of clinical data to determine safety and tolerability of the regimen. Only after the regimen has been determined to be safe and tolerable as detailed above can the dose expansion phase be initiated. The safety review should contain data from patients who have been receiving the regimen for a minimum of one cycle of treatment.

Stage 2: Dose expansion

Rationale:

Binimetinib is administered with a 7-day run-in in Cohort A to explore the hypothesis that MEK inhibition will increase the tumor immunogenicity, thereby enhancing the effect of immune checkpoint inhibition with pembrolizumab. Two cohorts, one with all agents administered simultaneously and the other with a 7-day run-in of binimetinib have been initiated to determine if there is any difference in biomarker expression and clinical efficacy between the two dosing strategies. The two cohorts are not comparators but two divisions of a single-arm study.

Design:

All enrolled patients, post-safety run-in (if no DLT in the safety lead-in) will be assigned to one of two treatment arms – Cohorts A or B. Patients must have biopsiable disease in order to be eligible for study enrollment, and a pre-treatment biopsy will be done after the patient is randomized to a treatment arm but prior to initiating treatment. A second on-treatment biopsy will also be done provided tumor is accessible and there is no foreseeable harm to the patient due to the biopsy.

All patients in the expansion cohort will have two biopsies while participating on this clinical trial. The first pre-treatment biopsy will be collected prior to treatment initiation but after randomization onto the study. The second on-treatment biopsy will occur following enrollment and the timepoint will be dependent upon the Cohort to which the patient is randomized. The on-treatment biopsies will occur during one of the following timepoints:

- Cohort A: Following the 7-day Binimetinib run-in period and prior to C1D1.
- Cohort B: Following completion of Cycle 1 and prior to C2D1.

To summarize, all patients in the expansion cohort will be required to submit two biopsies while participating on this clinical trial. The first pre-treatment biopsy will be performed on all patients after randomization onto the study, but prior to treatment initiation. . The second on-treatment biopsy will be completed following enrollment and the timepoint will be dependent on the subject's randomization cohort (see above).

In Cohort A, up to 32 patients will be treated with a 7-day run-in of binimetinib starting day -7 of cycle 1 only. Tumor biopsy will be performed prior to initiation of treatment, and again prior to cycle 1 day +1. Pembrolizumab and bevacizumab will then be added to binimetinib on cycle 1 day +1. Cycle 1 will end on day 21. Patients will start treatment with pembrolizumab, binimetinib, and bevacizumab on day 1 of all subsequent cycles.

In Cohort B, up to 32 patients will initiate pembrolizumab, bevacizumab, and binimetinib together on day 1 of all cycles including cycle 1. These patients will undergo biopsy prior to treatment and again at day 21 of cycle 1.

Patients in the safety run-in phase and in the dose expansion phase will continue to receive study therapy until disease progression according to RECIST v1.1, unacceptable toxicity, death, patient or physician decision to withdraw, pregnancy or maximum upper limit of pembrolizumab therapy (35 cycles), whichever occurs first. A rising carcinoembryonic antigen (CEA) level alone is not considered disease progression. Patients are allowed to receive study treatment beyond disease progression if certain conditions are met (Please see Section 6.1.1). Tumor tissues will be assessed for mismatch repair status at baseline, PD-L1 expression, and phosphorylated ERK expression in pre- and post-treatment specimens. In addition, mRNA expression of a panel of immune markers will also be assessed in both pre- and post-treatment tissues.

All patients will undergo imaging of the chest, abdomen, and pelvis after every three cycles for evaluation of response according to RECIST v1.1.

The study will end when all patients enrolled have been followed until death, have withdrawn consent, have been lost to follow-up, or the Sponsor decides to end the trial, whichever occurs first. The time from first patient in until end of follow-up as described above is expected to take approximately 12 months.

4.2 Study Endpoints

4.2.1 PRIMARY ENDPOINT

1. Response rate based on CT imaging, defined as complete or partial response according to RECIST v1.1

4.2.2 SECONDARY ENDPOINTS

1. Progression free survival, defined as the time from enrollment to the first observation of progressive disease or death from any cause
2. Overall survival, defined as the time from enrollment to death from any cause
3. Grade 1, 2, 3, 4 toxicities associated with pembrolizumab, bevacizumab, and binimetinib as defined by CTCAE v4

4.2.3 EXPLORATORY ENDPOINTS

1. Response rate according to mismatch repair status and pre-treatment PD-L1 tumor expression by IHC.
2. Change in pre- and post-treatment levels of PD-L1 and phosphorylated ERK expression by IHC.
3. Pattern of change in mRNA expression in a panel of immune related genes in tumor tissues prior to treatment, after binimetinib alone, and after binimetinib, pembrolizumab, and bevacizumab.
4. Compare the response rate determined according to RECIST v1.1 to that identified by Immune Related Response Criteria (irRC).

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 Subject Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision to sign and date the consent form.
2. Age ≥ 18 years.
3. Able to comply with the study protocol, in the investigator's judgment.
4. Patient must state willingness to undergo pre- and post-treatment biopsies. According to the investigator's judgement, the planned biopsies should not expose the patient to substantially increased risk of complications.
5. Patient must have biopsiable disease.
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
7. Histologically confirmed unresectable metastatic colorectal adenocarcinoma.
8. Progression or intolerance on at least two prior lines of therapy for unresectable metastatic colorectal adenocarcinoma.
    - Administration of bevacizumab previously does not impact study inclusion.
9. Measurable disease, according to RECIST v1.1. Note that lesions intended to be biopsied should not be target lesions. Lesions situated in a previously irradiated area are considered measureable if progression has been demonstrated in such lesions.
10. Adequate hematologic and end organ function, defined by the following laboratory results obtained within 14 days prior to first dose of study drug treatment:
    - WBC ≥ 2.5 and ≤ 15.0 × 10^9/L
    - ANC ≥ 1.5 × 10^9/L
    - Platelet count ≥ 100 × 10^9/L
    - Hemoglobin ≥ 9 g/dL without transfusion in the previous week
    - Albumin ≥ 2.5 g/dL
    - Serum bilirubin ≤ 1.5 x the upper limit of normal (ULN); patients with known Gilbert's disease may have a bilirubin ≤ 3.0 ×ULN
    - INR and PTT ≤ 1.5 × ULN; amylase and lipase ≤ 1.5 × ULN
    - AST, ALT, and alkaline phosphatase (ALP) ≤ 3 × ULN with the following exceptions:
        - Patients with documented liver metastases: AST and/or ALT ≤ 5 ×ULN
        - Patients with documented liver or bone metastases: ALP ≤ 5×ULN
    - Creatinine clearance ≥ 50 mL/min
11. For women of childbearing potential, defined as a woman who is post-menarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus):
    - Acknowledgment that she is not currently breastfeeding and agreement to remain abstinent (refrain from heterosexual intercourse) or agreement to use contraceptive methods, as defined:
        - Remain abstinent; the reliability of sexual abstinence should be

evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- Contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 180 days after the last study treatment. Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices and copper intrauterine devices.

12. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or agreement to use contraceptive methods, and to refrain from donating sperm, as defined:
    - With female partners of childbearing potential, pregnant female partners, or breastfeeding partners men must:
        - Remain abstinent; the reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception; or
        - Contraceptive methods; use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant. Agreement must occur during the treatment period and for at least 180 days after the last dose of study treatment. Men must refrain from donating sperm during this same period.

5.2 Subject Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Cancer-related exclusion criteria:
    - Patients with known MSI-high status or unknown MSI status are not eligible for study entry.
    - Patients with known BRAF V600E mutations are not eligible for the study.
    - Surgical procedure (surgical resection, wound revision or any other major surgery) or significant traumatic injury within 60 days prior to enrollment, or anticipation of need for major surgical procedure during the course of the study. Minor surgical procedure within 7 days (including placement of a vascular access device) of study Cycle 1 Day 1.
        1. Study-related biopsies are NOT considered surgical procedures under the exclusion criteria
    - Untreated CNS metastases. Treatment of brain metastases, either by surgical or radiation techniques, must have been completed at least 4 weeks prior to initiation of study treatment.
    - Treatment with any investigational agent or approved therapy within 21 days (Cycle 1 Day 1).
    - Malignancies other than CRC within 3 years prior to Cycle 1 Day 1 with the

exception of those with a negligible risk of metastasis or death (e.g., expected 5-year overall survival > 90%) treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated surgically with curative intent, ductal carcinoma in situ treated surgically with curative intent).

- Prior radiation therapy within 14 days prior to study Cycle 1 Day 1 and/or persistence of radiation-related adverse effects. However, palliative radiation therapy (as long as it does not involve target lesions) is permitted on the study.
- Prior allogeneic bone marrow transplantation or solid organ transplant for another malignancy in the past.
- Spinal cord compression not definitively treated with surgery and/or radiation.
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures.
- Uncontrolled tumor related pain. Patients who require narcotic pain medication during screening should be on a stable dose regimen prior to Cycle 1 Day 1.

2. Exclusion criteria related to study medication:
    - Current or recent (within 10 days of study enrollment) use of acetylsalicylic acid (> 325 mg/day), clopidogrel (> 75 mg/day) or current or recent (within 10 days of first dose of bevacizumab) use of therapeutic oral or parenteral anticoagulants or thrombolytic agents for therapeutic purpose. Note: The use of full-dose oral or parenteral anticoagulants is permitted as long as the INR or aPTT is within therapeutic limits (according to the medical standard of the enrolling institution) and the patient has been on a stable dose of anticoagulants for at least 2 weeks at the time of Cycle 1 Day 1. Prophylactic use of anticoagulants is allowed.
    - History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.
    - Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells, any components of Binimetinib, Pembrolizumab, or bevacizumab formulations or any premedications.
    - Prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti-PD-1, anti-PD L1, anti-PD-L2 or MAPK pathway inhibitors (eg; BRAF, MEK, ERK inhibitors).
    - Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to randomization.

3. Exclusion criteria based on autoimmune conditions:
    - History of autoimmune disease including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barre syndrome, multiple sclerosis, vasculitis, or glomerulonephritis.
    - History of non-infectious pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.
    - Has an autoimmune disease that has required systemic treatment in the past 2 years with use of disease modifying agents, corticosteroids, or immunosuppressive drugs. Replacement therapy (eg; thyroxine, insulin,

physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.

4. Exclusion criteria based on organ function or medical history:
    - History of clinically significant cardiac or pulmonary dysfunction including the following:
        1. Inadequately controlled hypertension (that is defined as systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg that is treated or untreated).
        2. History of myocardial infarction within 6 months prior to first dose of study drug in Cycle.
        3. Prior history of hypertensive crisis or hypertensive encephalopathy.
        4. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, evidence of active pneumonitis on screening chest CT scan or non-infectious pneumonitis requiring steroids.
    - Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent arterial thrombosis) within 6 months of Cycle 1 Day 1.
    - History of stroke or transient ischemic attack within 6 months prior to Cycle 1 Day 1.
    - Serious non-healing wound, active ulcer or untreated bone fracture.
    - History of abdominal fistula or gastrointestinal perforation within 6 months prior to Cycle 1 Day 1.
    - History of hemoptysis (≥one teaspoon of bright red blood per episode), or any other serious hemorrhage or at risk of bleeding (gastrointestinal history of bleeds, gastrointestinal ulcers, etc.). INR> 1.5 and aPTT > 1.5 × ULN within 14 days prior to Cycle 1 Day 1. History or evidence of inherited bleeding diathesis or significant coagulopathy at risk of bleeding.
    - Life expectancy of < 12 weeks.
    - Any previous venous thromboembolism≥ Grade 3.
    - Proteinuria at screening as demonstrated by urine dipstick ≥ 2+ and 24-hour. proteinuria > 1.0 g.
    - Left ventricular ejection fraction (LVEF) below institutional lower limit of normal.
    - Uncontrolled serious medical or psychiatric illness.
    - Pregnant or lactating, or intending to become pregnant during the study. Women who are not post-menopausal (≥ 12 continuous months of amenorrhea with no identified cause other than menopause) or surgically sterile must have a negative serum pregnancy test within 14 days prior to Cycle 1 Day 1.

5. Ocular exclusion criteria:
    - History or evidence of retinal pathology on ophthalmologic examination that is considered a risk factor for neurosensory retinal detachment/central serous chorioretinopathy, retinal vein occlusion or neovascular macular degeneration.
    - Patients will be excluded if they have the following risk factors for retinal vein occlusion: Uncontrolled glaucoma with intraocular pressure ≥21 mmHg. Serum cholesterol ≥ Grade 2. Hypertriglyceridemia ≥ Grade 2. Hyperglycemia (fasting) ≥ Grade 2

6. Exclusion criteria based on infectious diseases:
    - Active infection requiring IV antibiotics at screening.
    - Patients with active hepatitis B (chronic or acute; defined as having a positive hepatitis B surface antigen [HBsAg] test at screening). Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. HBV DNA test must be performed in these patients prior to Cycle 1 Day 1.
    - Patients with active hepatitis C. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
    - Known HIV infection.
    - Influenza vaccination should be given during influenza season. Patients must not receive live, attenuated influenza vaccine (e.g., FluMist®) within 4 weeks prior to Cycle 1 Day 1 or at any time during the study and for at least 5 months after the last dose of study drug.

5.3 Subject Withdrawal or Termination

5.3.1 REASONS FOR WITHDRAWAL OR TERMINATION

Subjects are free to withdraw from participation in the study at any time upon request. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the Sponsor-Investigator determines may jeopardize the patient's safety if he or she continues in the study.
- Sponsor-Investigator determines it is in the best interest of the patient
- Patient non-compliance

Patients must discontinue study treatment if they experience any of the following:

- Disease progression (Patients are allowed to receive study treatment beyond disease progression if certain conditions are met (Please see Section 6.1.1)).
- Symptomatic deterioration attributed to disease progression as determined by the investigator after integrated assessment of radiographic data, biopsy results, and clinical status
- Intolerable toxicity related to any study drug
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment
- Use of another non−protocol anti-cancer therapy
- Pregnancy

Patients must provide written consent to acknowledge deferring any standard treatment options that may exist in favor of continuing study treatment at the time of initial progression (section 7.3.1).

5.3.2 HANDLING OF SUBJECT WITHDRAWALS OR TERMINATION

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study or study drug discontinuation should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients enrolled in Stage 1 (safety run-in) who withdraw consent before completing the first cycle for reasons other than adverse events will be replaced. Patients who withdraw from Stage 2 of the study will not be replaced.

5.4 Premature Termination or Suspension of Study (Study Stopping Rules)

The Sponsor-Investigator has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

The Sponsor-Investigator will notify Merck and Pfizer if they decide to discontinue the study. Reasons for discontinuing the study may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

6 STUDY AGENTS

6.1 Study Agent(s) and Control Description

The study agents for this study are pembrolizumab, binimetinib and bevacizumab. Pembrolizumab and binimetinib packaging will be overseen by MERCK and Pfizer clinical trial supplies department respectively and will bear a label with identification required by local law. The packaging and labeling of the study drugs will be in accordance with the manufacturer's standards and local regulations. Local packaging and labeling requirements may differ in some countries.

Upon delivery of the investigational products to the site, site personnel should check for damage and verify proper identity, quality, integrity of seals and temperature conditions. Site personnel should report any deviations or product complaints to the study monitor and/or MERCK/Pfizer (depending on drug) upon discovery.

Pembrolizumab, binimetinib and bevacizumab will be stored at the clinical site under the required storage conditions as indicated on the study drug labels.

6.1.1 PEMBROLIZUMAB (KEYTRUDA)

ACQUISITION

Merck & Co, Inc. will provide Pembrolizumab from commercial supply.

FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Two drug product (DP) dosage forms are available for pembrolizumab: a white to off-white lyophilized powder, 50 mg/vial, and a liquid, 100 mg/vial, both in Type I glass vials intended for single use only.

KEYTRUDA for injection is a sterile, preservative-free, white to off-white lyophilized powder in single-use vials. Each vial is reconstituted and diluted for intravenous infusion. Each 2 mL of reconstituted solution contains 50 mg of pembrolizumab and is formulated in histidine (3.1 mg), polysorbate 80 (0.4 mg), and sucrose (140 mg). May contain hydrochloric acid/sodium hydroxide to adjust pH to 5.5.

KEYTRUDA injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for intravenous infusion. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP.

PRODUCT STORAGE AND STABILITY

KEYTRUDA for injection (lyophilized powder): carton containing one 50 mg single-use vial (NDC 00063029-02).

Store vials under refrigeration at 2°C to 8°C (36°F to 46°F).

KEYTRUDA injection (solution): carton containing one 100 mg/4 mL (25 mg/mL), single-use vial (NDC 0006-3026-02)

Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake.

Store the reconstituted and diluted solution from the KEYTRUDA 50 mg vial either:

At room temperature for no more than 6 hours from the time of reconstitution. This includes room temperature storage of reconstituted vials, storage of the infusion solution in the IV bag, and the duration of infusion.

Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 96 hours from the time of reconstitution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

The solution must be discarded after 6 hours at room temperature or 96 hours under refrigeration.

Store the diluted solution from the KEYTRUDA 100 mg/4 mL vial either:

At room temperature for no more than 6 hours from the time of dilution. This includes room temperature storage of the infusion solution in the IV bag, and the duration of infusion.

Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 96 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

The solution must be discarded after 6 hours at room temperature or 96 hours under refrigeration.

Do not freeze.

PREPARATION

Reconstitution of KEYTRUDA for Injection (Lyophilized Powder)
Add 2.3 mL of Sterile Water for Injection, USP by injecting the water along the walls of the vial and not directly on the lyophilized powder (resulting concentration 25 mg/mL).
Slowly swirl the vial. Allow up to 5 minutes for the bubbles to clear. Do not shake the vial.

Preparation for Intravenous Infusion
Visually inspect the solution for particulate matter and discoloration prior to administration. The solution is clear to slightly opalescent, colorless to slightly yellow. Discard the vial if visible particles are observed.

Dilute KEYTRUDA injection (solution) or reconstituted lyophilized powder prior to intravenous administration.

Withdraw the required volume from the vial(s) of KEYTRUDA and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Mix diluted solution by gentle inversion. The final concentration of the diluted solution should be between 1 mg/mL to 10 mg/mL.

Discard any unused portion left in the vial.

DOSING AND ADMINISTRATION

Dosing:

Patients will be treated on a 21-day cycle

Pembrolizumab 200mg IV Day 1

Administration:

Administer infusion solution intravenously over 30 minutes ± 10 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter.

Do not co-administer other drugs through the same infusion line.

ROUTE OF ADMINISTRATION

Intravenous administration

STARTING DOSE AND DOSE ESCALATION SCHEDULE

Not applicable.

DOSE ADJUSTMENTS/MODIFICATIONS/DELAYS

See Appendix I

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration section of the eCRF. Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event section of the eCRF.

Dosing of study treatment beyond RECIST v1.1 defined disease progression is allowed for patients on all treatment cohorts. Patients must meet all of the following criteria to be allowed to receive study treatment beyond disease progression:

- Evidence of clinical benefit as assessed by the investigator
- Absence of symptoms and signs indicating unequivocal progression of disease. Patients may continue to receive treatment beyond disease progression in the absence of clinical signs or symptoms of progression despite a rising CEA level.
- No decline in ECOG performance status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol allowed medical interventions.
- Patients must provide written consent to acknowledge deferring these treatment options in favor of continuing study treatment at the time of RECIST v1.1-defined disease progression.
- Approval by the study Medical Monitor

If the subsequent scan continues to show progression, all therapy will be discontinued and the patient will be taken off study.

DURATION OF THERAPY

Patients in the safety run-in phase and in the dose expansion phase will continue to receive study therapy until disease progression according to RECIST v1.1 (section 5.4.1), unacceptable toxicity, death, patient or physician decision to withdraw, pregnancy, or the maximum upper limit of pembrolizumab therapy (35 cycles), whichever occurs first.

TRACKING OF DOSE

Not applicable

6.1.2 BINIMETINIB

ACQUISITION+

Pfizer

FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Binimetinib drug product is supplied as film-coated tablets in a dosage strength of 15 mg. The film-coated tablets consist of binimetinib, lactose monohydrate, microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, magnesium stearate and a commercial film coating. The tablets are yellow to dark yellow and capsule shaped.

PRODUCT STORAGE AND STABILITY

Binimetinib film-coated tablets should not be stored above 25°C and should be protected from light. Tablets are packaged in plastic bottles acceptable for pharmaceutical use.

PREPARATION

Not applicable.

DOSING AND ADMINISTRATION

Binimetinib 45mg PO BID continuous without regard to food, taken with water.

ROUTE OF ADMINISTRATION

Oral

STARTING DOSE AND DOSE ESCALATION SCHEDULE

Not applicable.

DOSE ADJUSTMENTS/MODIFICATIONS/DELAYS

See Appendix I

Dose Level -1 = 30mg PO BID continuous
Dose Level -2 = 15mg PO BID continuous
Dose Level -3 = 15mg PO daily

Binimetinib may also be dose reduced per discretion of treating investigator.

DURATION OF THERAPY

Patients in the safety run-in phase and in the dose expansion phase will continue to receive study therapy until disease progression according to RECIST v1.1, unacceptable toxicity, death, patient or physician decision to withdraw, or pregnancy, whichever occurs first.

TRACKING OF DOSE

Patient will be given a drug diary to monitor and record drug compliance.

6.1.3 BEVACIZUMAB (BEVACIZUMAB-AWWB ALSO ALLOWED)

ACQUISITION

Standard of care medication obtained through normal commercial acquisition processes.

FORMULATION, APPEARANCE, PACKAGING, AND LABELING

• 100 mg per 4 mL single-use vial

• 400 mg per 16 mL single-use vial

PRODUCT STORAGE AND STABILITY

Bevacizumab vials [100 mg (NDC 50242-060-01) and 400 mg (NDC 50242-061-01)] are stable at 2−8°C (36−46°F). Bevacizumab vials should be protected from light. Do not freeze or shake. Diluted Bevacizumab solutions may be stored at 2−8°C (36−46°F) for up to 8 hours. Store in the original carton until time of use. No incompatibilities between Bevacizumab and polyvinylchloride or polyolefin bags have been observed.

PREPARATION

Use appropriate aseptic technique. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Withdraw necessary amount of Bevacizumab and dilute in a total volume of 100 mL of 0.9% Sodium Chloride Injection, USP. Discard any unused portion left in a vial, as the product contains no preservatives.

DO NOT ADMINISTER OR MIX WITH DEXTROSE SOLUTION.

DOSING AND ADMINISTRATION

Bevacizumab 7.5mg/kg Day 1 (bevacizumab-awwb allowed) to be given over 30 minutes ± 10 minutes intravenously.

ROUTE OF ADMINISTRATION

Intravenous infusion

STARTING DOSE AND DOSE ESCALATION SCHEDULE

Not applicable.

DOSE ADJUSTMENTS/MODIFICATIONS/DELAYS

See Appendix I

There are no recommended dose reductions.

Discontinue bevacizumab for:

- Gastrointestinal perforations (gastrointestinal perforations, fistula formation in the gastrointestinal tract, intra-abdominal abscess), fistula formation involving an internal organ
- Wound dehiscence and wound healing complications requiring medical intervention
- Serious hemorrhage (i.e., requiring medical intervention)
- Severe arterial thromboembolic events
- Life-threatening (Grade 4) venous thromboembolic events, including pulmonary

embolism

- Hypertensive crisis or hypertensive encephalopathy
- Posterior Reversible Encephalopathy Syndrome (PRES)
- Nephrotic syndrome

Temporarily suspend bevacizumab for:

- At least 4 weeks prior to elective surgery
- Severe hypertension not controlled with medical management
- Moderate to severe proteinuria
- Severe infusion reactions

DURATION OF THERAPY

Patients in the safety run-in phase and in the dose expansion phase will continue to receive study therapy until disease progression according to RECIST v1.1, unacceptable toxicity, death, patient or physician decision to withdraw, or pregnancy, whichever occurs first. A rising carcinoembryonic antigen (CEA) level alone is not considered disease progression. Patients are allowed to receive study treatment beyond disease progression if certain conditions are met.

TRACKING OF DOSE

Not applicable.

6.2 Study Agent Accountability Procedures

The study agent or Investigational Medicinal Product (IMPs) required for the completion of this study will be provided by MERCK/Pfizer where required by local health authority regulations. The study site will acknowledge receipt of IMPs. Any damaged shipments will be replaced.

The commercial formulation of bevacizumab (Avastin) will be used as per standard of care and will not be provided by Merck or Pfizer.

IMPs will be disposed at the study site according to the study site's institutional standard operating procedure.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

7 STUDY PROCEDURES AND SCHEDULE

7.1 Study Procedures/Evaluations

Please see Table 1 for the schedule of activities to be performed during the study.

7.2 Laboratory Procedures/Evaluations

Screening

- Hematology (CBC, hemoglobin, hematocrit, WBC count with differential [neutrophils, eosinophils, lymphocytes], and platelet count)
- Serum chemistries (non-fasting glucose, BUN or urea, creatinine, sodium, potassium, magnesium, calcium, phosphorus, total bilirubin, ALT, AST, ALP, CPK, lipase, amylase, and albumin)
- Coagulation (INR and aPTT)
- Serum pregnancy test for women of childbearing potential, including women who have had a tubal ligation.
- Thyroid function testing (thyroid-stimulating hormone [TSH], total T3, free T4)
- HBV serology: HBsAg, Hepatitis B surface antibody (anti-HBs), and anti-HBc
- HBV DNA should be obtained prior to enrollment if patient has a negative serology for HbsAg and a positive serology for anti-HBcAb.
- HCV serology: HCV antibody (anti-HCV)
- HCV RNA should be obtained prior to enrollment if patient tests positive for anti-HCV
- Urinalysis: dipstick, with 24-hour urine collection conducted in the event of proteinuria ≥ + 2 detected by dipstick test

On Study Treatment

- Hematology (CBC, hemoglobin, hematocrit, WBC count with differential [neutrophils, eosinophils, lymphocytes], and platelet count)
- Serum chemistries (non-fasting glucose, BUN or urea, creatinine, sodium, potassium, magnesium, calcium, phosphorus, total bilirubin, ALT, AST, ALP, CPK, lipase, amylase, and albumin)
- CEA
- Thyroid function testing (TSH, total T3, free T4)
- Coagulation (INR and aPTT)
- Urinalysis: dipstick, with 24-hour urine collection conducted in the event of proteinuria ≥ + 2 detected by dipstick test

7.2.1 CLINICAL LABORATORY EVALUATIONS (RESEARCH PROCEDURES)

The University of Colorado Developmental Therapeutics/Pitts laboratory will coordinate the sample collection of tissue and blood samples for research- related testing at central laboratories. Instruction manuals and supply kits will be provided for all central laboratory assessments including:

- **Blood samples will be obtained for biomarker evaluation** (including but not limited to biomarkers that are related to CRC or tumor immune biology) from all eligible patients in the expansion cohorts according to the schedule. Blood sample preparation (to be performed by the Pitts Laboratory) is as follows:
  - Collect whole blood in K2EDTA and CPT tubes.
  - Invert 8-10 times, let sit at room temperature for 30-60 minutes.
  - Load the K2EDTA specimen tubes in the centrifuge.
  - Centrifuge for 10 minutes at 4°C - 10°C at 1,600g with brake

position on.
- Ensure the centrifuge is balanced.
- Spin the specimen tubes.
- Remove plasma taking care to not disturb the white cellular interface ("buffy coat" layer)
- Transfer supernatant to a new centrifuge tube and store at -80
- Spin the CPT tube at room temp at 1600g with brake off. Remove plasma, taking care to not disturb the buffy coat.
- Aspirate the plasma layer and transfer to a separate tube, label and store in -80
- Aspirate buffy coat and transfer to an appropriately labeled 1.5mL microfuge tube. (Note, some contamination of the buffy coat by residual plasma or erythrocytes is unavoidable and will not interfere with later steps.)
- Wash with PBS and perform T-cell isolation
- Perform the above aspirations steps for each specimen.

7.2.2 OTHER ASSAYS OR PROCEDURES (RESEARCH)

Tumor Tissue Samples

A University of Colorado Cancer Center laboratory (The Developmental Therapeutics/Pitts Laboratory at the University of Colorado) will coordinate the sample collection of tissue samples for research related testing at the University of Colorado or at Merck/Pfizer. Instruction manuals and supply kits will be provided for all central laboratory assessments.

7.2.3 SPECIMEN PREPARATION, HANDLING, AND STORAGE

Fresh Tumor Sample should be collected according to *Section 4.1; Stage 2: Dose Expansion; Design* and collected as follows:

- The tumor sample must be obtained once patient has been enrolled in the study.
- Fine-needle aspiration, brushing, cell pellet from pleural effusion, and lavage samples are not acceptable.
- For core needle biopsy specimens, at least four cores should be submitted for evaluation at baseline, and at least two cores should be submitted for evaluation on-treatment.

Safely biopsied disease is defined as:

- cutaneous lesions (without evidence of active infection)
- peripherally accessible lymph nodes (cervical, axillary, inguinal, extremities)
- liver metastases (not immediately adjacent to major vessels)
- lung metastases easily accessible by percutaneous biopsy or endobronchial ultrasound
- rectal lesions

Lesions **not allowed** for biopsy include brain, mediastinum, pelvis, or any lesion deemed by the patient's primary oncologist, study investigator, or radiologist to represent greater risk to the subject.

Tumor tissues will be assessed for mismatch repair status at baseline, PD-L1 expression, and phosphorylated ERK expression in pre- and post-treatment specimens. In addition, mRNA expression of a panel of immune markers will also be assessed in both pre- and post-treatment tissues.

Tissue acquisition: Four core biopsies using an 18-22 gauge needle should yield sufficient material for analysis at baseline, and two core biopsies should yield sufficient material for analysis on-treatment. All of the tissue should be processed as follows:

Baseline Biopsy:

- **Core biopsy #1 and #2:** immediately placed into a provided specimen cup with RPMI. The container should immediately be brought over to the lab for injection into mice. This process has been approved by the Institutional Animal Research Committee.

- **Core biopsy #3 and #4:** immediately submerged in 10% Neutral Buffered Formalin in a container labeled "#2: Formalin" and placed into refrigerator (4°) or stored in ice.

On-Treatment Biopsy:

- **Core biopsy #1 and #2:** immediately submerged in 10% Neutral Buffered Formalin in a container labeled "#2: Formalin" and placed into refrigerator (4°) or stored in ice.

All samples should be labeled with date, protocol number, and subject identification number.

7.2.4 SPECIMEN SHIPMENT

All samples must be shipped on ice and delivered within 24 hours from the time of biopsy to:

PROGRAM FOR EXPERIMENTAL TARGETED THERAPEUTICS LABORATORY

To the address listed in the lab manual.

7.3 Study Schedule

Please see scheduling table for details.

7.3.1 SCREENING

Written informed consent must be obtained before performing any study-related procedures.

Demographic data, medical and CRC history, baseline disease characteristics, vital signs, weight, height, ECOG performance status, complete physical examination, list of

medications, ECHO or MUGA, 12-lead ECG, hematology, blood chemistry, HIV/HBV/HCV serologies, coagulation tests, ophthalmic exams, urine dipstick, pregnancy test, TFTs, and tumor baseline assessment must be completed as part of the screening process.

All screening evaluations must be completed and reviewed to confirm that all eligibility criteria are met prior to enrollment. The investigator will maintain a screening log to record details of all patients screened irrespective of eligibility.

Demographic Data and Medical History

Includes age, sex, self-reported ethnicity, detailed description of history of cancer, past medical and surgical history, list of medications including prescription, OTC, herbal, homeopathic, nutritional drugs, performance status, social history including alcohol, tobacco and recreational drug use, family history especially of malignancy and reproductive history.

History of cancer should include stage, date of first diagnosis, site of primary disease, previous biopsies particularly date and site of biopsy, location of metastases, previous treatments administered including all surgeries and radiation therapy, previous clinical trials especially details of any previous use of immunotherapies, ECOG performance status, MSI status, and mutational testing particularly RAS and BRAF.

Any pre-existing symptoms must be graded and recorded as per NCI-CTCAE v4.03.

Physical Examination

A complete physical examination should be performed. Any physical exam findings must be graded and recorded as per NCI-CTCAE v4.03.

Investigations

All of the above listed investigations must be completed, reviewed and recorded as part of the screening process. Any pre-existing baseline abnormality must be graded and recorded as per NCI-CTCAE v4.03.

Blood/Plasma Samples

Site staff will collect the blood samples for standard blood panels (CBC/CMP) per standard of care.

Left Ventricular Ejection Fraction

Must be performed with an echocardiogram or MUGA at screening. It is strongly encouraged that the same laboratory and operator perform the ECHO/MUGA scans for each individual patient. All post- screening ECHO/MUGA scans will be in reference to a subject's Cycle 1 Day 1, regardless of treatment delays. Page 46 outlines specific dates for study-related ECHOs.

Ophthalmologic Examination

All patients will require regular ophthalmologic examinations at screening and during study conduct. Ophthalmologic examination must be performed at the time-points listed below, regardless of treatment delays. All ophthalmologic exams post-screening are in reference to a subject's Cycle 1 Day 1:

- Screening
- Cycle 2 Day 1 ± 2 weeks
- Day 1 of Cycles 5, 8, and 11 (every three treatment cycles) ± 2 weeks
- Day 1 of Cycles 15, 19, and 23 (every four treatment cycles) ± 2 weeks
- Day 1 of Cycles 29, 35, 41, 47, etc. (every six treatment cycles) ± 2 weeks
- End-of-study-treatment visit

The objective of baseline ophthalmologic examination is to evaluate for evidence of retinal pathology that may be a risk factor for central serous retinopathy or retinal vein occlusion.

Ophthalmologic examination must be performed by an ophthalmologist. Risk factors for retinal vein occlusion include uncontrolled serum cholesterol, hypertriglyceridemia, hyperglycemia, hypertension, and glaucoma. Patients with such conditions will be excluded from the study as detailed in the inclusion/exclusion criteria.

Baseline and serial surveillance ophthalmologic examination will include visual acuity testing, intraocular pressure measurements by tonometry, slit-lamp ophthalmoscopy, indirect ophthalmoscopy, and optical coherence tomography (spectral- or time-domain). Spectral domain optical coherence tomography, if not available, may be substituted with time-domain optical coherence tomography.

Tumor and Response Evaluations

Baseline tumor assessments should be performed ≤ 28 days before Cycle 1 Day 1 and assessed according to RECIST v 1.1 (see Appendix 3) and irRC. The same procedure used to assess disease sites at baseline should be used throughout the study (e.g., the same contrast protocol for CT scans or MRI scans). To the extent that it is feasible, the same assessor should read and evaluate the tumor assessments for the same patient throughout the study. CT or MRI scans should include chest, abdomen, and pelvic scans; CT or MRI scans of the neck should be included if clinically indicated. At the investigator's discretion, CT scans may be repeated at any time if progressive disease is suspected.

Evaluation of tumor response conforming to RECIST v1.1 must be documented every 9 weeks ± 1 week (no matter where the patient is in the treatment cycle) until documented, investigator−determined, progressive disease, loss of clinical benefit, withdrawal of consent, death, or study termination by the Sponsor-Investigator, whichever occurs first. Schedule of tumor assessments are independent of any changes to the study treatment administration schedule (e.g., dose delay) and may occur mid-cycle depending on length of cycle. If a tumor assessment has to be performed early or late, subsequent assessments should be conducted according to the original schedule based on the date of first study drug administration (Cycle 1, Day 1). Confirmation of response (PR or complete response [CR]) will be done no earlier than 28 days from study entry. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval not less than 6 weeks. Patients who discontinue study treatment for any reason other than disease progression will continue to

undergo tumor response evaluations (approximately every 9 weeks) until progressive disease. Rising tumor markers (e.g., CEA) in the absence of radiological evidence of progression is not considered progressive disease.

Patients who continue to experience clinical benefit, despite evidence of radiographic progression as defined by RECIST v1.1, may continue treatment and will continue tumor assessments as per the schedule listed above.

7.3.2 ENROLLMENT/BASELINE

Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

7.3.3 TREATMENT PERIOD

Medical History

At subsequent visits, clinically significant history should be obtained.

Physical Examination

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF. Patients will be asked specifically about vision changes as part of each physical examination in addition to interval medical history.

Vital Signs

Must be collected:

- Within 60 min prior to infusion
- During infusion if clinically indicated or if symptoms occurred in the prior infusion.
- Within 30 min (+/- 10 minutes) after infusion if clinically indicated or if symptoms occurred in the prior infusion.
- Weight will be collected on Day 1 of each cycle.

Laboratory Samples

Hematology, serum chemistries (non-fasting glucose, BUN, creatinine, sodium, potassium, magnesium, calcium, phosphorous, total bilirubin, ALT, AST, ALP, CK, lipase, amylase and albumin), CEA, TFT, coagulation and urinalysis must be collected at clinical visits.

Site staff will collect blood samples and send to the Program for Experimental Targeted Therapeutics Laboratory at the University of Colorado when appropriate (please see below). Instruction manuals and supply kits will be provided for all central laboratory testing. Samples for the following lab tests will be sent to central laboratories for analysis:

1. **Biomarker assays** – blood samples will be obtained for biomarker evaluation (including but not limited to biomarkers that are related to CRC or tumor immune biology) from all eligible patients in the expansion cohorts according to the schedule. Samples will be processed to obtain plasma for the determination of changes in blood based biomarkers. Proposed biomarkers for exploratory research are cytokines and other immune regulators, a panel of oncogenic mutations and overall mutation loads by isolating ctDNA from plasma, immune cell infiltrates and protein expression (including but not limited to PD-L1 and MHC expression), MSI and CRC subtyping signatures from DNA and RNA extracted from tumor tissues.

For sampling procedures, storage conditions and shipment instructions, please see the laboratory manual.

Any remaining samples post analysis will be destroyed unless there is optional patient consent for banking.

Tumor Tissue Samples

Fresh tumor sample: tumor biopsy samples must be obtained for all study patients on expansion cohorts irrespective of availability of an archival sample or prior biopsy at enrollment and should be collected according to *Section 4.1; Stage 2: Dose Expansion; Design*.

Acceptable samples include core needle biopsies for deep tumor tissue or tumor tissue resection. At least two cores embedded into a single paraffin block should be submitted for evaluation. Cytological or fine-needle aspiration samples are not acceptable.

Biomarker testing will be performed on the fresh tumor samples which will include extended RAS, RAF, MSI, PD-LI tumor expression, phosphorylated ERK expression and mRNA expression of immune related genes.

Left Ventricular Ejection Fraction

Evaluation of LVEF by ECHO or MUGA must be performed at the following time-points:

- Screening
- Cycle 2 Day 1 ± 2 weeks
- Day 1 of Cycles 5, 8, and 11 (every three treatment cycles) ± 4 weeks and then every 3 months (± 4 weeks)
- End-of-study-treatment visit evaluation of LVEF

All post- screening ECHO/MUGA scans will be in reference to a subject's Cycle 1 Day 1, regardless of treatment delays.

Any patient who develops clinical signs or symptoms suspicious of cardiac failure should undergo an LVEF assessment. Evaluation of LVEF must be performed by the same method (ECHO or MUGA) for each patient. It is strongly encouraged that the same laboratory and operator perform ECHO/MUGA scans for each individual patient. Investigators must be aware of local institution regulations regarding repeat MUGA scans. The repeat administration of

radioisotopes is limited in some nuclear medicine laboratories, and some patients in this study could require monitoring on four or more occasions.

Ophthalmologic Examination

All patients will require regular ophthalmologic examinations at screening and during study conduct. Ophthalmologic examination must be performed at the time-points listed below, regardless of treatment delays. All ophthalmologic exams post-screening are in reference to a subject's Cycle 1 Day 1:

Ophthalmologic examination must be performed at the following time-points:

- Screening
- Cycle 2 Day 1 ± 2 weeks
- Day 1 of Cycles 5, 8, and 11 (every three treatment cycles) ± 2 weeks
- Day 1 of Cycles 15, 19, and 23 (every four treatment cycles) ± 2 weeks
- Day 1 of Cycles 29, 35, 41, 47, etc. (every six treatment cycles) ± 2 weeks
- End-of-study-treatment visit ± 2 weeks

The objective of baseline ophthalmologic examination is to evaluate for evidence of retinal pathology that may be a risk factor for central serous retinopathy or retinal vein occlusion. Ophthalmologic examination must be performed by an ophthalmologist. Risk factors for retinal vein occlusion include uncontrolled serum cholesterol, hypertriglyceridemia, hyperglycemia, hypertension, and glaucoma. Patients with such conditions will be excluded from the study as detailed in the inclusion/exclusion criteria.

Baseline and serial surveillance ophthalmologic examination will include visual acuity testing, intraocular pressure measurements by tonometry, slit-lamp ophthalmoscopy, indirect ophthalmoscopy, and optical coherence tomography (spectral- or time-domain).
Spectral domain optical coherence tomography, if not available, may be substituted with time-domain optical coherence tomography.

Tumor and Response Evaluation

Evaluation of tumor response conforming to RECIST v1.1 must be documented every 9 weeks ± 1 week (no matter where the patient is in the treatment cycle) until documented, investigator−determined, progressive disease, loss of clinical benefit, withdrawal of consent, death, or study termination by the Sponsor-Investigator, whichever occurs first. Schedule of tumor assessments are independent of any changes to the study treatment administration schedule (e.g., dose delay) and may occur mid-cycle depending on length of cycle. If a tumor assessment has to be performed early or late, subsequent assessments should be conducted according to the original schedule based on the date of first study drug administration (Cycle 1, Day 1). Confirmation of response (PR or complete response [CR]) will be done no earlier than 28 days from study entry. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval not less than 6 weeks. Patients who discontinue study treatment for any reason other than disease progression will continue to undergo tumor response evaluations (approximately every 9 weeks) until progressive disease. Rising tumor markers (e.g., CEA) in the absence of radiological evidence of progression is not considered progressive disease.

Patients who continue to experience clinical benefit, despite evidence of radiographic progression as defined by RECIST v1.1, may continue treatment and will continue tumor assessments as per the schedule listed above.

7.3.4 FINAL STUDY VISIT/EARLY TERMINATION VISIT

A final study visit is required if patients come off study for any reason. Patients who discontinue study drug will return to the clinic for a discontinuation visit 30 (+/- 7 days) after treatment discontinuation.

Participants may come off study for many reasons including:

- Voluntary withdrawal at any time for any reason by patient
- Withdrawal of patient by investigator due to concerns for patient safety or non-compliance with study drug(s)
- Radiological disease progression
- Symptomatic deterioration attributed to disease progression as determined by investigator
- Intolerable toxicity related to any study drug
- Any medical condition jeopardizing patient safety if they continue on study drug(s)
- Use of another non-protocol anti-cancer therapy
- Pregnancy
- Reached maximum recommended upper limit of pembrolizumab therapy (35 cycles)

During a final study visit/early termination visit (which can also be the end of treatment visit), a medical history along with a physical examination and measurement of vital signs must be performed. 12-lead ECG, tumor response evaluation, laboratory, biomarker, and other biologic samples, echo/MUGA, ophthalmological exam, and if needed, tumor tissue sample will be assessed. If tumor response evaluation, echo/MUGA, ophthalmological exam have been done within 3 weeks of final study visit/early termination visit then they need not be repeated during the final study visit/early termination visit.

7.3.5 SURVIVAL FOLLOW-UP

After treatment discontinuation, survival follow-up information will be collected via telephone calls and/or clinic visits every 3 months (+/- 2 weeks). Follow-up information will continue until the participant's death, withdrawal of consent, the participant is lost to follow-up, or study termination by the Sponsor-Investigator, whichever occurs first.

7.3.6 UNSCHEDULED VISIT

Investigator will review patient per standard of care and document all pertinent information as per section 7.3.3 Treatment Period.

7.3.7 SCHEDULE OF EVENTS

TABLE 1. Schedule of Events

	Screening[a]	Treatment Period q21d cycle (Pembrolizumab, Binimetinib and Bevacizumab)				Final Study/ Treatment Discontinuation Visit[b]	Survival Follow-Up[c]
		Cycle 1		Cycle 2	Cycles 3+		
Days *(window)*	**-28 to -1**	**d1-7**	**1** *(±2)*	**1** *(±2)*	**1** *(±2)*		
Informed consent[d]	x						
Demographic data	x						
Medical and CRC history	x						
Baseline disease characteristics	x						
Vital signs[e,f]	x		x	x	x	x	
Weight	x		x	x	x		
Height	x						
ECOG performance status	x			x	x	x	
Complete physical examination	x						
Limited physical examination			x	x	x	x	
ECHO or MUGA scan[g]	x			x	x	x	
12-lead ECG	x					x	
Hematology[h]	x		x	x	x	x	
Chemistry[i]	x		x	x	x	x	
HIV, HBV, and HCV serologies[j]	x						
Biomarker Blood Draw			x			x[r]	
Coagulation tests	x		x	x	x		
Ophthalmic exams[k]	x			x	x	x	
Urine dipstick[p]	x		x	x	x		
Pregnancy test[l]	x	Monthly as clinically indicated					
Thyroid function test[m]	x		x	x	x		
CEA			x	x	x		
Binimetinib Cohort A		x		x	x		
Binimetinib Cohort B & Run- in			x	x	x		
Pembrolizumab administration			x	x	x		
Bevacizumab administration			x	x	x		
Concomitant medications	x		x	x	x	x	
Adverse events			x	x	x	x	
Tumor biopsy- Cohort A[n]		x	x				
Tumor biopsy- Cohort B[o]			x	x			
Tumor assessments[q]	x				x	x	
Survival Follow-up Information							x

CEA= carcinoembryonic antigen; CRC = colorectal cancer; ECHO= echocardiogram; ECOG= Eastern Cooperative Oncology Group; HBV= hepatitis B virus; HCV= hepatitis C virus; MUGA=multigated acquisition scan.

[a] Results of standard of care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 1 may be used; such tests do not need to be repeated for screening

[b] Patients who discontinue study drug will return to the clinic for a discontinuation visit 30 (± 7 days) after treatment discontinuation.

[c] Required follow-up information will be collected via telephone calls and/or clinic visits every 3 months (+/- 2 weeks) until death, withdrawal of consent, the patient is lost to follow-up, or study termination by the Sponsor-Investigator, whichever occurs first.

[d] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained up to 28 days before initiation of study treatment.

[e] Includes heart rate, temperature, and systolic and diastolic blood pressure while the patient is in a seated position. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits record new or worsened clinically significant abnormalities on the Adverse Event eCRF

[f] Vital signs at the first Pembrolizumab infusion will be collected within 60 min prior to the infusion, every 15 (± 10) min during the pembrolizumab infusion and 30 (± 10) min after the infusion. For subsequent infusions, vital signs will be collected within 60 min prior to the infusion and should be collected during the infusion if clinically indicated or if symptoms occurred in the prior infusion, and 30 (± 10) min after the infusion.

[g] All patients will undergo evaluation of left ventricular dysfunction, either by ECHO or MUGA, screening. Evaluation of LVEF by ECHO or MUGA must be performed at the following timepoints, regardless of treatment delays (all ophthalmologic exams post-screening are in reference to a subject's Cycle 1 Day 1)::

- Screening,
- Cycle 2, Day 1 ± 2 weeks
- Day 1 of Cycles 5, 8, and 11 and every three treatment cycles thereafter ± 4 weeks
- End-of-study-treatment visit evaluation of LVEF

[h] Hematology (CBC, hemoglobin, hematocrit, WBC count with differential [neutrophils, eosinophils, lymphocytes], and platelet count).

[i] Serum chemistries (non-fasting glucose, BUN or urea, creatinine, sodium, potassium, magnesium, calcium, phosphorus, total bilirubin, ALT, AST, ALP,CPK, lipase, amylase, and albumin). Serum chemistry includes serum cholesterol and triglycerides at baseline.

[j] HBV serology: Hepatitis B surface antigen, hepatitis B surface antibody, and total hepatitis B core antibody. HBV DNA should be obtained prior to enrollment if patient has a negative serology for HbsAg and a positive serology for anti-HBcAb.

HCV serology: HCV antibody (anti-HCV). HCV RNA should be obtained prior to enrollment if patient tests positive for anti-HCV.

[k] All patients will undergo ophthalmologic examination (see Section 4.5.9 for exam requirements) at screening. Ophthalmologic examination must be performed at the following timepoints, regardless of treatment delays (all ophthalmologic exams post-screening are in reference to a subject's Cycle 1 Day 1):

- Screening
- Cycle 2 Day 1 ±2 weeks
- Day 1 of Cycles 5, 8, and 11 (every three treatment cycles) ±2 weeks
- Day 1 of Cycles 15, 19, and 23 (every four treatment cycles) ±2 weeks
- On Day 1 of Cycles 29, 35, 41, 47, etc. (every six treatment cycles) ±2 weeks
- End-of-study-treatment visit

[l] Serum pregnancy test within 14 days before Cycle 1, Day 1 *and then monthly as clinically indicated.*

[m] Thyroid function testing (thyroid-stimulating hormone [TSH], total T3, free T4) collected at Screening, Cycle 1 Day 1, and every cycle thereafter.

[n] Fresh tumor samples should be obtained prior to C1D-7 (after randomization) and then prior to C1D1.

[o] Fresh tumor samples should be obtained pre-treatment (after randomization, prior to C1D1) and on C1D21 (+/-5 day window).

[p] 24 hour urine collection conducted in the event of proteinuria ≥ + 2 detected by dipstick test.

[q] Evaluation of tumor response conforming to RECIST v1.1 and irRC must be documented every 9 weeks ± 1 week (no matter where the patient is in the treatment cycle)

[r] Biomarker blood draws will be taken for participants with disease progression at the Final Study Visit/End of Treatment. Participants with partial response or stable disease will have their blood drawn again at Cycle 4, Day 1. If blood is drawn at Cycle 4, Day 1 then blood will not drawn again at the Final Study Visit/End of Treatment.

Table 2. Schedule of Biomarkers for Expansion Cohort

Treatment Period	Time-point	Sample Type
Cycle 1 Day 1	Prior to infusion	Biomarker
Final Study Visit/Treatment Discontinuation Visit		Biomarker[ǂ]

[ǂ] Biomarker blood draws will be taken for participants with disease progression at the Final Study Visit/End of Treatment. Participants with partial response or stable disease will have their blood drawn again at Cycle 4, Day 1. If blood is drawn at Cycle 4, Day 1 then blood will not drawn again at the Final Study Visit/End of Treatment.

7.4 Justification for Sensitive Procedures

N/A

7.5 Concomitant Medications, Treatments, and Procedures

All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician.

Medications reported in the CRF are concomitant prescription medications, over-the-counter medications, and non-prescription medications.

7.6 Prohibited Medications, Treatments, and Procedures

Any concomitant therapy intended for the treatment of cancer, whether health authority approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the anti-cancer agent (see Section 4.1.3), and during study treatment until disease progression is documented and patient has discontinued study treatment. This includes but is not limited to chemotherapy, hormonal therapy, immunotherapy, radiotherapy, investigational agents, or herbal therapy.

The following medications are prohibited while receiving study treatment, unless otherwise noted:

- Traditional herbal medicines, as their use may result in unanticipated drug-drug interactions that may cause or confound assessment of toxicity.
- Denosumab: Patients who are receiving denosumab prior to enrollment must be willing and eligible to receive a bisphosphonate instead while in the study.
- Any live, attenuated vaccine (e.g., FluMist) within 4 weeks prior to Cycle 1 Day 1 or at any time during the study and for at least 5 months after the last dose of pembrolizumab.

For pembrolizumab:

- Use of steroids to premedicate patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance); in such patients, MRIs of the chest, abdomen, and pelvis with a non-contrast CT scan of the anatomical region of interest must be performed.
- Immunomodulatory agents, including but not limited to interferons or interleukin-2, during the entire study; these agents could potentially increase the risk for autoimmune conditions when administered with Pembrolizumab.
- Immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide; these agents could potentially alter the activity and the safety of pembrolizumab.
- Systemic corticosteroids and tumor necrosis factor-α (TNF-α) inhibitors may attenuate potential beneficial immunologic effects of treatment with pembrolizumab. Therefore, in situations where systemic corticosteroids or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered first by the treating physician. If the alternatives are not feasible, systemic corticosteroids and TNF-α inhibitors may be administered at the discretion of the treating physician (see Section 4.4.2).
- Initiation or increased dose of granulocyte colony-stimulating factors (e.g., granulocyte colony stimulating factor, granulocyte/macrophage colony-stimulating factor, and/or pegfilgrastim) is prohibited.

For Binimetinib:

- Concomitant use of strong inhibitors or inducers of UGT1A1, P-gp, BCRP and CYP2B6 should be used with caution. Binimetinib exposures may be increased or decreased in presence of these agents. Patients should be closely monitored for the occurrence of adverse events.

The above lists of medications are not necessarily comprehensive. Thus, the investigator should consult the prescribing information for any concomitant medication as well as the Internet references provided below when determining whether a certain medication is metabolized by or strongly inhibits or induces CYP. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf

http://medicine.iupui.edu/clinpharm/ddis/table.aspx

7.7 Prophylactic Medications, Treatments, and Procedures

The following therapies are permitted in the study:

- Oral contraceptives.
- Hormone-replacement therapy.
- Prophylactic or therapeutic anticoagulation therapy (such as low-molecular weight heparin or warfarin at a stable dose level).

- Palliative radiotherapy (e.g., treatment of known bone metastases) provided it does not interfere with assessment of tumor target lesions.
- It is not required to withhold any of the drugs during palliative radiotherapy.
- Inactive influenza vaccinations during influenza season ONLY.
- Megestrol administered as an appetite stimulant.
- Inhaled corticosteroids for chronic obstructive pulmonary disease.
- Mineralocorticoids (e.g., fludrocortisone).

7.8 Rescue Medications, Treatments, and Procedures

Anti-emetics and anti-diarrheal medications should not be administered prophylactically before initial treatment with study drugs. At the discretion of the investigator, prophylactic anti-emetic and anti-diarrheal medication(s) may be used per standard clinical practice before subsequent doses of study drugs.

Hematopoietic growth factors should not be administered prophylactically before initial treatment with study drugs. Hematopoietic growth factors may be administered according to local guidelines if indicated during the course of the study.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, as per local standards. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or famotidine or another H2 receptor antagonist as per standard practice (for sites outside the United States, equivalent medications may be substituted per local practice). Serious infusion−associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β2-adrenergic agonists).

Guidelines for known toxicities of study agents are provided in the Appendix 1.

All medications must be recorded on the Concomitant Medications eCRF.

7.9 Subject Access to Study Agent at Study Closure

The manufacturer will offer post-trial access to the study drug, Pembrolizumab free of charge to eligible patients in accordance with the MERCK Global Policy on Continued Access to Investigational Medicinal Product, as outlined below. Pfizer will provide binimetinib free of charge to eligible patients in accordance with their policies. Bevacizumab is part of standard of care therapy. A patient will be eligible to receive study drugs pembrolizumab and binimetinib after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued study drug treatment for his or her well-being.
- There are no appropriate alternative treatments available to the patient.
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them.

A patient will not be eligible to receive study drug after completing the study if any of the following conditions are met:

- The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient).
- Merck/Pfizer has discontinued development of the study drug or data suggest that the study drug is not effective for CRC.
- The Sponsor-Investigator has reasonable safety concerns regarding the study drug as treatment for CRC.
- Provision of study drug is not permitted under the laws and regulations of the patient's country.

8 ASSESSMENT OF SAFETY

8.1 Specifications of Safety Parameters

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Serious adverse event or **serious suspected adverse reaction**. An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or Merck/Pfizer, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/ birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.1.3 DEFINITION OF UNANTICIPATED PROBLEMS (UAP)

This study will use the COMIRB definition of UAP. An unanticipated problem is any event or information that was unforeseen and indicates that the research procedures caused harm (including physical, psychological, economic, or social harm) to participants or others or indicates that participants or others are at increased risk of harm than was previously known or recognized. (please see section 8.4.3)

8.2 Classifications of an Adverse Event

8.2.1 SEVERITY OF EVENT

For AEs not included in the protocol-defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the subject's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2 RELATIONSHIP TO STUDY AGENTS

The clinician's assessment of an AEs relationship to study agent (drug, biologic, device) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to the study agent assessed. In a clinical trial, the study product must always be suspect.

For all collected AEs, the clinician who examines and evaluates the subject will determine the AEs causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be Related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the subject's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study drug administration, and/ or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.2.3 EXPECTED ADVERSE EVENTS

The clinician will be responsible for determining whether an SAE is expected or unexpected. An SAE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.3 Time Period and Frequency for Event Assessment and Follow-up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study subject presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, date of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), action taken with study drug, treatment, expectedness and date of resolution/stabilization of the event. All AEs occurring

while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the study subject's condition deteriorates at any time during the study, it will be recorded as an AE. UAPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 90 days after last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.4 Reporting Procedures

8.4.1 ADVERSE EVENT REPORTING

The investigator is responsible for ensuring that all adverse events are recorded on the Adverse Event eCRF and reported to Merck. For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness, severity, and causality. Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF. Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations. Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported. After initiation of study drug, all serious adverse events will be reported until 90 days after the last dose of study drug.

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. The following table will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE (v4.0).

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events. Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event.

[d] Grade 4 and 5 events must be reported as serious adverse events.

Adverse Events that are secondary to other events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation time-points. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Merck/Pfizer immediately (i.e., no more than 24 hours after learning that the event became serious). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation time-points and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF

Abnormal Laboratory Values

- Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:
- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

Note: For oncology trials, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5x ULN associated with cholestasis), only the diagnosis (i.e., bile duct stenosis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF.

Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Preexisting Medical Conditions

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

The following hospitalization scenarios are not considered to be adverse events:

- Hospitalization for respite care.
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration).
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
    - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.
    - The patient has not experienced an adverse event.
    - Hospitalization due solely to progression of the underlying cancer.

The following hospitalization scenarios are not considered to be serious adverse events, but should be reported as adverse events instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours.

Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Merck/Pfizer immediately.

Deaths

Deaths that occur during the protocol- specified adverse event reporting period should be entered in the Adverse Event eCRF. All on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Merck/Pfizer.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term "sudden death" should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

During survival follow-up, deaths should be entered in the Adverse Event eCRF.

Adverse Events After the Reporting Period

After the end of the adverse event reporting period, all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF. In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior study drug treatment, the event should be reported through use of the Adverse Event eCRF.

8.4.2 SERIOUS ADVERSE EVENT REPORTING

The sponsor-investigator must notify FDA in an IND safety report of potential serious risks as soon as possible, but in no case later than 15 calendar days after it is determined that the information qualifies for reporting. (21 CFR 312.32(c)(1)).

The sponsor-investigator must notify FDA of any unexpected fatal or life-threatening adverse reactions as soon as possible, but in no case later than 7 calendar days after the sponsor-investigator's initial receipt of the information. (21 CFR 312.32(c)(2)).

The study clinician will complete an SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to Merck/Pfizer within 24 hours of site awareness.

- Other SAEs, regardless of relationship, will be submitted to Merck/Pfizer within 24 hours of site awareness.

All SAEs will be reported using the FDA 3500A Mandatory MedWatch report form. SAE form can be found at:

http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of study drug.

All SAEs will also be submitted within 24 hours of knowledge of the event, regardless of the relationship of the event to the treatment plan regimen, to the OCRS team for determination of further reporting to the FDA and COMIRB in accordance with the protocol. Please submit to DSMC within 5 business days. To submit an SAE, email as follows:

To:	CPDM.IIT@cuanschutz.edu Christopher.Lieu@cuanschutz.edu DSMC@cuanschutz.edu
Subject:	17-0466 SAE Report Form
Body of Email:	List the following information as assessed by the Investigator - • whether the event is expected or unexpected • causality of events in relation to all study medications • whether the SAE is related to disease progression • CTCAE grade

FAX SAE to Merck Global Safety using the Merck cover sheet within 24 hours of knowledge of the event.

Fax #: 1 (215) 993-1220

FAX SAE to Pfizer Drug Safety Unit using the Pfizer cover sheet kit within 24 hours of knowledge of the event.

Fax #: 1-866-997-8322

All SAEs will be followed until satisfactory resolution or until the site PI deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by Merck/Pfizer and should be provided as soon as possible.

The Sponsor-Investigator will be responsible for notifying FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor-investigator's initial receipt of the information.

8.4.3 UNANTICIPATED PROBLEM REPORTING

The study will follow COMIRB's guidance for UAP reporting and the DSMC's requirements as discussed herein. Events that meet the definition of an unanticipated problem must be reported to the COMIRB within 5 days of their occurrence.

8.4.4 EVENTS OF SPECIAL INTEREST

Adverse events of special interest (AESI) must meet the definition of an adverse event to be considered an AESI. Adverse events of special interest for Pembrolizumab are defined as Grade 2 or higher hypothyroidism, hyperthyroidism, pneumonitis, infusion reactions, colitis, severe skin reactions, adrenal insufficiency, myocarditis, hepatitis, hypophysitis, thyroiditis, uveitis, myositis, pancreatitis, T1DM, nephritis, Guillan-Barre syndrome, myasthenic syndrome, encephalitis, sarcoidosis, myelitis, vasculitis, sclerosing cholangitis, fatal Stevens-Johnson Syndrome, and Toxic Epidermal Necrosis.

AESIs for binimetinib are defined as Grade 2 or higher ocular events (retinal, vascular eye or other events), dermatologic events (rash and other skin events), edema, myopathy/rhabdomyolysis including CK elevation, cardiac events including LVEF decreases, hypertension, GI events, pneumonitis, hemorrhage, and thrombotic and embolic events.

Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported as applicable.

Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Serious Adverse Event/Adverse Event of Special Interest eCRF provided to investigators and submit to the respective drug manufacturer, Merck or Pfizer or their designee. AESIs related to pembrolizumab should be sent to Merck. AESIs for binimetinib should not be sent to Pfizer unless the AESI meets the criteria for a serious adverse event. All Serious Adverse Events/Adverse Events of Special Interest should be reported for each cycle (during the following cycle) either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

8.4.5 REPORTING OF PREGNANCY

Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 180 days after the last dose of study drug. A pregnancy report should be completed and submitted to Merck/Pfizer or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue

until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 180 days after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to Merck/Pfizer or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

Abortions

Any abortion should be classified as a serious adverse event (as Merck/Pfizer considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Merck/Pfizer immediately (i.e., no more than 24 hours after learning of the event).

Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to Merck/Pfizer immediately (i.e., no more than 24 hours after learning of the event).

8.5 Study Halting Rules

During the safety run-in if any of the following situations occur, then further enrollment and study treatments will be halted immediately until a thorough investigation and safety analysis has been conducted.

- If any patient experiences death due to an adverse event that is assessed as related to study treatment (by investigator and/or Merck/Pfizer, it will lead to temporary hold of study pending review by study team
- Approximately 3 or more of the 10 patients in the safety run-in meet individual stopping rules defined below. If any of the following situations of potentially overlapping toxicities occur and are assessed as related to study treatment by the investigator, the study treatment will be halted immediately for the individual patient, and a thorough investigation and safety analysis will be conducted:
  - Grade 3 hypertension for > 14 days.
  - Grade 3 hemorrhage (symptoms and transfusion of packed RBCs indicated)
  - Grade 3 pneumonitis (symptomatic, interfering with activities of daily living;

oxygen indicated)
- Recurrent Grade 2 pneumonitis
- Grade 3 left ventricular dysfunction (symptomatic congestive heart failure responsive to intervention)

- Grade 3 colitis or diarrhea not responsive to anti-diarrheal agents (greater than 7 stools per day over baseline; incontinence; IV fluids for 24 hours; hospitalization)
- ALT or AST greater than 5 xULN in combination with total bilirubin greater than 2 xULN.

9 STUDY OVERSIGHT AND CLINICAL MONITORING

Study Oversight

The sponsor investigator will be responsible for monitoring the trial per the trial monitoring plan, in addition to overseeing the safety and efficacy of the trial including any specimens collected, executing the data and safety monitoring (DSM) plan, and complying with all reporting requirements to local and federal authorities. This oversight will be accomplished through additional oversight from the Data and Safety Monitoring Committee (DSMC) at the University of Colorado Cancer Center (CU Cancer Center). The DSMC is responsible for ensuring data quality and study participant safety for all clinical studies at the CU Cancer Center, which is the coordinating institution of this trial. A summary of the DSMC's activities is as follows:

- Conduct of internal audits
- Ongoing review of all unanticipated adverse device effects, serious adverse events (SAEs), and unanticipated problems (UAPs)
- May submit recommendations for corrective actions to the CU Cancer Center's Executive Committee

Per the CU Cancer Center Institutional DSM Plan, SAEs and UAPs are reported to the DSMC, IRB and the sponsor investigator per protocol. All SAEs and UAPs including unanticipated adverse device effects are to be reported to the DSMC within 7 (for fatal or life-threatening events) or 15 (non-life-threatening events) calendar days of the sponsor investigator receiving notification of the occurrence.

Each subject's treatment outcomes will be discussed by the site PI and appropriate staff at regularly scheduled meetings. Data regarding number of subjects, adverse device effects, treatment modifications and treatment responses will be discussed and documented in the meeting's minutes.

The sponsor investigator will provide a DSM progress report to the CU Cancer Center DSMC on a recurring basis (either every six or twelve months based on DSMC vote). The DSM report will include a protocol summary, current enrollment numbers, summary of toxicity data to include, SAEs, UAPs and AEs, any dose modifications, all protocol deviations, and protocol amendments. The DSM progress report submitted to the DSMC will also include, if applicable, the results of any efficacy data analysis conducted. Results and recommendations from the review of this progress report by the DSMC will then be provided to the sponsor

investigator in a DSMC review letter. The sponsor investigator is then responsible for ensuring this letter is submitted to the site's IRB of record at the time of IRB continuing review.

Quality Control and Quality Assurance

1. Clinical site monitoring will be conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/ amendment(s), with GCP, and with applicable regulatory requirement(s).

   Monitoring for this study will be performed by CU Cancer Center Clinical Monitor in accordance with the clinical monitoring plan (CMP), incorporated herein by reference. The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of the monitoring reports.

2. Independent audits will be conducted by the CU Cancer Center DSMC to ensure monitoring practices are performed consistently across all participating sites, if applicable, and that monitors are following the CMP. In addition, audits may be conducted at any time by appropriate regulatory authorities and/or the IRB.

10 STATISTICAL CONSIDERATIONS

10.1 Statistical and Analytical Plans

The primary analysis will be based on patient data collected through study discontinuation or at the end of study. All analyses will be conducted using the safety-evaluable population, defined as all patients who receive any amount of study drug.

No formal hypothesis testing is planned. The safety, tolerability, and clinical activity of binimetinib with pembrolizumab and bevacizumab will be described and summarized.

Data will be described and summarized as warranted by sample size. That is, listings may be used in lieu of tables in the event of small sample size.

Descriptive statistics will be used to summarize the safety and clinical activity of treatment regimens. Continuous variables will be summarized using mean, standard deviation, median, and range; categorical variables will be summarized using count and percentage.

10.2 Statistical Hypotheses

- Primary Endpoint(s):
  Response rate based on CT imaging, defined as complete or partial response according to RECIST v1.1.

- Secondary Endpoint(s):
  1. Progression free survival, defined as the time from enrollment to the first observation of progressive disease or death from any cause.
  2. Overall survival, defined as the time from enrollment to death from any cause.
  3. Grade 1, 2, 3, 4 toxicities associated with pembrolizumab, bevacizumab, and binimetinib as defined by CTCAE v4.

10.3 Analysis Datasets

Not applicable.

10.4 Description of Statistical Methods

10.4.1 General Approach

This study will include up to 75 participants (to reach a total of 50 evaluable participants), who have advanced or metastatic colorectal adenocarcinoma refractory to standard therapy. The first 10 patients will be included in the safety lead-in.

The expected ORR for colorectal adenocarcinoma in the third line setting is less than 5%. We will thus use the null hypothesis that the ORR is 5%. The combination of pembrolizumab, trametinib, and bevacizumab will be considered worthy of further study if the observed ORR is promising (ie significantly greater than 5%).

The sample size was calculated based on using an upper 1-sided exact binomial test, controlling the type 1 error rate at 0.025 and using a null proportion of 0.05. Using 38 subjects would provide exactly 80.0% power to detect an alternative value of 0.20. A sample size of 40 subjects was decided upon in order to have slightly better power (83.9%). With 40 subjects, an upper one-sided exact binomial test will have at least 80% power to detect true ORR values of at least 0.20, when the null ORR is 0.05 and the type 1 error rate is controlled at 0.025. The table below displays the power available to detect a range of ORRs.

Alternative ORR	Power
0.20	0.839
0.25	0.957
0.30	0.991
0.35	0.999
0.40	> 0.999

10.4.2 Analysis of the Primary Efficacy Endpoint(s)

The primary efficacy endpoint of objective response rate (ORR) will be tested statistically using an upper 1-sided exact binomial test. The null ORR will be set to 0.05 and the type 1 error rate will be controlled at 0.025. The upper critical value is 6 (i.e. if 6 or more of the 40 subjects respond, the null hypothesis, H_0: $p = 0.05$, will be rejected).

Besides the results from the formal statistical test, the primary efficacy ORR endpoint will be summarized using the proportion and 95% exact binomial confidence interval. Individual subject-level results will also be reported using a listing.

10.4.3 Analyses of the Secondary Endpoints(s)

The secondary endpoints of progression-free survival (PFS) and overall survival (OS) will be measured from the start of protocol therapy until the first evidence of any disease progression or death, respectively. The Kaplan-Meier product-limit method will be used to summarize the time-to-event results. Point estimates (e.g. the median time-to-event and proportion at 6 months) and 95% confidence intervals will be calculated. Results will additionally be displayed in figures using Kaplan-Meier survival curves.

10.4.4 Safety Analyses

Safety will be assessed through summaries of adverse events. Adverse events will include exposure to the study treatment, changes in vital signs, and changes in laboratory values. Additionally, separate summaries will be created which will include only serious adverse events (SAEs). When subjects experience multiple events of varying severity, the highest grade will be used in the subject-level summaries.

Toxicity will be summarized and tabulated based on organ and severity.

10.4.5 Adherence and Retention Analyses

Subject retention and compliance with the protocol will be reported using:

1) A CONSORT diagram illustrating the subject flow through the trial
2) Tables summarizing retention and compliance
3) Listings showing retention and compliance results at the individual subject level

10.4.6 Baseline Descriptive Statistics

Subject characteristics at baseline will be summarized using descriptive statistics. Continuous variables will be summarized by reporting the mean, standard deviation and quartiles (minimum, Q1, median, Q3, and maximum). Categorical variables will be summarized using counts and percentages.

10.4.7 Planned Interim Analyses

Due to the small sample size, no planned interim analysis will be performed

10.4.8 Additional Sub-Group Analyses

No additional sub-group analyses are planned.

10.4.9 Multiple Comparison/Multiplicity

There will be no adjustments for multiple testing.

10.4.10 Tabulation of Individual Response Data

Tabulation data sets will be created which provide a tabular listing of subject data for all domains (e.g. demographics, outcomes, adverse events, etc).

10.4.11 Exploratory Analyses

Potential biomarkers include PD-L1 levels, phophoryalted ERK expression, mismatch repair status, among others. Exploratory analyses will be performed in an effort to investigate if there is an association between these potential biomarkers and 1) response to treatment and 2) adverse events.

10.5 Sample Size

This study will include up to 75 participants (to reach a total of 50 evaluable participants) with advanced or metastatic colorectal adenocarcinoma refractory to at least two lines of prior standard therapy. The first 10 participants will be included in the safety lead-in.

10.6 Measures to Minimize Bias

Subjects will be randomized to the 2 Cohorts (Cohort A vs Cohort B) using a blocked randomization. The randomization list will be generated by the study biostatistician and provided only to the study personnel who will be responsible for assigning the each subject to a cohort of the study.

11 QUALITY ASSURANCE AND QUALITY CONTROL

Quality Control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/ resolution.

Following written SOPs, the study monitor will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements [e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)].

The investigational site will provide direct access to all trial-related sites, source data/ documents, and reports for the purpose of monitoring and auditing by the DSMC audit team, and inspection by local and regulatory authorities.

12 ETHICS/PROTECTION OF HUMAN SUBJECTS

12.1 Ethical Standard

The PI will ensure that this study is conducted in full conformity with regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56. ICH E6 may also be followed to the extent it has been adopted by and is in accordance with FDA regulations.

12.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant (subject) materials will be submitted to the Colorado Multiple Institutional Review Board (COMIRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by COMIRB before the changes are implemented to the study. All changes to the consent form will COMIRB approved; a determination will be made regarding whether previously consented subjects need to be re-consented.

12.3 Informed Consent Process

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to Merck/Pfizer for review.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

12.3.1 Consent/Assent and Other Informational Documents Provided to Subjects

Consent forms describing in detail the study agent, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/ administering study product.

12.3.2 Consent Procedures and Documentation

Informed consent process will be initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the subjects and their families.

Consent forms will be IRB-approved and the subject will be asked to read and review the document. The investigator will explain the research study to the subject and answer any questions that may arise. All subjects will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research subjects. Subjects will have the opportunity to carefully review the written consent form and ask questions prior to signing. The subjects will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subject will sign the informed consent document prior to any procedures being done specifically for the study.

The subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The study allows the inclusion of non-English speaking and non-reading subjects. Witnesses to these consent processes will be individuals not associated with the trial and will not have a conflict of interest.

12.4 Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating PI, their staff, and Merck/Pfizer and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor-investigator.

The study monitor, other authorized representatives of the sponsor-investigator, representatives of the IRB or pharmaceutical company supplying study product may inspect

all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

The study subject's contact information will be securely stored for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study subject research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the University of Colorado Cancer Center. This will not include the subject's contact or identifying information. Rather, individual subjects and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site and by the University of Colorado Cancer Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the University of Colorado Cancer Center

12.4.1 Research Use of Stored Human Samples, Specimen, and Data

- **Intended Use:** Samples and data collected under this protocol may be used to assess Tumor Infiltrating Lymphocytes (TILs) to study patterns of resistance to immunotherapy. No genetic testing will be performed.
- **Storage:** Access to stored samples will be limited to research personnel only. Samples and data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.
- **Disposition at completion of the study**: Consent will be obtained from all patients for tumor tissue banking. Patients can withdraw consent for tumor banking at any time. All stored samples will be sent to the University of Colorado Biorepository. Study subjects who request destruction of samples will be notified of compliance with such
- request and all supporting details will be maintained for tracking.

12.5 Future use of Stored Specimens

Specimens collected during the study will not be banked nor used for future research.

13 DATA HANDLING AND RECORD KEEPING

13.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the PI. The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Source Documentation

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. When making changes or corrections, cross out the original entry with a

single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification, the investigators and institutions must provide Merck/Pfizer direct access to applicable source documents and reports for trial-related monitoring, Sponsor-Investigator audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research.

An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

Electronic Case Report Forms (eCRF)

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into a electronic data capture system provided by the University of Colorado.

eCRFs are to be completed through use of a Sponsor-Investigator designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. The data system includes password protection and internal quality checks, such as automatic range

checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents. All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, any hard copy of patient data received by the investigator for his or her site must be stored safely with the study records. Acknowledgement of receipt of the compact disc is required.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each subject enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the subject's official electronic study record.

Data Quality Assurance

The Sponsor-Investigator will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Site will be responsible for data entry into the EDC system.

The Sponsor-Investigator will produce an EDC Study Specification document that describes the quality checking to be performed on the data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor-Investigator and records retention for the study data will be consistent with the Sponsor-Investigator's standard procedures.

13.2 Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of an investigational marketing application and until there are no pending or contemplated marketing applications or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations, or institution policies. No records will be destroyed without the written consent of Merck/Pfizer, if applicable. It is the responsibility of the Merck/Pfizer to inform the PI when these documents no longer need to be retained.

13.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or SOP requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. These practices are consistent with ICH E6, sections:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3.
- 5.1 Quality Assurance and Quality Control, section 5.1.1.
- 5.20 Noncompliance, sections 5.20.1 and 5.20.2.

It is the responsibility of the study team to use continuous vigilance to identify and report deviations. Deviations will be reported to the DMSC and IRB according to UCCC DSM plan and institutional policy.

13.4 Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH-funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health o utcomes include any biomedical or health-related measures obtained in patients or subjects, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act (FDAAA) of 2007 requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor-investigator) register and report results of certain "applicable clinical trials".

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations, of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.

14 STUDY ADMINISTRATION

Not applicable.

15 CONFLICT OF INTEREST POLICY

Independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Any actual conflict of interest of persons who have a role

in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed.by the University of Colorado Denver's (UCD) Office of Regulatory Compliance

Conflict of Interest and Commitment Management (COIC) program. Persons with a perceived conflict of interest will have such conflicts managed in a way that is appropriate to their participation in the trial. Conflict of Interest management plans are project-specific and are reviewed at least annually. UCD has integrated the institutional conflict of interest management program with its existing program.

16 LITERATURE REFERENCES

1. National Cancer Institute - Surveillance, E., and End Results Program, *Cancer Stat Facts: Colon and Rectum Cancer.*
2. Martinelli, E., et al., *Cancer resistance to therapies against the EGFR-RAS-RAF pathway: The role of MEK.* Cancer Treat Rev, 2017. **53**: p. 61-69.
3. Andreyev, H.J., et al., *Kirsten ras mutations in patients with colorectal cancer: the 'RASCAL II' study.* Br J Cancer, 2001. **85**(5): p. 692-6.
4. Phipps, A.I., et al., *KRAS-mutation status in relation to colorectal cancer survival: the joint impact of correlated tumour markers.* Br J Cancer, 2013. **108**(8): p. 1757-64.
5. Hanahan, D. and R.A. Weinberg, *Hallmarks of cancer: the next generation.* Cell, 2011. **144**(5): p. 646-74.
6. Kakavand, H., et al., *PD-L1 Expression and Tumor-Infiltrating Lymphocytes Define Different Subsets of MAPK Inhibitor-Treated Melanoma Patients.* Clin Cancer Res, 2015. **21**(14): p. 3140-8.
7. Loi, S., et al., *RAS/MAPK Activation Is Associated with Reduced Tumor-Infiltrating Lymphocytes in Triple-Negative Breast Cancer: Therapeutic Cooperation Between MEK and PD-1/PD-L1 Immune Checkpoint Inhibitors.* Clin Cancer Res, 2016. **22**(6): p. 1499-509.
8. Liu, L., et al., *The BRAF and MEK Inhibitors Dabrafenib and Trametinib: Effects on Immune Function and in Combination with Immunomodulatory Antibodies Targeting PD-1, PD-L1, and CTLA-4.* Clin Cancer Res, 2015. **21**(7): p. 1639-51.
9. Blank, C., et al., *Blockade of PD-L1 (B7-H1) augments human tumor-specific T cell responses in vitro.* Int J Cancer, 2006. **119**(2): p. 317-27.
10. Iwai, Y., et al., *Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade.* Proc Natl Acad Sci U S A, 2002. **99**(19): p. 12293-7.
11. McDermott, D.F. and M.B. Atkins, *PD-1 as a potential target in cancer therapy.* Cancer Med, 2013. **2**(5): p. 662-73.
12. Nishimura, H., et al., *Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor.* Immunity, 1999. **11**(2): p. 141-51.
13. Nomi, T., et al., *Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer.* Clin Cancer Res, 2007. **13**(7): p. 2151-7.
14. Okudaira, K., et al., *Blockade of B7-H1 or B7-DC induces an anti-tumor effect in a mouse pancreatic cancer model.* Int J Oncol, 2009. **35**(4): p. 741-9.
15. Merck Sharp & Dohme, C., *Pembrolizumab - Investigator's Brochure.* 2021.
16. Gabrilovich, D.I., et al., *Production of vascular endothelial growth factor by human tumors inhibits the functional maturation of dendritic cells.* Nat Med, 1996. **2**(10): p. 1096-103.
17. Manzoni, M., et al., *Immunological effects of bevacizumab-based treatment in metastatic colorectal cancer.* Oncology, 2010. **79**(3-4): p. 187-96.
18. Ohm, J.E. and D.P. Carbone, *VEGF as a mediator of tumor-associated immunodeficiency.* Immunol Res, 2001. **23**(2-3): p. 263-72.
19. Ebert, P.J., et al., *MAP Kinase Inhibition Promotes T Cell and Anti-tumor Activity in Combination with PD-L1 Checkpoint Blockade.* Immunity, 2016. **44**(3): p. 609-21.

20. Ribas, A., et al., *Pembrolizumab in combination with dabrafenib and trametinib for BRAF-mutant advanced melanoma: Phase 1 KEYNOTE-022 study.* J Clin Oncol, 2016. **34**(suppl; abstr 3014).
21. Elamin, Y.Y., et al., *Immune effects of bevacizumab: killing two birds with one stone.* Cancer Microenviron, 2015. **8**(1): p. 15-21.
22. Osada, T., et al., *The effect of anti-VEGF therapy on immature myeloid cell and dendritic cells in cancer patients.* Cancer Immunol Immunother, 2008. **57**(8): p. 1115-24.
23. Terme, M., E. Tartour, and J. Taieb, *VEGFA/VEGFR2-targeted therapies prevent the VEGFA-induced proliferation of regulatory T cells in cancer.* Oncoimmunology, 2013. **2**(8): p. e25156.

17 APPENDICES

Appendix 1
GUIDELINES FOR TOXICITY MANAGEMENT

Binimetinib may continue at the discretion of the investigator per medical judgment if subjects are receiving benefit. Written communication or documentation should be present denoting that all research personnel are aware of the decision.

Table 3. Guidelines for the Management of Pembrolizumab- and Binimetinib-Associated Hepatotoxicity

LFT Abnormalities	Management
AST/ALT>ULN to≤3×ULN with total bilirubin<2×ULN *(Grade 1)*	• *Continue pembrolizumab, binimetinib, and bevacizumab.* • *Continue with the standard monitoring plan (i.e., LFTs q4w before dosing).*
AST/ALT >3 ×baseline values to <5 ×ULN with total bilirubin <2 ×ULN (Grade 2)	• *Hold binimetinib until LFT abnormalities decrease to grade 1.* • *Monitor LFTs at least weekly.* • *Consider referral to a hepatologist and liver biopsy.* • *For suspected immune related events of > 5 days duration* - *Consider withholding* pembrolizumab [c] - *Consider administering 0.5-1 mg/kg/day oral prednisone or equivalent followed by ≥ 1-month taper* - *Restart* pembrolizumab *if event resolves to Grade 1 or better within 12 weeks* [a, b] - *Permanently discontinue* pembrolizumab *and binimetinib if event does not resolve to Grade 1 or better within 12 weeks* [a, b, c]
AST/ALT >5 ×baseline values to <10 ×ULN with total bilirubin <2 ×ULN (Grade 3)	• *Hold binimetinib until LFT abnormalities decrease to grade 1.* • *Monitor LFTs at least weekly.* • *Consider referral to a hepatologist and liver biopsy.* • *For suspected immune-related events:* - *Withhold pembrolizumab* - *Consider administering 1-2 mg/kg/day oral prednisone or equivalent followed by ≥ 1 month taper* - *If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to* - *Grade 1 or better, taper corticosteroids over ≥1* - *month.* - *Permanently discontinue pembrolizumab and binimetinib if event does not resolve to Grade 1 or better within 12 weeks* [a, b, c]

Table 4. Guidelines for the Management of Pembrolizumab- and Binimetinib-Associated Hepatotoxicity (cont.)

AST/ALT > 3 × ULN with bilirubin > 2 × ULN	• *Bevacizumab may continue at the discretion of the investigator per medical judgment.* • *Withhold pembrolizumab and binimetinib.* • *Consult hepatologist and consider liver biopsy.* • *Consider administering 1-2 mg/kg/day oral prednisone or equivalent followed by ≥ 1 month taper (for possible autoimmune hepatitis).* • *If LFTs do not decrease within 48 hr after initiation of systemic steroids, consider adding an immunosuppressive agent (e.g., mycophenolate or TNF-antagonist).* • *Monitor LFTs every 48-72 hours until decreasing and then follow weekly.* • *Restart pembrolizumab at fixed dose and binimetinib at 1 dose reduction after discussion with medical monitor if AST/ALT > 3 x ULN with bilirubin > 2 x ULN and steroid dose < 10 mg oral prednisone equivalent per day.*[a,b,c] • *Permanently discontinue pembrolizumab and binimetinib for life-threatening hepatic events, and contact the Medical Monitor.*
AST/ALT > 10 × ULN	• *Bevacizumab may continue at the discretion of the investigator per medical judgment.* • *Permanently discontinue pembrolizumab and binimetinib.* [c] • *Consult hepatologist and consider liver biopsy.* • *Consider administering 1–2 mg/kg/day oral prednisone or equivalent (for possible autoimmune hepatitis). If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.* • *If LFTs do not decrease within 48 hours after initiation of systemic steroids, addition of an alternative immunosuppressive agent (e.g., mycophenolate or TNF-α antagonist) or dose escalation of corticosteroids may be considered.* • *Monitor LFTs every 48–72 hours until decreasing and then follow weekly.*

IV = intravenous; LFT = liver function test; q4w = every 4 weeks; TNF = tumor necrosis factor; ULN = upper limit of normal.

[a] *If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before pembrolizumab can be resumed.*

[b] *Pembrolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The investigator and the Medical Monitor must agree upon the acceptable length of the extended period of time.*

[c] *Resumption of pembrolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with pembrolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.*

Pulmonary Events

Mild-to-moderate events of pneumonitis have been reported with pembrolizumab and binimetinib. All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia/infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Patients who experience pulmonary events should be managed per the guidelines provided in Table 5.

For events concerning for pneumonitis, consider comprehensive infectious evaluation including viral etiologies.

Table 5. Guidelines for the Management of Pembrolizumab- and Binimetinib-Associated Pulmonary Events

Pulmonary Events	*Guidance*
General Guidance	• *Mild-to-moderate events of pneumonitis have been reported with pembrolizumab and binimetinib. All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia/infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension.* • *For events concerning for pneumonitis, consider comprehensive infectious evaluation including viral etiologies.*
Pneumonitis, Grade 1 (asymptomatic)	• *Continue pembrolizumab, bevacizumab, and binimetinib.* • *Re-evaluate on serial imaging.* • *Consider patient referral to pulmonary specialist.* • *For recurrent pneumonitis, treat as Grade 3 or 4 event.*
Pneumonitis, Grade 2	• *Bevacizumab may continue at the discretion of the investigator per medical judgment.* • *Withhold pembrolizumab and binimetinib.* • *Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL.* • *Add prophylactic antibiotics for opportunistic infections* • *If bronchoscopy is consistent with immune-related etiology, initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent.* • *Resume pembrolizumab and binimetinib if event resolves to Grade 1 or better within 12 weeks.* [a, b] • *Permanently discontinue pembrolizumab and binimetinib and contact Medical Monitor if event does not resolve to Grade 1 or better within 12 weeks.* [a, b, c] • *For recurrent events, treat as a Grade 3 or 4 event.*

Pneumonitis, Grade 3/4	• *Bevacizumab may continue at the discretion of the investigator per medical judgment.* • *Permanently discontinue* pembrolizumab *and binimetinib.*[c] • *Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL.* • *Add prophylactic antibiotics for opportunistic infections* • *If bronchoscopy is consistent with immune-related etiology, initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent.* • *If pulmonary event does not improve within 48 hr or worsens, consider adding an immunosuppressive agent (e.g., infliximab, cyclophosphamide, IV Ig, or mycophenolate mofetil).* • *If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.*

IV = intravenous; BAL = bronchoscopic alveolar lavage.

[a] *If corticosteroids have been initiated (initial dose of 1 to 2 mg/kg), they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before pembrolizumab can be resumed.*

[b] *Pembrolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.*

[c] *Resumption of pembrolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with pembrolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.*

Dermatologic Toxicity

Treatment-emergent rash has been associated with pembrolizumab and binimetinib. The majority of the cases of rash were mild in severity and self-limited, with or without pruritus.

A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated.

Dermatologic toxicity and rash should be managed according to the guidelines in Table 6.

Table 6. Guidelines for the Management of Pembrolizumab- and Binimetinib-Associated Rash

Dermatologic Toxicity	Management
General guidance	• *A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated.*
Dermatologic event, Grade 1-2	• *Continue pembrolizumab, bevacizumab and binimetinib.* • *Initiate supportive care (e.g., antihistamines, topical corticosteroids). If event does not improve consider treatment with higher-potency topical corticosteroids.* • *For Grade 2 rash, consider referral to dermatologist.* ***Acneiform rash:*** • *Consider topical corticosteroids (e.g., hydrocortisone 2.5%, alclometasone) and oral antibiotics (minocycline, doxycycline, or antibiotics covering skin flora) as clinically indicated.*

Dermatologic event, Grade 3	• *Bevacizumab may continue at the discretion of the investigator per medical judgment.* • *Withhold pembrolizumab and binimetinib.* • *Refer patient to dermatologist. A biopsy should be performed if appropriate.* • *Consider initiating treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1-2 mg/kg/day if event does not improve within 48-72 hours.* • *If event resolves to Grade 2 or better within 12 weeks, resume pembrolizumab at fixed dose. If not, permanently discontinue pembrolizumab and binimetinib.* [a,b] • *Permanently discontinue pembrolizumab and binimetinib and contact Medical Monitor if event does not resolve to Grade 1 or better within 12 weeks.* [a, b, c] • *If event resolves to Grade 2 or better within 28 days, resume binimetinib with dose reduced by one level. If not, permanently discontinue binimetinib.* ***Acneiform rash:*** • *Consider continuation of topical corticosteroids (e.g., 2.5% alclometasone) and oral antibiotics (e.g., minocycline, doxycycline or antibiotics covering skin flora) when restarting binimetinib.*
Dermatologic event, Grade 4	• *Permanently discontinue pembrolizumab and binimetinib, and contact Medical Monitor.* [c]

BID = twice daily; BSA = body surface area; PRN = as needed.

a If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before pembrolizumab can be resumed.

b Pembrolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

c Resumption of pembrolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with pembrolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Rhabdomyolysis and CPK Elevations

Rhabdomyolysis and CPK elevation have been seen with binimetinib (see binimetinib Investigator's Brochure). Permanent discontinuation of binimetinib treatment should be considered if rhabdomyolysis or symptomatic CPK elevations are attributed to binimetinib and do not improve after temporary interruption. Guidelines for the management of CPK elevations *and rhabdomyolysis* are provided in Table 7.

In case of CPK elevation or rhabdomyolysis treatment with bevacizumab may continue at the discretion of the investigator per medical judgment.

Table 7. Guidelines for the Management of Grade 3 or Higher Elevations in CPK *and Rhabdomyolysis*

Rhabdomyolysis or CPK elevation	Management
General guidance	• *Rule out cardiac cause (check ECG, serum cardiac troponin, and CPK-isoforms M and B fraction) and rule out rhabdomyolysis (clinical examination; serum creatinine, potassium, calcium, phosphorus, uric acid, and albumin; and urine myoglobin).* • *Assess patient for any history of strenuous physical activity, blunt trauma, or recent IM injections.*
Grade ≤ 3 CPK elevations *that are asymptomatic and deemed not clinically significant*	• Bevacizumab may continue at the discretion of the investigator per medical judgment. • *Binimetinib and* ***pembrolizumab*** *dosing does not need to be modified or interrupted to manage asymptomatic Grade ≤ 3 CPK elevations.* • *Recheck CPK at least once a week.*
For Grade 4 CPK elevations that are asymptomatic and deemed not clinically significant	• *Bevacizumab may continue at the discretion of the investigator per medical judgment.* • *Interrupt binimetinib and* ***pembrolizumab*** *treatment.* • *If improved to Grade ≤ 3 within 4 weeks, restart binimetinib at a dose reduced by 30 mg, if clinically indicated.* • *If CPK elevations do not improve to Grade ≤3 within 4 weeks following dose interruption, permanently discontinue binimetinib treatment.* • *Resumption of pembrolizumab may be considered in patients who are deriving benefit.*

IM = intramuscular.

Potential Eye Toxicity

An ophthalmologist should evaluate visual complaints.

Uveitis or episcleritis and other immune-mediated ocular disease may be associated with pembrolizumab and may be treated with topical corticosteroid eye drops. Pembrolizumab should be permanently discontinued for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy.

Pembrolizumab and/or binimetinib -associated ocular toxicity should be managed according to the guidelines in Table 8.

Serous retinopathy events have been associated with binimetinib with most events in clinical trials resolved or improved to asymptomatic grade 1 following dose interruption or reduction. If serous retinopathy is diagnosed, treatment should be withheld until visual symptoms improve to Grade ≤1. Serous retinopathy can be managed with treatment interruption, dose reduction or with treatment discontinuation.

Retinal vein occlusion (RVO) has been reported in patients treated with MEK inhibitors other than binimetinib.

Table 8. Guidelines for *the Management of* Pembrolizumab- *and Binimetinib*-Associated Ocular Toxicity

Ocular Toxicity	Management
General guidance	• *An ophthalmologist should evaluate visual complaints.* • *Uveitis or episcleritis and other immune–mediated ocular disease may be associated with pembrolizumab and may be treated with topical corticosteroid eye drops. Pembrolizumab should be permanently discontinued for immune-related ocular event that is unresponsive to local immunosuppressive therapy.* • *Serous retinopathy is associated with binimetinib. In clinical trials, most events were Grade 1 (asymptomatic) or 2 (symptomatic). Most events in clinical trials resolved or improved to asymptomatic grade 1 following dose interruption or reduction. If serous retinopathy is diagnosed, binimetinib should be withheld until visual symptoms improve to Grade ≤1. Serous retinopathy can be managed with treatment interruption, dose reduction or with treatment discontinuation.* • *RVO has been reported in patients treated with MEK inhibitors other than binimetinib.*
Serous retinopathy *Severity grade assessment based on NCI CTCAE v4 "Eye Disorders – Other" scale* [a-d]	***Serous retinopathy, Grade 1*** [a] ***or 2*** [b] ***(tolerable):*** • *Continue binimetinib, bevacizumab, and pembrolizumab without dose change.* • *Continue ophthalmology follow-up as clinically indicated.* ***Serous retinopathy, Grade 2*** [b] ***(intolerable) or 3/4*** [c/d]***:*** • *Interrupt binimetinib until Grade ≤1.* • *Continue pembrolizumab and bevacizumab as clinically indicated.* • *Consult ophthalmology and undergo complete ophthalmologic examination, which includes visual acuity testing, intra-ocular pressure measurements, slit lamp ophthalmoscopy, indirect ophthalmoscopy, visual field, and OCT. Consider a fluorescein angiogram and/or indocyanine green angiogram, if clinically indicated.* • *Binimetinib should be dose reduced by 1 dose level when restarting.* • *Consider permanent discontinuation of binimetinib if serous retinopathy recurs despite 2 dose level reductions*
Potential immune-related ocular toxicity (e.g., uveitis, iritis, episcleritis, or retinitis)	• *Follow guidelines provided in the pembrolizumab Investigator's Brochure.* • *Continue binimetinib and bevacizumab as clinically indicated.*

Retinal vein occlusion (any grade)	• *If RVO (any grade) is diagnosed, binimetinib dosing should be permanently discontinued and RVO treated per institutional guidelines.* • *Continue pembrolizumab.* • *B*evacizumab may continue at the discretion of the investigator per medical judgment.

ADL = activities of daily living; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; RVO = retinal vein occlusion; OCT = optical coherence tomography.

[a] *Grade 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.*

[b] *Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL.*

[c] *Grade 3: Severe or medically significant but not immediately sight threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL.*

[d] *Grade 4: Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye.*

Gastrointestinal Events: Diarrhea

Diarrhea can frequently be managed with anti-diarrheal agents but can also progress to clinically significant dehydration and/or electrolyte imbalances with effects on other organs, possibly resulting in renal, hepatic, and/or cardiac failure. Patients should be instructed to promptly contact the investigators if they develop diarrhea. Investigators should treat diarrhea and intervene promptly for patients who appear to be at increased risk of developing significant dehydration, electrolyte imbalances, and/or multi-organ failure. Patients should receive maximum supportive care per institutional guidelines.

In case of diarrhea, treatment with bevacizumab may continue at the discretion of the investigator per medical judgment.

Colitis

Immune-related colitis has been associated with the administration of pembrolizumab. For events of significant duration or severity or associated with signs of systemic inflammation or acute phase reactants, check for immune-related colitis .
In case of colitis, treatment with bevacizumab may continue at the discretion of the investigator per medical judgment.

Refer to Table 9 for guidelines for the management of colitis.

Gastrointestinal Obstruction

Guidelines for the management of gastrointestinal perforation and bowel obstruction are provided in Table 9.

Table 9. Guidelines for *the* Management of Gastrointestinal Toxicity

Gastrointestinal	*Guidance*
Gastrointestinal events: general guidance	• *All events of diarrhea or colitis should be thoroughly evaluated for more common etiologies other than drug-induced effects.* • *For events of significant duration or severity or associated with signs of systemic inflammation or acute phase reactants, check for immune-related colitis.* • *Administer anti-diarrheal agents and other maximal supportive care per institutional guidelines such as: at the first report of watery diarrhea or loose stool, initiate maximal anti-diarrheal supportive care (Lomotil and loperamide).* • *Suggested regimen:* o *Loperamide: Initiate dose with 4 mg, then 4 mg every 6 hours around the clock, alternating with Lomotil.* o *Lomotil (diphenoxylate and atropine): 2 tablets (diphenoxylate 5 mg, atropine 0.05 mg) every 6 hours around the clock* o *Continue Lomotil and loperamide until no loose stools for 24 hours.* o *If Grade ≤2 diarrhea persists after 48 hours total treatment with Lomotil and loperamide, consider second-line agents (e.g., octreotide, budesonide, tincture of opium).* • *Oral supplementation:* o *Initiate oral supplementation of potassium and/or magnesium if serum levels are <LLN.* o *Consider oral rehydration therapy (e.g., Pedialyte®) for Grade ≥1 diarrhea or vomiting.* • *Dietary modifications:* o *Stop all lactose-containing products and eat small meals.* o *The BRAT (banana, rice, apples, toast) diet, without fiber (other vegetables and fruits), may be helpful.* • *Encourage adequate hydration with salt-containing liquids, such as broth or Gatorade.*
Diarrhea, Grade 1 or Grade 2 (tolerable)	• *Continue pembrolizumab, bevacizumab, and binimetinib.* • *Initiate supportive care and monitor patient closely.* • *Investigate etiology, referring patient to GI specialist for evaluation of possible colitis if appropriate.*

Diarrhea, Grade 2 (intolerable) or Grade 3	• *Bevacizumab may continue at the discretion of the investigator per medical judgment.* • *Withhold pembrolizumab and binimetinib.* • *Initiate supportive care and monitor patient closely.* • *Discontinue medications that may exacerbate colitis (e.g., NSAIDS) while investigating etiology.* • *Investigate etiology, referring patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate.* • *If event resolves to Grade 1 or better within 12 weeks, resume pembrolizumab at fixed dose. If not, permanently discontinue pembrolizumab and binimetinib.*[a-c] • *If event resolves to Grade 1 or better within 28 days, resume binimetinib with dose reduced by one level. If not, permanently discontinue binimetinib.*
Diarrhea, Grade 4	• *Bevacizumab may continue at the discretion of the investigator per medical judgment.* • *Permanently discontinue pembrolizumab and binimetinib, and contact Medical Monitor.*[c] • *Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion* • *Initiate supportive care and monitor patient closely.* • *Discontinue medications that may exacerbate colitis (e.g., NSAIDS) while investigating etiology.* • *Rule out bowel perforation.* • *Investigate etiology, referring patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate.*
Colitis, Grade 1	• *Continue pembrolizumab, bevacizumab and binimetinib.* • *Initiate supportive care and monitor patient closely.* • *Discontinue medications that may exacerbate colitis (e.g., NSAIDS).* • *Refer patient to gastrointestinal specialist for evaluation and confirmatory biopsy if symptoms persist for > 7 days.*

Colitis, Grade 2	• *Bevacizumab may continue at the discretion of the investigator per medical judgment.* • *Withhold pembrolizumab and binimetinib.* • *Initiate supportive care and monitor patient closely.* • *Discontinue medications that may exacerbate colitis (e.g., NSAIDS).* • *Refer patient to gastrointestinal specialist for evaluation and confirmatory biopsy.* • *For recurrent events or events that persist >5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent.* • *If event resolves to Grade 1 or better within 12 weeks, resume pembrolizumab at fixed dose. If not, permanently discontinue pembrolizumab and binimetinib.* [a-c] • *If event resolves to Grade 1 or better within 28 days, resume binimetinib with dose reduced by one level. If not, permanently discontinue binimetinib.*
Colitis, Grade 3	• *Bevacizumab may continue at the discretion of the investigator per medical judgment.* • *Withhold pembrolizumab and binimetinib.* • *Initiate supportive care and monitor patient closely.* • *Discontinue medications that may exacerbate colitis (e.g., NSAIDS).* • *Refer patient to gastrointestinal specialist for evaluation and confirmatory biopsy.* • *Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.* • *If event resolves to Grade 1 or better within 12 weeks, resume pembrolizumab at fixed dose. If not, permanently discontinue pembrolizumab and binimetinib.* [a-c] • *If event resolves to Grade 1 or better within 28 days, resume binimetinib with dose reduced by one level. If not, permanently discontinue binimetinib.*

Colitis, Grade 4	• *Bevacizumab may continue at the discretion of the investigator per medical judgment.* • *Permanently discontinue pembrolizumab and binimetinib, and contact Medical Monitor.*[c] • *Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion* • *Initiate supportive care and monitor patient closely.* • *Discontinue medications that may exacerbate colitis (e.g., NSAIDS).* • *Refer patient to GI specialist for evaluation and confirmatory biopsy.* • *Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.* • *If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • *If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.*
Gastrointestinal perforation, any grade	• *Discontinue bevacizumab.* • *Binimetinib may continue without interruption and/or dose reduction at the discretion of the investigator per medical judgment.* • *Pembrolizumab may continue without interruption at the discretion of the investigator per medical judgment.*
Bowel obstruction, Grade 2	• *Hold binimetinib and bevacizumab for partial obstruction requiring medical intervention. Patient may restart upon complete resolution.* • *Pembrolizumab may continue without interruption at the discretion of the investigator per medical judgment.*
Bowel obstruction, Grade 3–4	• *Hold binimetinib and bevacizumab for complete obstruction. If surgery is necessary, patient may restart binimetinib and bevacizumab after full recovery from surgery and at investigator's discretion.* • *Pembrolizumab may continue without interruption at the discretion of the investigator per medical judgment.*

GI = gastrointestinal; IV = intravenous; LLN = lower limit of normal; NSAID = non-steroidal anti-inflammatory drug.

[a] *If corticosteroids have been initiated (initial dose of 1 to 2 mg/kg), they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before pembrolizumab can be resumed.*

[b] *Pembrolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.*

[C] *Resumption of pembrolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with pembrolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.*

Guidelines for the management of reduction in left ventricular ejection fraction are provided in Table 10.

In case of cardiac adverse events treatment with pembrolizumab may continue without interruption at the discretion of the investigator per medical judgment.

Table 10. Guidelines for the Management of Reduction in Left Ventricular Ejection Fraction

Left Ventricular Ejection Fraction (LVEF) Decrease From Baseline				
Patient	*LVEF value*	*Recommended action with binimetinib, bevacizumab and pembrolizumab*	*LVEF value following treatment break*	*Recommended binimetinib daily dose*
Asymptomatic	*≥50% (or 40% –49% and <10% absolute decrease from BL)*	*Continue pembrolizumab, bevacizumab and binimetinib at current dose*	*N/A*	*N/A*
	<40% (or 40% –49% and ≥10% absolute decrease from BL)	*Interrupt binimetinib treatment for 2 wk* *Continue pembrolizumab as clinically indicated* *Hold bevacizumab and strong consideration should be given to permanently discontinuing bevacizumab if deemed causally related.*	*<10% absolute decrease from BL*	*First occurrence: 40 mg*
				Second occurrence: 20 mg
				Third occurrence: permanent discontinuation
			<40% (or ≥10% absolute decrease from BL)	*Permanent discontinuation*

Table 10. Guidelines for the Management of Reduction in Left Ventricular Ejection Fraction (cont.)

Symptomatic	*N/A*	*Interrupt binimetinib treatment for 4 wk.* *Hold bevacizumab and strong consideration should be given to permanently discontinuing bevacizumab if deemed causally related.* *Consider withholding pembrolizumab* *Discuss with Medical Monitor regarding resumption of pembrolizumab.* *Cardiology consultation is strongly recommended.*	*Asymptomatic and <10% absolute decrease from BL*	*First occurrence: 40 mg*
				Second occurrence: 20 mg
				Third occurrence: Permanent discontinuation
			Asymptomatic and <40% (or ≥10% absolute decrease from BL)	*Permanent discontinuation*
			Symptomatic regardless of LVEF	*Permanent discontinuation*

BL = baseline; LVEF = left ventricular ejection fraction; N/A = not applicable.

Hypertension

For hypertension Grade 2 or above, start antihypertensive therapy.

Guidelines for the management of Grade 2 or higher hypertension are provided in Table 11.

Table 11. Guidelines for the Management of Hypertension

Event	*Guidance*
Hypertension Grade 2	• *Hold bevacizumab.* • *Once blood pressure <140/90 mmHg, patient may continue bevacizumab therapy.* • Binimetinib may continue without interruption and/or dose reduction at the discretion of the investigator per medical judgment. [a] • Pembrolizumab may continue without interruption at the discretion of the investigator per medical judgment. [b]
Hypertension Grade 3	• *If blood pressure is not controlled to 140/90 mmHg with medication, discontinue bevacizumab* • *If bevacizumab is discontinued, binimetinib should be held at the same time that bevacizumab is discontinued. When the event resolves to Grade ≤3, binimetinib may be re-initiated without dose reduction at the discretion of the investigator per medical judgment.* [a] • If bevacizumab is not discontinued, binimetinib may continue without interruption and/or dose reduction at the discretion of the investigator per medical judgment. [a] • Pembrolizumab may continue without interruption at the discretion of the investigator per medical judgment. [b]
Hypertension Grade 4	• *Discontinue bevacizumab.* • Binimetinib should be held at the same time that bevacizumab is permanently discontinued. When the event resolves to Grade ≤ 3, binimetinib may be re-initiated without dose reduction at the discretion of the investigator per medical judgment. [a] • Pembrolizumab may continue without interruption at the discretion of the investigator per medical judgment. [b]

[a] Events of hypertension have been reported in binimetinib clinical studies. Although primarily reported as non-serious and low grade events, or reported as occurring in patients with important confounding risk factors, in the pivotal study reported events were more frequent in the active binimetinib arm than the control arm. [Reference: Binimetinib IB]

[b] Vascular disorders (including hypertension and hypotension) are possible adverse events of pembrolizumab, considering the mechanism of action.

Hemorrhage

Guidelines for the management of hemorrhage are provided in Table 12.

Table 12. Guidelines for the Management of Hemorrhage

Hemorrhage	*Action to be Taken*
Grade 3 hemorrhage	• *Patients who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab. All other patients will* • *have bevacizumab held until all of the following criteria are met:* • *The bleeding has resolved and hemoglobin is stable.* • *No bleeding diathesis would increase the risk of therapy.* • *No anatomic or pathologic condition significantly increases the risk of hemorrhage recurrence* • *After administration of bevacizumab is restarted, if the patient experiences another Grade 3 hemorrhagic event, bevacizumab should be discontinued.* • *Interrupt binimetinib treatment. There are no data on the effectiveness of binimetinib dose modification for hemorrhage events. Clinical judgment should be applied when considering restarting binimetinib treatment.* • *Continue pembrolizumab treatment.*
Grade 4 hemorrhage, or any grade pulmonary hemorrhage, or any grade cerebral Hemorrhage	• *Discontinue bevacizumab.*[a] • *Interrupt binimetinib treatment. Permanently discontinue binimetinib for hemorrhage events attributed to binimetinib.* • *Continue pembrolizumab treatment.*

a Note for Grade 1 events: Patients who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab. All other patients will have bevacizumab held until all of the following criteria are met: the bleeding has resolved and hemoglobin is stable; no bleeding diathesis would increase the risk of therapy; and no anatomic or pathologic condition significantly increases the risk of hemorrhage recurrence. After administration of bevacizumab is restarted, if the patient experiences another Grade 1 pulmonary or CNS (intracranial) hemorrhagic event, bevacizumab should be discontinued.

Thromboembolic Events

Guidelines for the management of venous thromboembolism and arterial thromboembolic events are provided in Table 13 and Table 14, respectively.

Table 13. Guidelines for Management of Venous Thromboembolic Events

Event	*Guidance*
Venous thromboembolic event Grade ≥ 3	• *For Grade 3 thromboembolic events, h*old bevacizumab for > 3 weeks. Bevacizumab treatment may be resumed during the period of therapeutic-dose event Grade ≥ 3 anticoagulant therapy once the level of anticoagulation therapy is stabilized: - Patients receiving heparin treatment should have an a PTT 1.5–2.5 × ULN. - Patients receiving full-dose LMWH should receive the dose appropriate for the patient's weight according to the Package Insert. - Patients receiving coumarin derivatives should have an INR between 2.0 and 3.0 assessed in 2 consecutive measurements 1□4 days apart. - After administration of bevacizumab is restarted, if the patient experiences another Grade 3 venous thromboembolic event, bevacizumab should be discontinued. • *For Grade 4 thromboembolic events, discontinue bevacizumab.* *Binimetinib may continue without interruption and/or dose reduction at the discretion of the investigator per medical judgment.* *Pembrolizumab may continue without interruption at the discretion of the investigator per medical judgment.*

LMWH = low-weight molecular heparin.

Table 14. Guidelines for the Management of Arterial Thromboembolic Events

Event	*Guidance*
Arterial thromboembolic event, any Grade	*Discontinue bevacizumab.* Binimetinib may continue without interruption and/or dose reduction at the discretion of the investigator per medical judgment. Pembrolizumab may continue without interruption at the discretion of the investigator per medical judgment.

Proteinuria

Guidelines for the management of proteinuria are provided in Table 15.

Table 15. Guidelines for the Management of Proteinuria

Event	*Guidance*
Proteinuria first occurrence, no nephrotic syndrome	*No bevacizumab dose interruptions for proteinuria <2 + by dipstick.* *For proteinuria 2 + or 3 + by dipstick, administer bevacizumab as planned and collect 24-hour urine for determination of total protein within 3 days before next scheduled bevacizumab administration.* *If 24-hour proteinuria ≤2 g, the next bevacizumab dose can be administered as scheduled.* *If 24-hour proteinuria >2 g, hold bevacizumab treatment. Continue to do 24-hour urine collections for determination of total protein within 3 days of each scheduled bevacizumab dose and continue to hold scheduled bevacizumab until proteinuria has decreased to ≤2 g/24 hours.* *When proteinuria has decreased to ≤2 g/24 hours, scheduled bevacizumab may be administered as planned. However, continue to do 24-hour urine collections for determination of total protein within 3 days of each scheduled bevacizumab dose until proteinuria has improved to ≤1 g/24 hours.* *Binimetinib may continue without interruption and/or dose reduction at the discretion of the investigator per medical judgment.* *Pembrolizumab may continue without interruption at the discretion of the investigator per medical judgment.*
Proteinuria subsequent occurrences, no diagnosis of nephrotic syndrome	*No bevacizumab dose interruptions for proteinuria <3 + by dipstick.* *For proteinuria 3 + by dipstick, administer bevacizumab as planned and collect 24-hour urine for determination of total protein within 3 days before next scheduled bevacizumab administration.* *If 24-hour proteinuria ≤2 g, the next bevacizumab dose can be administered as scheduled.* *If 24-hour proteinuria >2 g, hold bevacizumab treatment. Continue to do 24-hour urine collections for determination of total protein within 3 days of each scheduled bevacizumab dose, and continue to hold scheduled bevacizumab until proteinuria has decreased to ≤2 g/24 hours.* *If urine protein continues to be >2 grams by dipstick, recommend checking 24-hour urine protein every 3 months to ensure that proteinuria is < 2 grams per day* *When proteinuria has decreased to ≤2 g/24 hours, scheduled bevacizumab may be administered as planned.* *However, continue to do 24-hour urine collections for determination of total protein within 3 days of each scheduled bevacizumab dose until proteinuria has improved to ≤1 g/24 hr.* *Binimetinib may continue without interruption and/or dose reduction at the discretion of the investigator per medical judgment.* *Pembrolizumab may continue without interruption at the discretion of the investigator per medical judgment.*

Proteinuria with diagnosis nephrotic syndrome	*Discontinue bevacizumab.* *Binimetinib may continue without interruption and/or dose reduction at the of discretion of the investigator per medical judgment.* *Pembrolizumab may continue without interruption at the discretion of the investigator per medical judgment*

Fistula

Guidelines for the management of proteinuria are provided in Table 16.

Table 16. Guidelines for the Management of Fistula

Event	*Guidance*
Tracheoesophagael fistula, any grade	• *Discontinue bevacizumab.* • Binimetinib may continue without interruption and/or dose reduction at the discretion of the investigator per medical judgment. • Pembrolizumab may continue without interruption at the discretion of the investigator per medical judgment.
Fistula (non-tracheoesophageal), Grade 4	• *Discontinue bevacizumab.* • Binimetinib may continue without interruption and/or dose reduction at the discretion of the investigator per medical judgment • Pembrolizumab may continue without interruption at the discretion of the investigator per medical judgment.

Wound Dehiscence

Guidelines for the management of wound are provided in Table 17.

Table 17. Guidelines for the Management of Wound Dehiscence

Event	*Guidance*
Wound dehiscence, any grade	• *Discontinue bevacizumab.* • Binimetinib may continue without interruption and/or dose reduction at the discretion of the investigator per medical judgment. • Pembrolizumab may continue without interruption at the discretion of the investigator per medical judgment or the surgical therapy.

Posterior Reversible Encephalopathy Syndrome/Reversible Posterior Leukoencephalopathy Syndrome

Guidelines for the management of posterior reversible encephalopathy/reverse posterior leukoencephalopathy are provided in Table 18.

Table 18. Guidelines for the Management of Posterior Reversible Encephalopathy Syndrome/Reversible Posterior Leukoencephalopathy Syndrome

Event	*Guidance*
PRES/RPLS, any grade confirmed by MRI	• *Discontinue bevacizumab.* • Binimetinib may continue without interruption and/or dose reduction at the discretion of the investigator per medical judgment. • Pembrolizumab may continue without interruption at the discretion of the investigator per medical judgment.

MRI=magnetic resonance imaging; PRES=posterior reversible encephalopathy syndrome; RPLS= reversible posterior leukoencephalopathy syndrome.

Pancreatitis

In case of pancreatitis, treatment with bevacizumab and binimetinib may continue without interruption (and in the case of binimetinib without dose reduction) at the discretion of the investigator per medical judgment. For pembrolizumab treatment modification, refer to the Pembrolizumab Investigator's Brochure.

Neurologic Disorders

In case of autoimmune neuropathy, treatment with bevacizumab and binimetinib may continue without interruption (and in the case of binimetinib without dose reduction) at the discretion of the investigator per medical judgment. For pembrolizumab treatment modification, refer to the Pembrolizumab Investigator's Brochure.

Guidelines for the management Guillain-Barre are provided in Table 19 .

Table 19. Management Guidelines for Guillain-Barre

Event	*Guidance*
Grade 1-4	• *For pembrolizumab information, see Investigator's Brochure.* • Hold bevacizumab for myasthenia gravis or Guillain-Barre. Patient may restart upon complete resolution. • Binimetinib may continue without interruption and/or dose reduction at the discretion of the investigator per medical judgment.

Infusion-Related Reactions

Patient may development infusion-related reactions during the administration of bevacizumab and/or pembrolizumab.

Close observation of the patient during and following the administration of bevacizumab is recommended as expected for any infusion of a therapeutic humanized monoclonal antibody. If a reaction occurs, the infusion should be discontinued and appropriate medical therapies should be administered. Medical therapies are at discretion of the investigator per medical judgment and may include antihistamines, antipyretics, glucocorticoids, epinephrine, bronchodilators, and oxygen. A systemic premedication is not warranted.

Premedication is allowed for administration of Cycle 1 of pembrolizumab. Patients who are not premedicated and who experience an infusion-related reaction with Cycle 1 of pembrolizumab may receive premedication with antihistamines or antipyretics/analgesics (e.g., acetaminophen) for subsequent infusions.

Guidelines for the management of infusion-related reactions are provided in Table 20. For severe hypersensitivity reactions, permanently discontinue all study treatment. For anaphylaxis precautions, refer to Appendix 4.

Table 20. Management Guidelines for infusion-related reactions

Event	Binimetinib	Bevacizumab	Pembrolizumab
Infusion-related reactions Grade 1	Binimetinib may continue without interruption at the discretion of the investigator per medical judgment. If the infusion is interrupted, it may be resumed at ≤ 50% of the rate prior to the reaction after the patient's symptoms have adequately resolved and increased in 50% increments up to the full rate if well tolerated. Infusions may be restarted at the full rate during the next cycle.	Reduce infusion rate to ≤ 50% or interrupt infusion at the discretion of the investigator per medical judgment.	*For pembrolizumab information, see the Investigator's Brochure.*
Infusion-related reactions Grade 2	Binimetinib may continue without interruption and/or dose reduction at the discretion of the investigator per medical judgment. If the infusion is interrupted, it may be resumed at ≤ 50% of the rate prior to the reaction after the patient's symptoms have adequately resolved and increased in 50% increments up to the full rate if well tolerated. Infusions may be restarted at the full rate during the next cycle.	Reduce infusion rate to ≤ 50% or interrupt infusion at the discretion of the investigator per medical judgment.	*For pembrolizumab information, see the Investigator's Brochure.*

Event	Binimetinib	Bevacizumab	Pembrolizumab
Infusion-related reactions Grade 3-4	Binimetinib may continue without interruption and/or dose reduction at the discretion of the investigator per medical judgment.	Stop infusion Discontinue bevacizumab	*For pembrolizumab information, see the Investigator's Brochure.*

IRR= infusion-related reactions

Endocrine Events

Thyroid disorders or adrenal insufficiency has been associated with the administration of pembrolizumab.

Patients with unexplained symptoms such as fatigue, myalgias, impotence, mental status changes, or constipation should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies, as well as for hyponatremia or hyperkalemia. An endocrinologist should be consulted if an endocrinopathy is suspected.

Thyroid-stimulating hormone and free thyroxine (T4) levels should be obtained to determine whether thyroid abnormalities are present. Thyroid-stimulating hormone, prolactin, and a morning cortisol level will help to differentiate primary adrenal insufficiency from primary pituitary insufficiency.

For pembrolizumab information, see the Investigator's Brochure. Binimetinib and bevacizumab may continue without interruption and/or dose reduction at the discretion of the investigator per medical judgment.

Immune Related Adverse Events

Down-modulating PD-L1/PD-1 signaling may permit the emergence of auto-reactive T cells and clinical autoimmunity. Adverse events associated with drug exposure and consistent with an autoimmune etiology are termed immune related adverse events.

Patients should be informed of and carefully monitored for evidence of clinically significant systemic immune related adverse event (e.g., systemic lupus erythematosus-like diseases) or organ-specific immune related adverse event (e.g., rash, colitis, uveitis, hepatitis, thyroid disease). Efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes prior to labeling an adverse event an immune related adverse events. Serological, immunological, and histological (biopsy) data should be used to

support the diagnosis of an immune-mediated toxicity.

Although many low-grade immune-related adverse events respond well to symptomatic therapy, high-grade immune-related adverse events require corticosteroid therapy and, in rare corticosteroid-refractory cases, the use of other immune-suppressive therapies, such as infliximab or mycophenolate mofetil.

Other Unspecified Adverse Events

Guidelines for the management of non-laboratory related adverse events are provided in Table 21, and guidelines for the management of unspecified Grade 3 and higher laboratory related adverse events are provided in Table 22.

Table 21. Guidelines for the Management of Unspecified Related Adverse Events Grade 3 or Higher Other than Laboratory Abnormalities

Event	Modification(s)
Other unspecified related events (other than laboratory abnormalities), Grade 3	Interrupt dosing of attributable study drug at the discretion of the investigator. During this time, treatment may continue with non-attributable study drugs. If attributable study drug has been held and the event resolves to Grade ≤ 1 within 28 days, then restart dosing of attributable study drug). If attributable has been held and the event does not resolve to Grade ≤ 1 within 28 days, then discontinue attributable study drug. If attributable study drug is discontinued, treatment may continue with other study drugs at the discretion of the investigator.
Other unspecified related events (other than laboratory abnormalities), Grade 4 first occurrence	If the Grade 4 event is attributed to bevacizumab: Discontinue bevacizumab. During this time, treatment may continue with non-attributable study drugs. If the Grade 4 event is attributed to binimetinib or pembrolizumab: Interrupt dosing of the attributable study drug at the discretion of the investigator. During this time, treatment may continue with non-attributable study drugs. If the attributable study drug has been held and the event resolves to Grade ≤ 1 within 28 days, then restart dosing of the attributable study drug. If the attributable study drug has been held and the event does not resolve to Grade ≤ 1 within 28 days, then discontinue the attributable study drug. If the attributable study drug is discontinued, treatment may continue with other study drugs at the discretion of the investigator.
Other unspecified related events (other than laboratory abnormalities), Grade 4 second occurence	If the Grade 4 event is attributed to binimetinib or pembrolizumab: If the Grade 4 event recurs despite reduction of the attributable study drug by 1 dose level, discontinue the attributable study drug at the discretion of the investigator. During this time, treatment may continue with non-attributable study drugs. [Not applicable to bevacizumab, which would be discontinued after the first Grade 4 occurrence attributed to bevacizumab.]

Table 22. Guidelines for Grade 3 and Higher Unspecified Laboratory Abnormality Adverse Events

Event	Modification(s)
Other unspecified events that laboratory abnormalities, Grade ≥ 3	For Grade ≥ 3 toxicities associated primarily with laboratory abnormalities only and for which guidance has not already been specified elsewhere in this protocol (e.g., elevation of lipase or amylase, or decreases in phosphorus are without clinical or other evidence of pancreatitis or other hepatic dysfunction), all study drugs may continue without interruption and/or dose reduction (binimetinib or pembrolizumab) or as scheduled (bevacizumab) at the discretion of the investigator per medical judgment.

Note: Not every laboratory abnormality qualifies as an adverse event. Refer to Section 5.3.5.5 for more information.

CONSENT AND AUTHORIZATION FORM

Principal Investigator:	**Christopher Lieu, MD**
COMIRB No:	**17-0466**
Version Date:	**April 15, 2021**
Study Title:	***Phase II study of pembrolizumab in combination with binimetinib and bevacizumab in patients with refractory colorectal cancer***

You are being asked to participate in a research study. A member of the research team will explain what is involved in this study and how it will affect you. This consent form describes the study procedures, the risks and benefits of participation, as well as how your confidentiality will be maintained. Please take your time to ask questions and feel comfortable making a decision whether to participate or not. This process is called informed consent. If you decide to participate in this study, you will be asked to sign this form.

Why is this study being done?

The purpose of this study is to see how well the combination of three drugs, pembrolizumab, binimetinib, and bevacizumab works in people with refractory colorectal cancer.

You are being asked to be in this research study because you have colorectal cancer that has not responded to standard treatment for this disease.

Binimetinib is an experimental drug, which means that it is not approved by the U.S. FDA. Pembrolizumab and bevacizumab are approved by the FDA for the treatment of certain cancers but not specifically for refractory colorectal cancer. Therefore, the use of pembrolizumab and bevacizumab in this study is also considered experimental.

Throughout the rest of this form, when these drugs are referenced by themselves they will be called pembrolizumab, binimetinib, and bevacizumab, but when referenced together or in combination they will be called the “study drug combination.”

Other people in this study

Up to 70 people from your area will participate in the study.

What happens if I join this study?

If you join the study, you will be asked to sign this consent form. You will be given a copy to keep and the original form will be kept at the clinic. You can withdraw from the study at any time and without giving a reason. This will not affect the standard medical care you receive.

There are two parts to this study. In Stage 1, subjects will be enrolled to see if pembrolizumab, binimetinib, and bevacizumab can be given safely in combination without serious or severe side effects.

If the study drug combination is safe and tolerable, subjects will be enrolled into Stage 2 of the study to see if the study drug combination is effective for your disease. Whether you participate in Stage 1 or Stage 2 of the study will depend on when you are enrolled.

Pembrolizumab (200mg) will be given on Day 1 of each 21-day cycle intravenously (IV). Binimetinib (45 mg) is taken by mouth (orally) twice daily during each cycle. Bevacizumab (7.5mg/kg) will be given on Day 1 of each 21-day cycle intravenously (IV).

In Stage 2, subjects will be assigned to one of two groups to receive the study drug combination. If you are enrolled into Stage 2 of the study, Group A will receive binimetinib alone for 7 days prior to Cycle 1 then go on to receive pembrolizumab and bevacizumab on Day 1 of Cycle 1. The study drug combination will be given starting Day 1 of each subsequent cycle. Group B will receive the study drug combination starting on Day 1 of Cycle 1 and each cycle thereafter.

This next section is an overview of what will be expected of you, and what you can expect if you take part in this study.

Study Procedures:

The time points when these study procedures will take place are specified in the Study Procedures Table.

Below are the study procedures and schedule of events (when each procedure will take place) for this study. Some procedures you receive while taking part in this study are "standard of care procedures" for treatment of your disease. If you have had some of these procedures recently, they may not need to be repeated. Some procedures are required only for this research study and will be called "research" procedures.

- **Informed Consent**
  This informed consent form will be discussed with you and you will be given a copy of this document. If you join the study, you will be asked to sign this consent form before you receive any study related tests or procedures.

- **Medical and Cancer History**
  Before you start the study, we will record your date of birth, race, ethnicity, and complete medical history. This medical history will look at the background and history of your cancer and any treatments you have received for your disease.

- **Physical Examination**
  A physical examination will be completed as part of your standard of care at screening and throughout the duration of the study. After you join the study, we will assess if the study drugs are affecting your body functions including lungs, heart, abdomen, extremities, skin, head (eyes, ears, nose, hair, etc.) and your neurological function.

- **Vital Signs**
  We will take your blood pressure, heart rate, respiratory rate, body temperature and weight. Height will be measured only during screening.

- **Performance Status**
  We will assess how well you are performing your daily activities.

- **Current Medications**
  Your study doctor will let you know which drugs you can and cannot take while taking part in this study. You will need to check with the study doctor before taking any new medications, including over the counter drugs and herbal supplements. From the time you first receive the study drugs through 30 days after the last dose, we will record medications you may be taking.

- **Review of Side Effects (AEs)—Research**
  Some risks have been identified because of the disease process or through use of the study drugs. These are commonly called side effects and will be followed very closely by your doctor and the study staff. More information about these will be provided in the Risk section of this consent form.

- **Echocardiogram (ECHO) or Multigated Acquisition (MUGA) Scan—Research**
  This is a noninvasive scan of the heart using sound waves. This test will be used to see how well your heart pumps blood.

- **Electrocardiogram (ECG) —Research**
  This is a noninvasive procedure that records the electrical activity of the heart. Electrodes are placed on the skin of the chest and connected in a specific order to a machine. Output usually appears on a long scroll of paper that displays a printed graph. This will check the electrical activity of your heart.

- **Blood and Urine Samples—Standard of Care**
  These tests are sometimes called safety labs so the study doctor can be sure it is safe for you to take part in this study and to be given the study drugs.
    - Pregnancy test: Women who are able to become pregnant will be given either a urine or a blood pregnancy test. A positive pregnancy test prior to being given the study drugs will exclude you from starting or continuing to take part in the study.

- Complete blood count (CBC)
- Comprehensive metabolic panel (CMP)
- Blood clotting tests (PT/INR, and PTT)
- Thyroid function tests (TSH)
- Testing for HIV (human immunodeficiency virus), HBV (hepatitis B virus), and HCV (hepatitis C virus)

- **Blood Samples—Research**
  These tests are being done specifically because you are participating in this study.
  - Biomarker blood testing: These tests will look at how and if your cancer is responding to the treatment.
  - Carcinoembryonic Antigen (CEA) test: This test will look at how and if your cancer is responding to the treatment.

Your doctor may order additional blood tests that he/she feels are needed to plan treatment, dose modification, or further evaluations.

- **Eye Exam—Research**
  An ophthalmologist will examine your eyes to check for signs of damage to the retina that may be caused by the study drug combination.

- **Imaging (CT or MRI) —Standard of Care**
  These tests will be performed to check the status of your disease.
  - CT: A computed tomography scan uses x-rays to make detailed pictures of parts of the body and the structures inside the body.
  - MRI: Magnetic resonance imaging is a test that uses a magnetic field and pulses of radio wave energy to make pictures of organs and structures inside the body.

- **Tumor Tissue Samples—Research**
  - Archived Tissue: If you had surgery for your cancer in the past, you must agree to allow us to contact the institution where you had your surgery and ask them to send us a portion of your tumor tissue that they have stored so we may use it for this research.

- **Survival Follow-up Information**
  - Follow-up information will be collected by telephone calls or clinic visits every 3 months.

Table 1. Study Procedures

	Screening	**Treatment Period (21-day cycle) (Pembrolizumab, Binimetinib and Bevacizumab)**				**Final Study/ Treatment Discontinuation Visit**	**Survival Follow-Up**
		Cycle 1		**Cycle 2**	**Cycles 3+**		
Days *(window)*	**-28 to -1**	**Day -7**	**Day 1** *(±2)*	**Day 1** *(±2)*	**Day 1** *(±2)*	30 days after treatment *(±7)*	Every 3 months ***(±2 weeks)***
Informed consent	x						
Demographic data; medical & CRC History; baseline characteristics	x						
Complete physical examination	x						
Vital signs	x		x	x	x	x	
Weight	x		x	x	x		
Height	x						
ECOG performance status	x			x	x	x	
Concomitant medications	x		x	x	x		
ECHO or MUGA scan	x			x	x	x	
12-lead ECG	x					x	
Hematology & Chemistry	x		x	x	x	x	
HIV, HBV, and HCV testing	x						
Imaging (CT or MRI)	x				x	x	

	Screening	**Treatment Period (21-day cycle) (Pembrolizumab, Binimetinib and Bevacizumab)**				**Final Study/ Treatment Discontinuation Visit**	**Survival Follow-Up**
		Cycle 1		**Cycle 2**	**Cycles 3+**		
Days *(window)*	**-28 to -1**	**Day -7**	**Day 1** *(±2)*	**Day 1** *(±2)*	**Day 1** *(±2)*	30 days after treatment *(±7)*	Every 3 months ***(±2 weeks)***
Coagulation tests	x		x	x	x		
Ophthalmic exams	x			x	x	x	
Urine collection	x		x	x	x		
Pregnancy test	x	*Monthly as* clinically indicated					
Thyroid function test	x		x	x	x		
Limited physical examination			x	x	x	x	
CEA test			x	x	x		
Binimetinib Group A		x		x	x		
Binimetinib Group B & Run-in			x	x	x		
Pembrolizumab administration			x	x	x		
Bevacizumab administration			x	x	x		
Biomarker blood draw			x	x	x	x	
Adverse events			x	x	x	x	
Tumor biopsy-Arm A		x	x				
Tumor biopsy-Arm B			x	x			
Survival Follow-up Information							x

How long will I be in the study?

Your study participation is expected to last at least 1 year. The amount of time you participate in this study will depend on how your disease responds and how you tolerate the treatment. You will continue in the study until there is evidence that your disease has relapsed, your side effects are too severe, you request to stop participation, the study doctor feels that you will not benefit from further dosing, you do not follow the study instructions, or (for women) you become pregnant.

Reasonably Foreseeable Side Effects and Risks of the Study

As with any study drug, side effects may occur when taking this study drug. While taking part in this study, and being treated with the study drugs, you will be watched carefully for any side effects. Some side effects may go away after you stop taking the study drug. Some side effects can be long lasting and may never go away or may even lead to **death**.

You should talk to your study doctor about any side effects or discomfort you may have. The study doctor may give you some medicine that will help with some side effects. The study doctor may also interrupt or discontinue the study drug.

You will be notified by your study doctor of any new side effects seen in other patients that occur during the time you are on the study. This may affect you wanting to continue in this research study.

Risks of Binimetinib

Binimetinib is an investigational drug and not all of the side effects are known. Serious side effects, including **death**, are possible. The long-term effects of binimetinib are also unknown.

Side effects in cancer patients treated with binimetinib may include those described below.

VERY COMMON SIDE EFFECTS (more than 20 out of 100 people):

- Alteration of the light sensing part of the back of the eye that may affect your vision*
- Feeling weak, tired, or lacking in energy
- Rash, acne or skin irritation including redness, raised bumps, dryness or itching
- Swelling due to fluid retention or a worsening of pre-existing fluid retention in specific areas of the body. This can occur throughout your body or in specific areas such as your abdomen or arms, legs, hands, feet or face.

COMMON SIDE EFFECTS (more than 10 but less than 20 out of 100 people:

- Muscle spasms, muscle pain or inflammation

UNCOMMON SIDE EFFECTS (1 person up to 10 out of 100 people):

- Alteration in how things taste or loss of the ability of taste
- Blockage or tear in stomach or intestine (especially if you have had cancer or surgery in this area of your body) that can cause pain, bloating, constipation, and vomiting
- Bleeding events involving the nose or stomach
- Blood clots in veins in the legs, in veins of the eyes or in arteries of the lungs
- Changes in heart rhythm
- Decrease in the heart's ability to pump blood (decreased ejection fraction or left ventricular dysfunction)*
- Diarrhea
- Dizziness
- Fever
- High blood pressure
- Increase in lab test results that check how well the liver is working
- Increase in a lab test result called creatinine phosphokinase (an enzyme found in the blood that may indicate muscle inflammation or damage)
- Infection of the skin or beneath the skin
- Muscle weakness including weakness of the neck muscles resulting in difficulty holding the head up
- Nausea
- Reduction in red blood cells
- Skin cracking
- Stomach pain
- Vomiting

*****Additional information about eye disorders and decreased ejection fraction side effects:

Eye disorders: Binimetinib has caused mild to moderate visual changes in some subjects. These changes include swelling and/or inflammation in and around the eyes and changes in the retina. While this type of visual impairment may resolve, there is a risk that the visual changes may continue. Blurred vision and, in some cases, loss of vision may be observed with binimetinib. There is the possibility that these changes could affect the activities of your daily life (i.e. driving a car or operating machinery). Participants with a history of or current retina blood vessel abnormalities will not be able to participate in this study. It is important to tell your doctor about any pre-existing eye problems you have and visual changes that occur while taking the study drug as your doctor may decide to change or stop your treatment with the study drug.

Decreased ejection fraction: A decrease in ejection fraction has been reported in studies with binimetinib. This means that the heart's ability to pump blood throughout the body is decreased. This side effect has also been seen with other similar drugs. Your cardiac function will be evaluated before and during the study. Participants with severe and recent cardiac abnormalities or events should not receive binimetinib.

Rare but important serious side effects seen in subjects receiving binimetinib (less than 1 person out of 100 people):

- One participant experienced acute liver failure (the liver rapidly lost its ability to function normally) leading to **death**. Due to this event and the observed increase in the value of liver enzymes, your liver function will be evaluated frequently.
- Hypertensive crisis was described in a single agent study with binimetinib. Increase of blood pressure may be a potential risk when receiving binimetinib. Subjects at risk for high blood pressure will be monitored closely. If necessary these subjects will receive specific treatment for hypertension.
- Cases of serious adverse events of inflammation of the lung tissue (pneumonitis) have been reported in clinical studies of binimetinib. Difficulty breathing, often accompanied by a cough and fever, is the most common symptom of pneumonitis. Please inform your doctor should you experience any of the symptoms described above.
- A severe skin reaction including serious illness with blistering of the skin, mouth, eyes and genitals has been reported in a patient who received binimetinib in combination with another experimental drug (BYL719). It is possible that one of these drugs may have caused this reaction. Please contact your physician immediately in case of such symptoms.
- A small number of patients and subjects in clinical trials developed hives and/or swelling in the throat, also known as angioedema, which can be a sign of an allergic reaction. Your doctor should be notified immediately if you experience tightness in your throat which may be associated with difficulty breathing.
- Severe muscle damage with breakdown of muscle tissue (rhabdomyolysis) which may result in organ damage such as kidney failure.

Risks of Pembrolizumab

Pembrolizumab, which is approved in the USA and some other countries, is available by prescription to treat several different cancers, but may not be approved to treat your type of cancer.

Pembrolizumab works by helping your immune system to fight your cancer.

However, pembrolizumab can also cause your immune system to attack normal organs and tissues in your body and can affect the way they work, which can result in side effects that may become serious or **life-threatening**, and in some cases, may lead to **death**, and/or may occur after you stop taking pembrolizumab. These side effects can affect more than one of your normal organs and tissues at the same time.

VERY COMMON, SOME MAY BE SERIOUS (i.e. causing hospitalization, **life-threatening** or where noted, may cause **death**) – occurring in more than 20 people out of 100 people:

- Itching of the skin
- Loose or watery stools
- Cough

COMMON, SOME MAY BE SERIOUS (i.e. causing hospitalization, **life-threatening**, or where noted, may cause **death**) occurring in at least 5 but less than 20 people out of 100 people:

- Joint pain
- Rash
- Fever
- Back pain
- Pain in your belly
- Loss of skin color
- Not enough thyroid hormone, so you may feel tired, gain weight, feel cold, or have infrequent or hard stools (hypothyroidism)
- Low levels of salt in the blood that may cause you to feel tired, feel confused, have a headache, have muscle cramps, and/or feel sick to your stomach (hyponatremia)

UNCOMMON, SOME MAY BE SERIOUS **-** i.e. causing hospitalization, **life-threatening**, or where noted, may cause **death**)– occurring in at least 1 to less than 5 people out of 100 people:

- Inflammation of the lungs so you may feel short of breath and cough. Rarely this might lead to **death.** (pneumonitis)
- Too much thyroid hormone, so you may feel anxious, feel angry, have trouble sleeping, feel weak, tremble, sweat, feel tired, have loose and watery stools (hyperthyroidism)
- Infusion reaction, where you may feel dizzy or faint, feel flushed, get a rash, have a fever, feel short of breath, experience a decrease in your blood pressure at the time of receiving your infusion (IV) or just after, or have pain at the site of infusion
- Inflammation of the bowels/gut that can cause severe stomach pain with loose or watery stools, or stools that are black, tarry, sticky or stools with blood or mucus (colitis)
- A condition called Stevens Johnson Syndrome (SJS) or Toxic Epidermal Necrosis (TEN). This condition involves inflammation of the skin so you may have peeling of the skin, itchiness, and/or skin redness. The skin inflammation (i.e., peeling, itching and redness) could also be widespread throughout your body. More severe skin reactions may involve the inside of your mouth, the surface of your eye and genital areas, and/or may cause the

top layer of your skin to peel from all over your body, which can cause severe infection. These severe conditions can rarely lead to **death**.

RARE, SOME MAY BE SERIOUS (i.e. causing hospitalization, **life-threatening**, or where noted, may cause **death**) – in less than 1 out of 100 people:

- Inflammation of the nerves (Guillain-Barré syndrome) that may cause
  - Pain
  - Weakness
  - Tingling in the hands and feet, and may spread to the legs, arms and upper body leading to severe muscle weakness and possible temporary paralysis
- Inflammation of the muscles (myositis), so you may feel weak or have pain in the muscles
- Inflammation of the pancreas (pancreatitis), a gland in your abdomen that controls sugar levels so you may
  - Have severe upper belly pain that may move to the back
  - Feel sick to your stomach
  - Have vomiting that gets worse when you eat
- Inflammation of the eye (uveitis) that may cause
  - Eye redness
  - Blurred vision
  - Sensitivity to light
  - Eye pain
  - Floaters
  - Headaches
- Inflammation of the liver (hepatitis) that may make you have
  - Upset stomach and vomiting
  - Feel like not eating
  - Feel tired
  - Mild fever
  - Pain in the right side of your belly
  - Yellow eyes and skin
  - Dark urine
- Inflammation of the pituitary gland (hypophysitis), a gland in the head, which may cause you to have
  - Upset stomach or headaches
  - Changes in behavior
  - Double vision
  - Few to no menstrual cycles
  - Weakness
  - Vomiting and dizziness
  - Fainting

- Adrenal glands (adrenal insufficiency), glands on top of the kidneys, that may not produce enough hormone which could cause
    - Tiredness
    - Weight loss
    - Muscle weakness
    - Feeling faint
    - Joint, muscle, and belly aches
    - Nausea
    - Vomiting
    - Loose or watery stools
    - Fever
    - Salt craving
    - Darkening of the skin like a suntan
- Type 1 Diabetes, a condition that can cause too much sugar in the blood, which may make you
    - Feel thirstier than usual
    - Frequently urinate
    - Lose weight
    - Need regular insulin shots
- Inflammation of the kidney (nephritis) where you may
    - Pass less urine
    - Have cloudy or bloody urine
    - Have swelling
    - Have low back pain
- Inflammation of the middle layer of your heart (myocarditis) that may cause your heart to have difficulty pumping blood throughout your body, which can cause
    - Chest pain
    - Shortness of breath
    - Swelling of the legs
    - Fast or irregular heartbeat (that may cause dizziness or fainting)
    - **Death**
- Inflammation of the thyroid gland (thyroiditis), an organ that makes and stores thyroid hormones. This condition may lead to change in your
    - Heart rate
    - Blood pressure
    - Body temperature
    - Metabolism (the rate at which food is converted into energy)
- A condition that may make you feel weak and tired and may cause drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, or difficulty breathing (myasthenic syndrome/myasthenia gravis including exacerbation)
- The formation of small clusters of immune cells (called granulomas) in parts of your body such as your lymph nodes, eyes, skin, or lungs (sarcoidosis)

- Inflammation of the brain (encephalitis) with confusion and fever, which may include:
    - Disorientation
    - Memory problems
    - Seizures (fits)
    - Changes in personality and behavior
    - Difficulty speaking
    - Weakness or loss of movement in some parts of your body
    - Loss of consciousness
- Inflammation of the spinal cord (myelitis), which may cause
    - Pain
    - Numbness
    - Tingling or weakness in the arms or legs
    - Bladder or bowel problems including needing to urinate frequently
    - Urinary incontinence
    - Difficulty urinating
    - Constipation
- Inflammation of the blood vessels (vasculitis)

Additionally, since pembrolizumab was approved in September 2014, the following side effects have been reported by people receiving pembrolizumab. These side effects were voluntarily reported from a group of people of unknown size. It is not possible to estimate the frequency of this side effect:

- Inflammation of the joints which may include joint pain, stiffness and/or Swelling (arthritis).
- Severe responses of the immune system that cause the body to attack its own blood cells, spleen, liver, lymph nodes, skin and brain. This may include fever, rash, inflammation of the liver, yellowing of the skin, an enlarged liver and spleen, low blood counts, and enlarged lymph nodes. The nervous system may also be affected and cause confusion, seizures, and even coma (hemophagocytic lymphohistiocytosis).
- Changes in eyesight, eye pain, whitish patches on the skin and hearing loss (Vogt-Koyanagi-Harrada syndrome).
- Inflammation and scarring of the bile ducts (tubes that carry digestive fluid that is made in the liver). This can cause symptoms similar to those seen with inflammation of the liver (hepatitis) such as pain in right side of your bellow, yellow eyes and skin, feeling tired, and itching (sclerosing cholangitis).

If you have had an allogeneic stem cell transplant (a procedure in which a person receives blood-forming stem cells from a donor), you may experience graft versus host disease (GvHD), which may include diarrhea, skin rashes, and liver damage, after receiving pembrolizumab. Sometimes this condition can lead to **death**.

Risks of Bevacizumab

COMMON SIDE EFFECT (In 100 people receiving bevacizumab, more than 20 and up to 100 may have):

- High blood pressure which may cause headache or blurred vision

OCCASIONAL SIDE EFFECTS (In 100 people receiving bevacizumab, from 4 to 20 may have):

- Anemia, which may require blood transfusion
- Low white cell count that may increase the risk of infection
- Infection, including collection of pus in the belly or rectum
- Abnormal heartbeat which may cause palpitations or fainting
- Pain in the belly, rectum, chest, joints, muscles, or tumor
- Low appetite, constipation, diarrhea, heartburn, nausea, vomiting, or dehydration
- Internal bleeding which may cause black tarry stool, blood in vomit, coughing up of blood, or blood in urine
- Bleeding from other sites, including the vagina or nose
- Blockage of internal organs, which may cause vomiting or inability to pass stool
- Sores in mouth
- Allergic reaction during or after infusion of bevacizumab, which may cause fever, chills, rash, itching, hives, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Delay in healing of wounds or spontaneous opening of wounds
- Weight loss, tiredness, or dizziness
- Damage to the jawbone, which may cause loss of teeth
- Headache
- Numbness, tingling, or pain in the fingers or toes
- Hoarseness, stuffy nose, or cough
- Blood clot in limbs or lungs, which may cause swelling, pain, or shortness of breath
- Leakage of protein in the urine, which can rarely lead to damage to the kidney

RARE AND SERIOUS SIDE EFFECTS (In 100 people receiving bevacizumab, 3 or fewer may have):

- Clots in the arteries, causing stroke (which may cause paralysis or weakness) or heart attack (which may cause chest pain or shortness of breath). This risk is significantly increased in patients who are elderly or with history of diabetes

- Heart failure which may cause shortness of breath, swelling of ankles, or tiredness
- Bowel perforation (a tear in the bowel) that can cause pain or bleeding and require surgery to repair
- A tear or hole (fistula) in internal organs such as the nose, throat, lungs, esophagus, rectum, or vagina. These conditions may cause serious infections or bleeding and require surgery to repair
- Flesh-eating bacteria syndrome, an infection in the deep layers of skin
- Bleeding in the tumor, brain, belly, or lungs, which may cause confusion, blood in stool or coughing up blood
- Brain damage, which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome)
- Kidney damage which may require dialysis

Additional Notes on Possible Side Effects for Bevacizumab:

- Risk in pre-menopausal women: more likely to develop menopause when taking bevacizumab.

Risks Associated with Study Procedures

Risks of Having an IV Inserted in Your Vein

In this study we will insert a needle, connected to a plastic tube, into a vein in your arm. We will use the tube to take blood samples and to give you the study drugs and fluids. You will feel some pain when we first insert the tube into your vein. You may have some redness, swelling, or bruising where the tube goes under your skin. In some cases, this type of tube can cause an infection where it goes under the skin. In rare cases, it can cause a blood clot in the vein. You will have this tube inserted for about 24 hours.

Risks of Having Blood Taken

In this study, depending on the study visit, we will need to get about 4-10 tablespoons of blood from you at each study visit. We will get blood by putting a needle into one of your veins and letting the blood flow into a vacuum tube. You may feel some pain when the needle goes into your vein. A day or two later, you may have a small bruise where the needle went under the skin. There is also a small risk of infection or rarely, fainting.

Risks of Biopsy

In this study, if you agree to participate, we will take 2 biopsies from you. There are some risks to taking a biopsy. There is a small chance that you could get an infection where the needle goes in. You may also experience redness, swelling, minor bleeding or bruising at the site where the cut was made or the needle inserted. You may experience mild to moderate pain at the site of the needle puncture. There is also a small chance that you could have an allergic reaction to the numbing medicine. After your skin heals up, you may have a small scar where we take the samples. If an X-ray is used to help place the needle, you will be exposed to additional radiation. The amount of radiation you receive during each biopsy procedure is approximately equal to the radiation you would receive in about 4 years in your normal environment.

Risks of having an EKG

An electrocardiogram (EKG) is a test that records the electrical activity of the heart. Skin irritation is rare but could occur during an EKG from the electrodes or gel that is used.

Risks of Magnetic Resonance Imaging (MRI)

In this study we may take an MRI of your chest, abdomen, and pelvis, The MRI machine uses powerful magnetic waves to take pictures inside the body. The waves themselves are not harmful, but they can cause metal to heat up and electronics to stop working.

You should NOT have an MRI if you have metal or electronic devices inside your body. Heart pacemakers and insulin pumps are examples of electronic devices.

The MRI machine is a small round tube. It might make you uncomfortable if you do not like tight spaces.

The most common side effect of having an MRI is flashing lights in the eyes. This is caused by the magnetic waves and is not harmful. Some people also experience warmth and reddening of the skin. This usually goes away after a few minutes.

Risks of Computed Tomography (CT) Scans

As part of this study we may perform a CT scan of your chest, abdomen, and pelvis (CAP). CT is a way of taking detailed pictures inside your body by using X-rays, which is a type of radiation.

You get some radiation from your environment. You get radiation from bricks and concrete, from some foods, and from radon gas, which is an invisible gas that seeps out of the ground. The amount of radiation that this CT scan will deliver to

your body (give you) is about the same as you would get from living in your environment for 5 years.

This is an estimate. The amount of radiation you get could be higher or lower, depending on the machine, the power setting, and your body weight. Exposure to radiation at high levels increases a risk of developing cancer. There is no evidence of such risks for diagnostic procedures.

The risk of this procedure is not equal for everyone. The risk is much higher for unborn babies if the mother has this procedure. The risk is also much higher for young children and teenagers. The risk is much lower for people over the age of 30.

Risks associated with HIV and/or Hepatitis B & C testing

If you test positive for HIV (Human Immunodeficiency Virus) and/or Hepatitis in this study, we must report your name to the Colorado Department of Public Health and Environment. Finding out that you have HIV or Hepatitis may make it hard for you to get insurance.

Other Risks

Loss of Confidentiality

There is a risk that people outside of the research team will see your research information. We will do all that we can to protect your information, but it cannot be guaranteed.

Reproductive Risks

The use of the study drugs in pregnant females and nursing mothers has not been studied. The effects of the study drugs on human eggs and sperm has not been studied. The risks to a human fetus are unknown. However, based on the way the drugs work, it cannot be ruled out that there is potential for the study drugs to cause birth defects in humans. If the study drugs are taken during pregnancy, they may cause birth defects or death to an unborn baby. Females must not become pregnant while taking the study drugs.

If you are a woman that can get pregnant you must agree to remain abstinent (refrain from heterosexual intercourse) or agree to use highly effective contraception for the duration of the study and for 6 months after your last dose of the study drugs.

If you are a man you must agree to remain abstinent (refrain from heterosexual intercourse) or agree to use a condom with your female partner for the duration of the study and for 6 months after your last dose of the study drugs. Men must also refrain from donating sperm during this same period.

Your physician will discuss your contraception method to ensure that it is appropriate for your participation in this study.

There may be other risks that could arise which are not reasonably foreseeable. If new information becomes available which could influence your willingness to continue, this new information will be discussed with you.

What are the possible benefits of the study?

If you agree to take part in this study, there may or may not be direct medical benefit to you. Also, there could be risks to being in this study. These risks are described in the "Reasonably Foreseeable Side Effects and Risks of the Study" section. We hope the information learned from this study will benefit other individuals with colorectal cancer in the future.

Are there alternative treatments?

There may be other ways of treating your colorectal cancer. These other ways include:

- Receiving an approved drug or approved drug combination for your disease
- Participation in another clinical trial for your disease
- Comfort Care, also referred to as palliative care, where treatment is directed at your symptoms and not your disease
- You can also choose to receive no treatment

Third-line standard of care treatment options do exist for the treatment of refractory colorectal cancer. Research studies show that these options may increase your overall life expectancy and these options should be discussed with your treating physician.

You should talk to your doctor about your choices. Make sure you understand all of your choices before you decide to take part in this study. You may leave this study and still have these other choices available to you.

Who is paying for this study?

Merck & Co, Inc. is providing a grant of funding support for this study. Merck manufactures one of the study drugs, Pembrolizumab, and will provide this drug for the study. The funding for this study will also pay for any tests or procedures that are related to the research study.

Pfizer, Inc. manufactures one of the study drugs, binimetinib, and will provide this drug for the study.

This research is being conducted by Dr. Christopher Lieu.

Will I be paid for being in the study?

You will not be paid to be in the study.

Will I have to pay for anything?

The drug Bevacizumab is considered standard treatment for your type of cancer. This drug will be obtained through your insurance, and you will be responsible for any applicable copays required by your insurance policy.

There are some medical procedures that you would get for your condition whether you were in this study or not, such as blood draws and tumor imaging. These are considered standard of care. You and/or your health insurance may be billed for the costs of medical care during this study, if these expenses are related to standard of care procedures. If you have health insurance, the cost of these services will be billed to your insurance company. If your insurance does not cover these costs, or you do not have insurance, these costs will be your responsibility.

Ask your study doctor to discuss the costs that will or will not be covered by this research study. This discussion should include the costs of treating possible side effect. Otherwise, you might have unexpected expenses from being in this study.

Is my participation voluntary?

Taking part in this study is voluntary. You have the right to choose not to take part in this study. If you choose to take part, you have the right to stop at any time. If you refuse or decide to withdraw later, you will not lose any benefits or rights to which you are entitled.

If you leave this study, you will still receive your normal medical care. The only medical care that you will lose is the medical care you are getting as part of this study. You might be able to get that same kind of medical care outside of the study. Ask your study doctor.

Can I be removed from this study?

The study doctor may decide to stop your participation without your permission if the study doctor thinks that being in the study may cause you harm, or for any other reason. Also, the funder of the study may stop the study at any time.

What happens if I am injured or hurt during the study?

If you have an injury while you are in this study, you should call Dr. Lieu immediately. His phone number is 303-724-6390.
We will arrange to get you medical care if you have an injury that is caused by this research. However, you or your insurance company will have to pay for that care.

Who do I call if I have questions?

The researcher carrying out this study is Dr. Christopher Lieu. You may ask any questions you have now. If you have questions, concerns, or complaints later, you may call Dr. Lieu at 303-724-6390. You will be given a copy of this form to keep.

You may have questions about your rights as someone in this study. You can call Dr. Lieu with questions. You can also call the responsible Institutional Review Board (COMIRB). You can call them at 303-724-1055.

A description of this clinical trial will be available on http://www.Clinical Trials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Who will see my research information?

The University of Colorado Denver (UCD) and its affiliated hospital(s) have rules to protect information about you. Federal and state laws including the Health Insurance Portability and Accountability Act (HIPAA) also protect your privacy. This part of the consent form tells you what information about you may be collected in this study and who might see or use it.

The institutions involved in this study include:

- University of Colorado Denver
- University of Colorado Hospital

We cannot do this study without your permission to see, use and give out your information. You do not have to give us this permission. If you do not, then you may not join this study.

We will see, use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside the UCD and its affiliate hospitals may not be covered by this obligation.

We will do everything we can to maintain the confidentiality of your personal information but confidentiality cannot be guaranteed.
The use and disclosure of your information has no time limit. You can cancel your permission to use and disclose your information at any time by writing to the study's Principal Investigator (PI), at the name and address listed below. If you do cancel your permission to use and disclose your information, your part in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in this study.

Dr. Christopher Lieu, MD
University of Colorado Denver
Anschutz Medical Campus
8117 HSC
12801 East 17th Avenue
Aurora, CO 80045

Both the research records that identify you and the consent form signed by you may be looked at by others who have a legal right to see that information, such as:.

- Federal offices such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP) that protect research subjects like you.
- People at the Colorado Multiple Institutional Review Board (COMIRB)
- The study doctor and the rest of the study team.
- Merck & Co., who is the company funding this research study and providing Pembrolizumab.
- Pfizer, a company providing binimetinib.
- Officials at the institution where the research is conducted and officials who are in charge of making sure that we follow all of the rules for research.

We might talk about this research study at meetings. We might also print the results of this research study in relevant journals. But we will always keep the names of the research subjects, like you, private.

You have the right to request access to your personal health information from the Investigator.

Information about you that will be seen, collected, used and disclosed in this study:

- Name and Demographic Information (age, sex, ethnicity, address, phone number, etc.)
- Portions of your previous and current Medical Records that are relevant to this study, including but not limited to Diagnosis(es), History and Physical, laboratory or tissue studies, radiology studies, procedure results
- Research Visit and Research Test records
- Testing for or infection with diseases reportable to the Public Health department, including but not limited to: Human Immunodeficiency Virus (HIV), hepatitis (all forms) tuberculosis, or other sexually transmitted diseases.
- Tissue samples and the data with the samples.
- Billing or financial information

What happens to Data, Tissue, Blood and Specimens that are collected in this study?

Scientists at the University of Colorado Denver and the hospitals involved in this study work to find the causes and cures of disease. The data, tissue, blood and specimens collected from you during this study are important to this study. If you join this study:

- The data, tissue, blood, or other specimens given by you to the investigators for this research no longer belong to you.
- Both the investigators and any sponsor of this research may study your data, tissue, blood, or other specimens collected from you.
- If data, tissue, blood, or other specimens are in a form that identifies you, UCD or the hospitals involved in this study may use them for future research only with your consent or Institutional Review Board (IRB) approval.
- Any product or idea created by the researchers working on this study will not belong to you.
- There is no plan for you to receive any financial benefit from the creation, use or sale of such a product or idea.
- If you wish to no longer participate in the study and have your specimens used for this research, please contact the PI in writing at the address included in this form. The PI will destroy any remaining specimens. However, the PI may continue to use the data generated from the specimens already collected.

Agreement to be in this study and use my data

The research project and the procedures associated with it have been explained to me. The experimental procedures have been identified and no guarantee has been given about the possible results. I will receive a signed copy of this consent form for my records.

I agree to participate in this study. My participation is voluntary and I do not have to sign this form if I do not want to be part of this research study.

Signature:_____ Date:_____

Print Name:_____

Consent form explained by:_____ Date:_____

Print Name: _____

Witness Signature:_____ Date:_____

Witness Print Name: _____

Witness of Signature ☐

Witness of consent process ☐