Mayo Clinic Cancer Center

Phase I/II Trial of Pembrolizumab in Combination with Binimetinib in Unresectable Locally Advanced or Metastatic Triple Negative Breast Cancer

Study Chairs: [redacted]

Study Cochairs: [redacted]

Statistician: [redacted]

√Study contributor(s) not responsible for patient care

Drug Availability

Drug Company Supplied:

Pfizer Inc. (formerly Array Biopharma LLC and Array Biopharma Inc.): Binimetinib **(**IND# 132,753)

Merck: Pembrolizumab **(**IND# 132,753)

Document History	**(Effective Date)**
Activation	09/26/2017
Amendment #1	03/07/2018
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Amendment #8	05/07/2021
Amendment #9	07/19/2021

Protocol Resources

Questions:	Contact Name:
Patient eligibility*, test schedule, treatment delays/interruptions/adjustments, dose modifications, adverse events, forms completion and submission	[redacted]
Forms completion and submission	[redacted]
Protocol document, consent form, regulatory issues	[redacted]
Laboratory Contact	[redacted]
Serious Adverse Event Reporting	[redacted]

*No waivers of eligibility allowed

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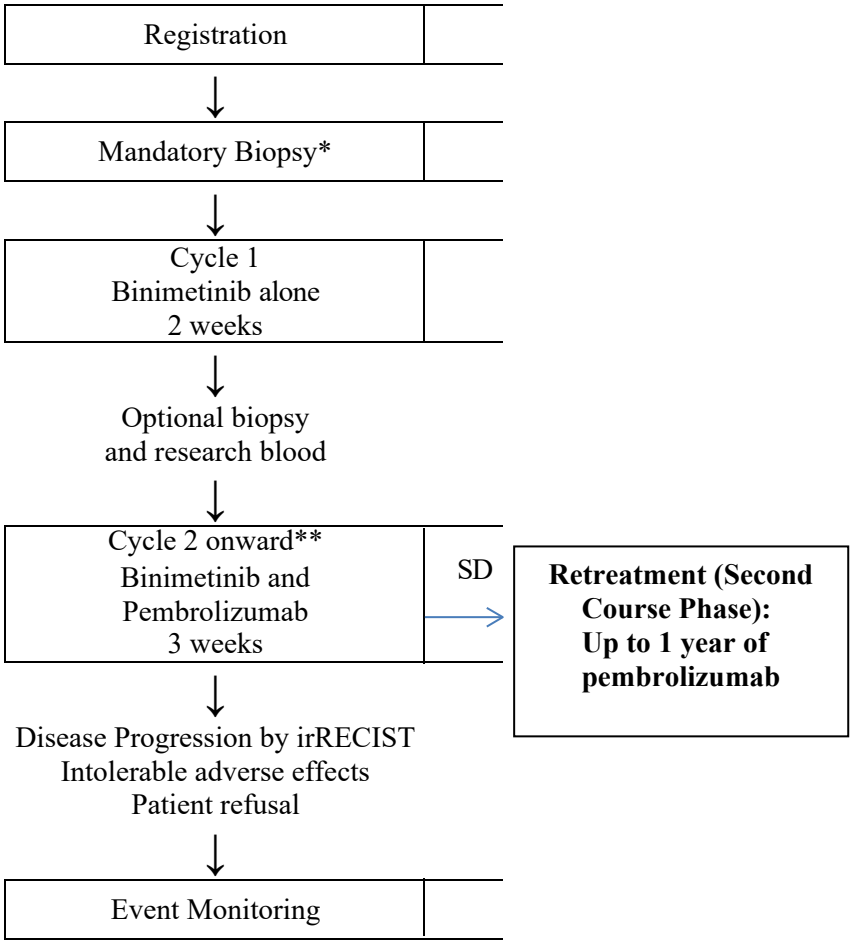
Schema

Phase I Only: Prior to discussing protocol entry with the patient, call the MCCC Registration Office (507-284-2753) for dose level and to insure that a place on the protocol is open to the patient.



*Unless adequate tissue is available from biopsy obtained ≤90 days prior to registration (see Section 17.0)
**Retreatment (Second Course Phase): Patients who stop pembrolizumab and binimetinib with SD or better may be eligible for up to one year of additional pembrolizumab and binimetinib therapy if they progress after stopping study treatment. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the patient meets the requirements as outlined in section 7.5.
Cycle 1 = 14 days
Cycle length for Cycle 2 onward = 21 days

Generic name: pembrolizumab, MK-3475 Brand name(s): Keytruda™ Mayo Abbreviation: MK3475 Availability: Mayo Clinic Pharmacy	Generic name: binimetinib, MEK162 Brand name(s): Mayo Abbreviation: MEK162 Availability: Mayo Clinic Pharmacy

1.0 Background

Emerging studies suggest that breast cancer, particularly triple negative breast cancer (TNBC), is also sensitive to immunotherapy. While the initial early phase clinical trials showed promising results with prolonged durable response with immune checkpoint blockade agents in TNBC, the number of patients who responded to immunotherapy is fairly small. TNBC is an aggressive form of breast cancer that lacks drug targets, namely estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). Despite advancements in targeted therapies, this group of patients continues to have poor outcome with a median overall survival (OS) of 13 months {Anders 2008}. Due to the lack of a validated drug target, TNBC represents not only a significant clinical challenge but also a critical unmet medical need.

1.1 Triple Negative Breast Cancer

Approximately 15-20% of all breast cancers do not express functional cell surface receptors like ER, PR, and HER2. Triple-negative tumors are typically associated with a higher histologic grade, increased mitotic count, pushing margins of invasion, and a stromal lymphocytic response. Patients with TNBC often have poorer prognosis compared to other breast cancer subtypes. It is commonly misconceived that TNBC is more sensitive to chemotherapy. Although higher pathologic complete response rate (pCR) was observed in TNBC (25–45%) compared to luminal breast cancers (6–7%), patients with TNBC had worse four-year distant disease free and overall survival {Irvin & Carey 2008}.

1.2 Immunotherapy and Pembrolizumab

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD 1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as

subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

1.3 Immunotherapy in TNBC

Over recent years, several studies demonstrated that the genetic and epigenetic alterations in TNBC may provide a set of tumor-associated antigens that the immune system can recognize and use to distinguish tumor cells from normal cells {Shah 2012; Stephens 2012}. More recently, the presence of tumor-infiltrating lymphocytes (TILs) at the time of the diagnosis has been shown to correlate with a significant increase in complete pathological response (pCR) to neoadjuvant chemotherapy (NAC) {Denkert 2010}. Subsequently, TILs also has been shown to correlate with both disease free survival (DFS) and OS among TNBC patients in a large adjuvant BIG 02-98 trial (Loi 2013). This observation was confirmed in a subsequent retrospective analysis of the Eastern Cooperative Oncology Group (ECOG) 2197 and 1199 trials {Adams 2014}. Although preclinical evidence suggests that antitumor immunity can control TNBC progression, tumors progress despite having tumor-specific CD8+ T cells infiltration. This paradox is mainly due to the exhausted nature of tumor-infiltrating T cells and the presence of immunosuppressive factors in the tumor microenvironment. T-cell exhaustion is a result of the upregulation of inhibitory receptors and serves as immune checkpoints in order to prevent uncontrolled immune reactions. In the past few years, there are several immune checkpoint blockade agents that have shown promising activities across several cancer types, including breast cancer. In a phase Ib trial of Pembrolizumab (Keynote-012) {Nanda 2014}, a humanized anti-PD1 monoclonal antibody, in TNBC, the overall response rate (ORR) was 18.5% and an additional 25.9% of patients had stable disease. Furthermore, among patients who responded, their responses appeared to be durable and lasted 15-40+ weeks. Another clinical trial with anti-PD-L1, MPDL3280A9, also showed promising activity of immune checkpoint blockade agent with ORR of 33%. From a total of 9 evaluable patients, one patient had complete response (CR) and 2 patients had partial response (PR).

1.4 MAPK Pathway and Binimetinib

Growth factor-mediated proliferative signals are transmitted from the extracellular environment to the nucleus through several pathways, including the RAS/RAF/MEK/ERK pathway {Roberts 2007}. This pathway comprises an evolutionarily conserved signaling cascade initiated by the RAS family of small GTPases, which activate the RAF kinases. Activated RAF kinases, phosphorylate and thereby activate the MEK1 and MEK2 kinases, which in turn phosphorylate and activate the ERK1 and ERK2 kinases. Subsequent phosphorylation of a variety of downstream effector proteins, including transcription factors, by activated ERK serve to regulate key cellular activities including proliferation, differentiation, migration, survival and angiogenesis. Aberrant signaling through this pathway has been shown to lead to unconstrained cell growth and cell transformation {Yoon 2006} and is a characteristic feature of many cancers. Inappropriate activation of the RAS/RAF/MEK/ERK pathway can occur through a variety of mechanisms, including activating mutations in RAS and BRAF {Lea 2007}, activated growth factor signaling {Nakazawa 2005} and stress response signals {McCubrey 2000}. Preclinical studies indicate that the presence of mutations that activate RAS/RAF/MEK/ERK pathway signaling, typically those occurring in the BRAF, NRAS and KRAS genes, are predictive for response to MEK inhibitors {Barretina 2012}. Collectively, these data suggest that targeting MEK may inhibit cancer signaling mediated by a wide variety of signals, making MEK an attractive target for the treatment of cancer and its associated symptoms. The identification of an allosteric regulatory site on the MEK enzyme allows the design of highly specific inhibitor molecules {Ohren 2004}. Other than binimetinib, there are a number of approved and investigational small-molecule MEK inhibitors of significance that are undergoing clinical evaluation for different tumor types (solid and hematologic malignancies). These compounds include: trametinib, selumetinib, cobimetinib, rafametinib and pimasertib. Trametinib (www.fda.gov) was the first MEK inhibitor approved by the US FDA and is indicated as a single-agent treatment and in combination with the BRAF inhibitor dabrafenib for the treatment of patients with unresectable or metastatic melanoma with BRAFV600E or BRAFV600K mutations.

Binimetinib (also known as binimetinib or ARRY-438162) is a potent, selective, allosteric small-molecule inhibitor of mitogen-activated protein (MAP) kinase kinase (MEK) that is uncompetitive with adenosine triphosphate (ATP). Binimetinib is currently being evaluated clinically in healthy subjects, in Noonan syndrome patients and in cancer patients. Previously, binimetinib has also been evaluated in the treatment of rheumatoid arthritis.

1.5 Rationale

Optimizing immune checkpoint blockade will be possible with the conduct of trials utilizing combination-targeted therapies. One such target is MEK. Balko and colleagues {Balko 2014} evaluated genomic alterations in tumors that may be associated TILs in residual tumor after NAC in TNBC. In parallel to previous studies, increased TILs are associated with favorable outcomes, including DFS ($p = 0.0008$) and OS ($p = 0.007$). There appeared to be a trend toward reduction in TIL level among patients who did not achieve pCR ($p = 0.07$). Using next-generation sequencing, lower TIL level in residual disease after NAC was associated with genetic alteration in the Ras/MAPK pathways, including KRAS, BRAF and RAF1 amplifications and NF1 truncations ($p = 0.005$). There was also an inverse correlation between the MEK activation signature and TILs in residual disease samples ($p = 0.00028$). These findings suggested that the association between TIL levels and dysregulation of Ras/MAPK pathway may be pathway specific.

The investigators further evaluate the effects of MEK inhibition in several TNBC cell lines and found that MEK inhibition, using AZD6244, up-regulates major histocompatibility complex (MHC) class I and II molecules in both *in vitro* and *in vivo* models. The investigators also went back and evaluated the expression of HLA-A and HLA-DR in their patient samples and found the inverse correlation between the expression level of these MHC class I and II molecules and the MEK activation signature. However, there was also a significant increase in the PD-L1 expression after MEK inhibition treatment, which has opposing inhibitory effects on tumor immune surveillance. The investigators further investigated the combination of MEK inhibitor and anti-PD-L1 antibody in *in vivo* mouse model and found that the combination can completely eradicate the tumors, while each single agent only had modest effects on tumor growth.

Currently, there is no clinical trial evaluating the combination of pembrolizumab and binimetinib in breast cancer. Based on the intriguing preclinical data above, it is logical to develop and conduct a phase I/II trial of pembrolizumab in combination with binimetinib in patients with unresectable locally advanced or metastatic triple negative breast cancer.

1.6 Correlative studies

Currently, there are several correlative studies that are being investigated as biomarkers for immunotherapy in cancer. Immune checkpoint blockade agents, like pembrolizumab, exerts its activity by blocking the distinct immunosuppressive checkpoints PD-1 or its major ligand PD-L1. Previous studies demonstrated that PD-L1 expression in the tumors appears to correlate with improved outcome in patients treated with immune checkpoint blockade agents {Topalian, 2012}. Furthermore, studies also showed that immune checkpoint blockade agent can also increase tumor infiltrating lymphocytes and improve response to adoptive cell therapy (1).

As described in the previous rationale section, MEK inhibition has been shown to upregulate cell surface MHC expression as well as PD-L1 in both in vivo and in vitro triple negative breast cancer models. Moreover, the combination of MEK and immune checkpoint blockade agent were synergistic and enhanced antitumor immune responses were observed in vivo breast cancer syngeneic mouse models {Balko 2014}. Nevertheless, the effects of MEK inhibitors to immune response in human remain largely unknown.

To evaluate immunologic response to single agent binimetinib and the combination of binimetinib and pembrolizumab, several correlative studies will be carried out as followed:

1.61 Correlative studies for tumor tissue

We will perform the following correlative studies using tumor tissue.

1. Tumor infiltrating lymphocytes: Tumor infiltrating lymphocytes will be quantified based on the H&E as described (2). Furthermore, the composition of different subsets of lymphocytes will also be quantify using immunohistochemistry staining for CD4 for T helper cells, CD8 for cytotoxic T cells as well as CD25 and FOXP3 for regulatory T cells as we previously published (3).
2. PD-L1 expression: PD-L1 expression in the tumor will be assessed by immunohistochemistry as previously described {Topalian, 2012}

3. Gene expression analysis: Global assessment of immune-related gene expression in pre- and post-treatment tumors will be assessed using the NanoString PanCancer Immune Profiling Panel which includes 770 genes for 24 different immune cell types and populations, 30 common cancer antigens and genes that represent all categories of immune response including key checkpoint blockade genes.
4. PDJ amplification: We have recently reported that approximately 30% of patients with TNBC harbor PDJ amplification (4). Locating at chromosome 9p24.1, this amplicon encompasses JAK2, PD-L1, and PD-L2 genes. TNBC patients with PDJ amplification had worse disease free (25.0% vs. 66.0%, p = 0.005) and overall survival (25.0% vs. 69.0%, p = 0.004). This amplicon has been previously described in the majority of Hodgkin's lymphoma, which has been reported to have remarkable response to Nivolumab (86% clinical benefit rate in heavily pretreated patients)(5). Based on these intriguing results, we plan to correlate PDJ amplification measured by fluorescent in situ hybridization and clinical outcome of patients in this trial.

1.62 Correlative studies for blood

We will perform the following correlative studies using blood specimens.

1. Immunoregulatory cell quantification: To evaluate the systemic immune response to binimetinib and binimetinib in combination with pembrolizumab, peripheral blood mononuclear cells will be collected and quantified for CD4 helper T cells, cytotoxic CD8 T cells, FOXP3 positive regulatory T cells, myeloid derived suppressor cells, and NK cells.
2. Cytokine profiling: Systemic cytokine response before and after treatment will also be evaluated using Luminex Multianalyte assay which allows simultaneous quantification of multiple cytokines in a single sample. A panel of 17 cytokines and chemokines will be analyzed using a multiplexed approach with commercially available human 17-plex kits. The following cytokines will be assessed: IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, CXCL8 (IL-8), IL-10, IL-12, IL-13, IL-17A, IFN-IFN-γ, TNF-α, CCL2 (MCP-1), CCL4 (MIP-1β), G-CSF, and GM-CSF. A panel of 17 cytokines and chemokines will be analyzed using a multiplexed approach with commercially available human 17-plex kits. The following cytokines will be analyzed using the manufacturer-supplied reagents.
3. Circulating tumor cells: Circulating tumor cell (CTC) quantification will be performed by Creatv MicroTech, Inc. using CellSieve microfiltration technique. Furthermore, the expression of other targets, including PD-L1 and phosphorylated ERK (p-ERK), will also be assessed before and after treatment. Previously, we demonstrated another unique form of CTCs that are associated with macrophage in the circulation of patients with metastatic breast, pancreatic, and prostate cancer, termed circulating cancer-associated macrophage-like cells or CAMLs. CAMLs are large multinucleated cells in peripheral blood that express epithelial, monocytic, and endothelial surface makers. The role of CAMLs, particularly in the context of immune therapy, is largely unknown.

2.0 Goals

2.1 Primary Goal

2.11 Phase I
To determine the maximum tolerated dose (MTD) of binimetinib in combination with pembrolizumab.

2.12 Phase II
To evaluate the objective response rate (ORR) of binimetinib in combination with pembrolizumab in patients with unresectable locally advanced or metastatic triple negative breast cancer by RECIST.

2.2 Secondary Goals

2.21 To evaluate the safety and tolerability of binimetinib in combination with pembrolizumab.

2.22 To evaluate the ORR by immune-related RECIST criteria (irRECIST)

2.23 To evaluate the progression free survival (PFS), duration of response (DoR), and disease control rate (DCR) by RECIST and irRECIST.

2.24 To assess overall survival (OS).

2.3 Correlative Research

2.31 To assess the correlation between ORR, PFS, or OS and baseline and/or change in TILs.

2.32 To assess the correlation between ORR, PFS, or OS and baseline and/or change in immune related gene signature and PDJ amplification.

2.33 To assess the change in immunoregulatory cells (IRC).

2.34 To assess the change in the cytokine profile.

2.35 To assess the change in circulating tumor cells (CTC).

3.0 Patient Eligibility

Phase I Only: Prior to discussing protocol entry with the patient, call the MCCC Registration Office [redacted] for dose level and to insure that a place on the protocol is open to the patient.

3.1 Registration – Inclusion Criteria

3.11 Age ≥18 years.

3.12 Histological confirmation of adenocarcinoma of the breast.

3.13 Estrogen receptor (ER) and progesterone receptor (PR) negative; defined as ER≤10% and PR≤10% staining by immunohistochemistry (IHC).

3.14 HER2 negative in the primary or metastatic tumor tissue defined as:

- Immunohistochemistry (IHC) Grade 0 as defined by no staining observed or membrane staining that is incomplete and is faint/barely perceptible and within ≤10% of the invasive tumor cell; OR
- IHC 1+ as defined by incomplete membrane staining that is faint/barely perceptible and within >10% of the invasive tumor cell; OR
- IHC Grade 2+ staining intensity by means of IHC analysis with no gene amplification below; OR
- No gene amplification on ISH based on:
  - Single-probe average HER2 copy number <4.0 signals/cell
    OR
  - Dual-probe HER2/CEP17 ratio <2.0 with an average HER2 copy number <4.0 signals/cell

3.15 For phase II part of the trial: ≤3 prior lines of treatment in the metastatic setting for the current breast cancer. However, there is no limit on number of prior line of therapy in phase I part of the trial.

3.16 Measurable disease as defined in Section 11.0.

3.17 ECOG Performance Status (PS) 0 or 1 (Appendix I).

3.18 The following laboratory values obtained ≤14 days prior to registration.

- Hemoglobin ≥9.0 g/dL (Must be ≥7 days after most recent transfusion)
- Absolute neutrophil count (ANC) ≥1500/mm^3 or ≥1.5 X 10^9/L
- Platelet count ≥100,000/mm^3 or ≥100 X 10^9/L (Must be ≥7 days after most recent transfusion)
- Total bilirubin ≤1.5 x upper limit of normal (ULN)
- Aspartate transaminase (AST) and alanine transaminase (ALT) ≤2.5 x ULN or ≤5 x ULN for patients with liver metastases
- Creatinine ≤1.5 x ULN
  OR
- Calculated creatinine clearance must be ≥50 ml/min using the Cockcroft-Gault formula below:

Cockcroft-Gault Equation:

Creatinine clearance for males = $\frac{(140 - age)(weight\ in\ kg)}{(72)(serum\ creatinine\ in\ mg/dL)}$

Creatinine clearance for females = $\frac{(140 - age)(weight\ in\ kg)(0.85)}{(72)(serum\ creatinine\ in\ mg/dL)}$

- International Normalized Ratio (INR) or Prothrombin Time (PT) and activated Partial Thromboplastin Time (aPTT) ≤1.5 x ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

3.19a Adequate cardiac function:
- Left ventricular ejection fraction (LVEF) ≥50% as determined by multigated acquisition (MUGA) scan or echocardiogram (echo)
- QTc interval ≤480 ms

3.19b Negative serum pregnancy test done ≤7 days prior to registration, for women of childbearing potential only.

3.19c Able to swallow oral medication.

3.19d Both female and male patients of reproductive potential must agree to avoid pregnancy or impregnating a partner (respectively) while receiving drug and for 120 days after last dose of study drug. (See Section 9.0 for specific requirements).

3.19e Provide written informed consent.

3.19f Willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).

3.19g Willing to provide mandatory tissue and blood for correlative research purposes (see Sections 6, 14 and 17).

3.2 Registration – Exclusion Criteria

3.21 Any of the following because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown:
- Pregnant women
- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate contraception as defined in Section 9.0.

3.22 Receiving any other investigational agent which would be considered as a treatment for the primary neoplasm
OR
Participated in a study of an investigational agent, received study therapy or used an investigational device ≤4 weeks prior to registration

3.24 Immunocompromised patients and patients with known immunodeficiency; or receiving systemic steroid therapy or any other immunosuppressive therapy ≤7 days prior to registration.

NOTE: Inhaled steroids and low-dose corticosteroids are allowed (see Section 9.0).

3.25 History of active tuberculosis (TB), human immunodeficiency virus (HIV), active hepatitis B (e.g., HBsAg reactive) and/or active hepatitis C infection (e.g. HCV RNA qualitative is detected).

3.26 Received a live vaccine ≤30 days prior to registration.

NOTE: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

3.27 Hypersensitivity to pembrolizumab, binimetinib, or any excipients of either drug.

3.28 Prior anti-cancer therapy with a monoclonal antibody (mAb) ≤4 weeks prior to registration
OR Failure to recover (to ≤Grade1) from adverse events (AE) attributable to agents received >4 weeks prior to registration.

3.29a Prior therapy including chemotherapy, targeted small molecule therapy or radiation therapy ≤2 weeks prior to registration
OR Failure to recover (to ≤Grade1 or to baseline) from adverse events (AE) attributable to agents received >4 weeks prior to registration.

NOTE: Exception for neuropathy ≤Grade 2, which is allowed.

3.29b Any active central nervous system (CNS) lesion (i.e., those with radiographically unstable, symptomatic lesions) and/or leptomeningeal metastases.

NOTE: Patients treated with stereotactic radiotherapy or surgery are eligible if no evidence of CNS disease progression ≥4 weeks and patients must be off corticosteroid therapy for ≥3 weeks.

NOTE: Carcinomatous meningitis is excluded regardless of clinical stability.

3.29c Active autoimmune disease requiring systemic treatment in the past 2 years (i.e. use of disease modifying agents, corticosteroids or immunosuppressive drugs).

NOTE: Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

3.29d Known history of, or any evidence of active, non-infectious pneumonitis.

3.29e Active infection requiring systemic therapy.

3.29f Known history of acute or chronic pancreatitis.

3.29g History of or current evidence of retinal vein occlusion (RVO) or predisposing factors to RVO (e.g. uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes).

3.29h History of retinal degenerative disease.

3.29i History of Gilbert's syndrome.

3.29j Other active malignancy ≤3 years prior to registration.
EXCEPTIONS: Adequately treated non-melanotic skin cancer (adequate wound healing is required prior to study entry) or carcinoma-in-situ of the cervix.
NOTE: If there is a history of prior solid tumor malignancy, it must have been treated curatively with no evidence of recurrence ≤3 years prior to registration.

3.29k Impaired cardiovascular function or clinically specific cardiovascular disease including any of the following:

- History of acute coronary syndromes (including myocardial infarction unstable angina, coronary artery bypass grafting, coronary angioplasty, or stenting) ≤6 months; OR
- Symptomatic chronic heart failure history or current evidence of clinically significant cardiac arrhythmia and/or conduction abnormality <6 months prior to screening; except atrial fibrillation and paroxysmal supraventricular tachycardia.

3.29l Uncontrolled arterial hypertension defined as persistent elevation of systolic blood pressure ≥150 mmHg or diastolic blood pressure ≥100mmHg despite medical treatment.

3.29m History of neuromuscular disorders that are associated with elevated CK (e.g., inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy).

3.29n Planning to embark on a new strenuous exercise regimen after first dose of study treatment.
Note: Muscular activities, such as strenuous exercise, that can result in significant increases in plasma CK levels should be avoided while on binimetinib treatment.

3.29o Impairment of gastrointestinal function or gastrointestinal disease (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection).
NOTE: Gastric bypass is allowed.

3.29p Any other condition that would, in the Investigator's judgment, contraindicate the patient's participation in the clinical study due to safety concerns or compliance with clinical study procedures, e.g., infection/inflammation, intestinal obstruction, unable to swallow medication, social/ psychological issues, etc.

3.29q Major surgery ≤3 weeks prior to registration or failure to adequately recover from surgery.

3.29r Medical, psychiatric, cognitive or other conditions that may compromise the patient's ability to understand the patient information, give informed consent, comply with the study protocol or complete the study

3.3 Retreatment Registration – Inclusion Criteria

3.31 Treatment cannot begin prior to registering to the retreatment phase and will ideally begin ≤7 days after registration for the retreatmentphase.

3.32 Stopped initial treatment with pembrolizumab and binimetinib after attaining an investigator-determined confirmed CR according to RECIST 1.1, and:

- Was treated for at least 24 weeks with pembrolizumab and binimetinib before discontinuing therapy
- Received at least 2 cycles with pembrolizumab and binimetinib beyond the date when the initial CR was declared

OR

- Had SD, PR, or CR and stopped pembrolizumab and binimetinib treatment after 24 months of study therapy for reasons other than disease progression or intolerability

3.33 ECOG Performance Status (PS) 0 or 1 (Appendix I).

3.34 Demonstrates adequate organ fuction. The following laboratory values obtained ≤14 days prior to re-registration:

- Hemoglobin ≥9.0 g/dL (Must be ≥7 days after most recent transfusion)
- Absolute neutrophil count (ANC) ≥1500/mm^3 or ≥1.5 X 10^9/L
- Platelet count ≥100,000/mm^3 or ≥100 X 10^9/L (Must be ≥7 days after most recent transfusion)
- Total bilirubin ≤1.5 x upper limit of normal (ULN)
- Aspartate transaminase (AST) and alanine transaminase (ALT) ≤2.5 x ULN or ≤5 x ULN for patients with liver metastases
- Creatinine ≤1.5 x ULN
  OR
- Calculated creatinine clearance must be ≥50 ml/min using the Cockcroft-Gault formula below:

Cockcroft-Gault Equation:

Creatinine clearance for males = $\frac{(140 - age)(weight\ in\ kg)}{(72)(serum\ creatinine\ in\ mg/dL)}$

Creatinine clearance for females = $\frac{(140 - age)(weight\ in\ kg)(0.85)}{(72)(serum\ creatinine\ in\ mg/dL)}$

International Normalized Ratio (INR) or Prothrombin Time (PT) and activated Partial Thromboplastin Time (aPTT) ≤1.5 x ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

3.35 Females of childbearing potential should have a negative serum or urine pregnancy test ≤72 hours prior to re-registration.

3.36 Females or males of childbearing potential must be willing to use adequate methods of contraception as outline in section 9.9b or abstain from heterosexual activity for the course of th study through 120 days after last dose of study medication.

3.37 Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab and binimetinib.

3.4 Retreatment Registration – Exclusion Criteria

3.41 Received any type anti-cancer treatment since the last dose of pembrolizumab

3.42 History or current evidence of any condition, therapy, or laboratory abnormality that might interfere with subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

4.0 Study Calendar

4.1 Test Schedule for Breast Cancer[1]

			Active Treatment							End of Treatment	Post-Treatment
Tests and procedures	≤28 days prior to registration	≤14 days prior to registration	Pre-Tx biopsy	Cycle 1 binimetinib alone	Cycles 2-3 with pembro: Prior to C2 D1	Cycles 2-3 with pembro: Prior to C3 D1	Cycles 4-8: Prior to Day 1	Cycle 9: Prior to Day 1	Cycle 10 and beyond	At time of disease progression	Safety follow up: 30 days post-discontinuation
Window					±3 days	±3 days	±3 days	±3 days	±3 days	±7 days	±7 days
Clinical Procedures											
History and exam[12], vital signs (temp, BP, heart rate), weight, ECOG PS	X				X	X	X	X	X	X	X
Height	X										
Concomitant medications	X				X	X	X	X	X		X
Pregnancy test[2]		X[2]									
Hematology: CBC/diff with PLT		X			X	X	X	X	X		X
Chemistry Panel[3]		X			X	X	X	X	X		X
CA15-3		X			X	X	X	X	X		X
Creatine Kinase (CK/CPK), troponin T[4,R]		X			X	X	X	X	X		X
Urinalysis		X			X	X	X	X	X		X
Coagulation INR (PT), PTT		X									
Total T3, Free T4, TSH[R]		X			X	X	X	X	X		X
Tumor measurement by CT or MRI[5]	X						X				
Bone scan (only if clinically indicated)	X										

*Retreatment Phase-Patients entering the study for retreatment will follow the test and procedures as indicated in the study calendar for Cycle 2 and beyond. Labs and blood forms are not required to be entered into RAVE during the Retreatment Phase.

[1] All tests and procedures are clinically indicated, unless noted with an R to indicate funding by research

[2] For women of childbearing potential only: Serum βHCG must be done ≤7 days prior to registration, and if necessary, again ≤72 hours prior to Cycle 1, Day 1

[3] AST (SGOT), ALT (SGPT), alkaline phosphatase, total bilirubin (direct if TBili is elevated), BUN, creatinine with calculated creatinine clearance, albumin, total protein, uric acid, bicarbonate, calcium, chloride, glucose, LDH, magnesium, phosphorus, potassium, sodium

[4] Follow up for total creatine kinase (CK/CPK) ≥3 X ULN will include weekly assessment of isoenzymes and myoglobin in blood/or urine, and troponin T as applicable

[5] Every 12-16 weeks after Cycle 4 during active treatment (per the treating physician's discretion). Same method should be used throughout the study. Note: PET/CT is not allowed as CT portion of PET/CT is not adequate for RECIST.

			Active Treatment							End of Treatment	Post-Treatment
Tests and procedures	≤28 days prior to registration	≤14 days prior to registration	Pre-Tx biopsy	Cycle 1 binimetinib alone	Cycles 2-3 with pembro: Prior to C2 D1	Cycles 2-3 with pembro: Prior to C3 D1	Cycles 4-8: Prior to Day 1	Cycle 9: Prior to Day 1	Cycle 10 and beyond	At time of disease progression	Safety follow up: 30 days post-discontinuation
Window					±3 days	±3 days	±3 days	±3 days	±3 days	±7 days	±7 days
ECG, 12 lead, triplicate[R]	X					X					
Echocardiogram (ECHO)[6] – limited, LVEF only	X				X[6]		X[6]		X[6]		X
Full ophthalmic evaluation [7]	X					X[7]	X[7]		X[7]		X
Adverse event assessment	X			X	X	X	X	X	X	X	X
Research Blood and Tissue- Analysis											
Blood for correlative research [8,R] (See Section 14.0)			X		X	X		X			X
Mandatory tissue sample (see Section 17.0) [9,10,R]			X								
Optional follow up tissue sample(see Section 17.0)[11,R]					X					X	

[6] Echocardiogram will be performed at baseline, on Cycle 2 Day 1, and Cycle 5 Day 1, then every 12 weeks to determine cardiac ejection fraction in patients who continue on binimetinib. Follow-up echocardiogram is not required in patients who discontinue binimetinib.

[7] Full ophthalmic examination will be performed at baseline, at Cycle 3 Day 1 ± 7 days, and then every 12 weeks ± 7 days in patients who continue on binimetinib. Follow-up ophthalmic examination is not required in patients who discontinue binimetinib. Full ophthalmic examination includes best corrected visual acuity, slit lamp examination, intraocular pressure, dilated fundoscopy and Ocular Coherence Tomography (OCT). Examination of the retina is required, especially to identify findings associated with serous retinopathy and RVO. For patients with clinical suspicion of retinal abnormalities of any grade (e.g., serous retinopathy, RVO, photopsia, metamorphopsia, impairment of visual acuity), these additional assessments should be mandatory:

- For non-vasclular abnormalities: spectral domain OCT recommended
- For Vascular abnormalities: fluorescein angiography of central 30 degrees.

[8] Whole blood samples for correlative research will be collected at the following timepoints: Baseline, 2nd week of binimetinib prior to starting pembrolizumab, After 1 cycle of bini and pembro at Cycle 3, Cycle 9, Day 1 (only if >6 months of stable disease/CR/PR), and at the end of therapy (i.e., ≤4 weeks after final administered dose of therapy), or at the time of tumor recurrence.

[9] Submission of tissue from the primary or metastatic tumor is mandatory

[10] Mandatory tumor biopsy except in patients who have adequate tumor tissue samples collected ≤90 days prior to registration. Adequate sample is defined as core needle, punch, or incisional biopsy samples that can provide ≥10 unstained sections of 5 υM thickness. Fine needle aspiration (FNA) sample alone is not sufficient.

[11] An optional newly-obtained core or excisional biopsy (FNA not adequate) is requested after 10 days of binimetinib prior to starting pembrolizumab and at the end of treatment for any reason.

[12] Physical exam includes gross perimeter test. After baseline, patients receiving binimetinib should be assessed at every physical examination for decreased

			Active Treatment							End of Treatment	Post-Treatment
Tests and procedures	≤28 days prior to registration	≤14 days prior to registration	Pre-Tx biopsy	Cycle 1 binimetinib alone	Cycles 2-3 with pembro: Prior to C2 D1	Cycles 2-3 with pembro: Prior to C3 D1	Cycles 4-8: Prior to Day 1	Cycle 9: Prior to Day 1	Cycle 10 and beyond	At time of disease progression	Safety follow up: 30 days post-discontinuation
Window					±3 days	±3 days	±3 days	±3 days	±3 days	±7 days	±7 days
Patient Medication Diary (See Appendix II)				X		X	X	X	X	X	

visual acuity using a gross perimetry test (as opposed to automated visual field testing). Symptomatic patients should be referred for a full ophthalmic consultation.

4.2 Event Monitoring/Survival Follow-up

	Event Monitoring Phase[1]				
	q. 3 months until PD	At PD	After PD q. 6 months	Death	New Primary
Event Monitoring	X	X	X	X	At each occurrence

1. If a patient is still alive 3 years after registration, no further follow-up is required.

5.0 Grouping Factor

Phase I vs. Phase II

6.0 Registration Procedures

6.1 Phase I Registration

Prior to discussing protocol entry with the patient, call the MCCC Registration Office [redacted] for dose level and to insure that a place on the protocol is open to the patient.

6.11 Registration

To register a patient, fax [redacted] a completed eligibility checklist to the Mayo Clinic Cancer Center (MCCC) Registration Office between 8 a.m. and 4:30 p.m. central time Monday through Friday.

6.12 Prior to accepting the registration, the registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient pre registration eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.13 Registration tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.2 Phase II Registration

6.21 Registration

To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the remote registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the MCCC Registration Office at [redacted] between the hours of 8 a.m. and 5:00 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the MCCC web page [redacted] and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and a MCCC

subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the MCCC Registration Office [redacted] If the patient was fully registered, the MCCC Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

6.22 Verification

Prior to accepting the registration, registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information
- Grouping factor

6.3 Both Phase I and Phase II

6.31 Documentation of IRB approval

Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office [redacted] If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

6.32 Correlative studies

6.321 Mandatory correlative studies

A mandatory correlative component is part of this study. The patient will be automatically registered onto this component (see Section 3.1 and 17.0).

6.322 Optional correlative studies

An optional correlative component is part of this study. At the time of registration, the following will be recorded:

- Patient has/has not given permission to store and use his/her sample(s) for future research of breast cancer at Mayo.
- Patient has/has not given permission to store and use his/her sample(s) for future research to learn, prevent, or treat other health problems.
- Patient has/has not given permission for MCCC to give his/her sample(s) to researchers at other institutions.

6.33 Treatment on protocol

Treatment on this protocol must commence at Mayo Clinic under the supervision of a medical oncologist.

6.34 Treatment start

Treatment cannot begin prior to registration and must begin ≤14 days after registration.

6.35 Pretreatment

Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.36 Baseline symptoms

All required baseline symptoms (see Section 10.6) must be documented and graded.

6.37 Study drug availability

Study drug is available on site for this patient.

6.38 Retreatment Registration

6.38a To register a patient, fax [redacted] a completed retreatment eligibility checklist to the Mayo Clinic Cancer Center (MCCC) Registration Office between 8 a.m. and 4:30 p.m. central time Monday through Friday.

6.38b Treatment cannot begin prior to registration to the retreatment phase and will begin ≤7 days after registration for the retreatment phase.

7.0 Protocol Treatment

7.1 Treatment Schedule

7.11 Phase I treatment medication tables

Cycle 1:

Agent	Dose Level	Route	Day
Binimetinib	As assigned by Registration Office	PO BID	1-14

Cycle 2 and all subsequent cycles:

Agent	Dose Level	Route	Day	ReRx
Binimetinib	As assigned by Registration Office	PO BID	1-21	q3w
Pembrolizumab	200 mg	IV	1	q3w

7.12 Phase II treatment medication tables

Cycle 1:

Agent	Dose Level	Route	Day
Binimetinib	As determined by Phase I	PO BID	1-14

Cycle 2 and all subsequent cycles:

Agent	Dose Level	Route	Day	ReRx
Binimetinib	As determined by Phase I	PO BID	1-21	q3w
Pembrolizumab	200 mg	IV	1	q3w

7.13 Treatment Plan

All trial treatments will be administered on an outpatient basis.

In Cycle 1, patients will receive binimetinib for 2 weeks followed by blood draw and optional tumor biopsy to evaluate the effects of binimetinib single agent on immune system and tumors prior to starting pembrolizumab in Cycle 2 and every subsequent cycle.

7.14 Pembrolizumab

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed. Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

Pembrolizumab at the fixed dose of 200 mg will be administered as a 30 minute IV infusion once every 3 weeks. Every effort should be made to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

7.15 Binimetinib

Binimetinib is an oral medication. Binimetinib will be administered by patients twice daily on a continuous basis.

Given that food-effect clinical studies have shown influence of food on PK of binimetinib is mild and not clinically relevant (see binimetinib Investigator Brochure), binimetinib can be taken with food.

7.2 Return to consenting institution

For this protocol, the patient must return to the consenting institution for evaluation at least every 21 days during treatment (Active Monitoring Phase).

7.3 Treatment by local medical doctor (LMD)

Treatment by a local medical doctor (LMD) is not allowed.

7.4 Phase I – determination of Maximum Tolerated Dose (MTD)

7.41 Dose De-Escalation

Dose level	Pembrolizumab**	Binimetinib
-2	200 mg IV q3w	15 mg PO twice daily
-1	200 mg IV q3w	30 mg PO twice daily
0*	200 mg IV q3w	45 mg PO twice daily

***starting dose level**

**NOTE: There are no dose modifications for pembrolizumab

If dose level -1 does not meet MTD determination, the study will be stopped and evaluated by the principal investigator and the industry partners to determine an appropriate dose level.

7.411 Treatment by a local medical doctor is not allowed.

7.412 Three patients will be treated at each dose level and observed for a minimum of 21 days after start of pembrolizumab, to assess toxicities, before new patients are treated. Doses will not be escalated in any individual patient. Decisions on when and how to enroll patients at each dose level are described in Section 16.42.

7.413 Investigators are to contact the Study Chair as soon as any dose-limiting toxicity (DLT) occurs.

7.42 Definitions of DLT

7.421 For this protocol, DLT will be defined as follows for Cycle 2 only:

CTCAE SOC/AE*	**Definition (CTCAE Grade)**
Blood and lymphatic system disorders • Febrile neutropenia	Grade 4
Eye disorders • Blurred vision • Flashing lights • Floaters	≥Grade 3
Eye disorders • Retinopathy	Grade 2 lasting >14 consecutive days confirmed by ophthalmic examination Or Grade 3
Eye disorders • Retinal vascular disorder	Any grade confirmed by ophthalmic examination

CTCAE SOC/AE*	Definition (CTCAE Grade)
Eye disorders • Eye disorders, Other specify	Any visual event ≥Grade 3 confirmed by ophthalmic examination
Investigations • Alanine aminotransferase increased OR • Aspartate aminotransferase increased	≥Grade 3
Investigations • Blood bilirubin increased	≥Grade 3
Investigations • CPK increased	≥Grade 3 associated with an increase in creatinine ≥1.5 times patient's baseline (screening) creatinine level
Investigations • Creatinine increased	≥Grade 3
Investigations • Ejection fraction decreased	≥Grade 3 Or Absolute decrease of LVEF >10% compared to Baseline and is below the institution's LLN
Investigations • Electrocardiogram QT corrected interval prolonged	≥Grade 3 on at least two separate ECGs
Investigations • Neutrophil count decreased	Grade 4 lasting >7 consecutive days
Investigations • Platelet count decreased	Grade 3 with signs of clinically significant bleeding Or Grade 4
Gastrointestinal disorders • Diarrhea	≥Grade 3 for ≥48 hours despite optimal anti-diarrheal therapy Or Grade 4
Gastrointestinal disorders • Nausea • Vomiting	Grade 3 for ≥48 hours despite optimal anti-emetic therapy Or Grade 4
General disorders and administration site conditions • Fatigue	Grade 3 lasting >14 consecutive days
Skin and subcutaneous tissue disorders • Rash maculo-papular • Palmar-plantar erythrodysesthesia syndrome • Photosensitivity	Grade 3 lasting >14 consecutive days despite maximal skin toxicity treatment per local practice Or Grade 4
Vascular disorders • Hypertension	Grade 3 lasting >14 consecutive days Or Grade 4
Other events**	Any ≥Grade 3

*Adverse event at least possibly related to the study medication.
** Lymphocyte count decreased ≥Grade 3 (unless clinically significant) and Grade 3 alopecia will not be considered a DLT

7.5 Retreatment (Second Course Phase)

Patients who stop pembrolizumab and binimetinib with SD or better may be eligible for up to one year of additional pembrolizumab and binimetinib therapy if they progress after

stopping study treatment. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the patient meets the following conditions:

EITHER

- Stopped initial treatment with pembrolizumab and binimetinib after attaining an investigator-determined confirmed CR according to RECIST 1.1, and
    - Was treated for at least 24 weeks with pembrolizumab and binimetinib before discontinuing therapy
    - Received at least two cycles with pembrolizumab and binimetinib beyond the date when the initial CR was declared

OR

- Had SD, PR or CR and stopped pembrolizumab and binimetinib treatment after 24 months of study therapy for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab and binimetinib
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab and binimetinib
- Has a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrates adequate organ function (as required for initial eligibility in Section 3.0)
- Females of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication
- Females or males of childbearing potential must be willing to use adequate methods of contraception as outlined in Section 9.9b or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication.
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

Baseline procedures as outlined in the pretrial screening should be repeated ≤28 days prior to retreatment.

Patients who restart treatment will be retreated at the same dose and dose interval as when they last received pembrolizumab and binimetinib. Patients may continue treatment for up to one additional year and will follow the original treatment schedule starting at cycle 2.

8.0 Dosage Modification Based on Adverse Events

Strictly follow the modifications in this table for the first **two** cycles, until individual treatment tolerance can be ascertained. Thereafter, these modifications should be regarded as guidelines to produce mild-to-moderate, but not debilitating, side effects. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

→***ALERT:*** ***ADR reporting may be required for some adverse events (See Section 10.0)***←

** Use the following to describe actions in the Action column:

- Omit = Treatment is not given for this cycle
- Hold/Delay = Treatment can be made up as part of this cycle
- Discontinue = Treatment is totally stopped

NOTE: If the patient experiences a significant adverse event requiring a dose reduction at the start of the next cycle, then the dose will remain lowered.

8.1 Dose Levels (Based on Adverse Events in Table 8.2)

Dose Level	Binimetinib
0*	45 mg BID
-1	30 mg BID
-2	15 mg BID
-3	Discontinue

*Dose level 0 refers to the starting dose.

NOTE: If binimetinib is discontinued, the patient can continue treatment on single-agent pembrolizumab. The patient will continue to follow the test schedule (Section 4.1)

For binimetinib, if dose reduction goes below -2 dose level, then binimetinib must be discontinued. If binimetinib is started at -2 dose level, then there are no further dose reductions.

NOTE: There are no dose changes for pembrolizumab, only dose schedule modifications.

For patients who do not tolerate the 45 mg BID dosing schedule, dose adjustment to 30 mg BID is permitted in order to allow the patient to continue on study drug. The following guidelines need to be applied and these changes must be recorded on the on the specific section of the patient record.

A dose reduction below 15 mg BID is not allowed. Dose interruptions of more than 21 days are not allowed.

Missed/skipped doses will not be made up (i.e. the patient should not double their dose if the previous dose was missed). When the adverse event that resulted in a dose reduction improves to and remains stable at Grade 1 or less for a minimum of 21 days, the dose can be re-escalated at the investigators discretion provided there are no other concomitant adverse events.

No dose re-escalation is allowed after dose reduction due to left ventricular dysfunction or prolonged QTcF >500 msec.

Dose reduction/interruption/discontinuation decisions should be based on the CTCAE grade of the adverse event (AE) and the guidelines provided below. In general, doses should not be reduced or interrupted for Grade 1 events, but treatment to control symptoms should be provided as appropriate. All AEs should be followed weekly or as clinically appropriate until stabilization or resolution.

A patient with a Grade 4 AE may resume treatment at the lower dose level if the AE recovers to grade ≤1 within 21 days of interrupting drug and, if in the opinion of the Investigator and Medical Monitor, the event is not life-threatening, and the patient can be managed and monitored for recurrence of AE. Dose interruptions of more than 21 days are not allowed unless approved by the Investigator, and the Pfizer Inc. (formerly Array Biopharma LLC and Array Biopharma Inc.) Medical Monitor or designee.

Please refer to the table below for dose adjustment recommendations for binimetinib-induced adverse events.

For adverse events that can be attributed to either pembrolizumab or binimetinib, dose adjustment for both agents will be applied. These toxicities include but are not limited to diarrhea and liver function abnormalities.

→ → ***Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) current version 4.0* unless otherwise specified*** ← ←

* Located at http:/ctep.cancer.gov/protocolDevelopment/electronic_applications.ctc.htm

8.2 Dose Modifications for Binimetinib

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	Grade	ACTION FOR BINIMETINIB[C]
Cardiac disorders	Left ventricular systolic dysfunction	Grade 1-2 Asymptomatic absolute decrease of >10% compared to baseline and below institutional LLN	Hold binimetinib and repeat evaluation of LVEF within 2 weeks: o If the LVEF recovers (defined as LVEF ≥50% or ≥LLN and absolute decrease ≤10% compared to Baseline) in ≤21 days, reduce 1 dose level after approval of the Principal Investigator. Monitor LVEF 2 weeks after resuming binimetinib, every 4 weeks for 12 weeks and subsequently as per protocol o If the LVEF does not recover in ≤21 days, permanently discontinue binimetinib. Closely monitor LVEF until resolution or for up to 16 weeks No dose re-escalation allowed after dose reduction for LVEF
Eye disorders[a,b]	Retinal detachment	Grade 1	Maintain dose level of binimetinib and increase frequency of ophthalmic monitoring to at least every 14 days until stabilization or resolution
		Grade 2	Maintain dose level of binimetinib and refer the patient to ophthalmologist within 1 week: o If resolved to Grade ≤1 in ≤21 days, maintain dose of binimetinib o If not resolved to Grade ≤1 in ≤21 days, reduce 1 dose level of binimetinib or maintain dose of binimetinib based upon the Investigator's discretion after consultation with the ophthalmologist
		Grade 3	Hold binimetinib and refer the patient to ophthalmologist within 1 week: o If resolved to Grade ≤1 in ≤21 days, reduce 1 dose level of binimetinib o If not resolved to Grade ≤1 in ≤21 days, permanently discontinue binimetinib and close follow-up with ophthalmic monitoring until stabilization or resolution
		Grade 4	Permanently discontinue binimetinib and immediate follow-up with ophthalmic monitoring until stabilization or resolution
	Retinal vascular disorder (RVO)	Any	Permanently discontinue binimetinib and immediate follow-up with ophthalmic monitoring until stabilization or resolution
	Eye disorders – Other specify – any non-retinal events	Grade 1-2	Maintain dose level of binimetinib and increase frequency of ophthalmic monitoring to at least every 14 days until stabilization or resolution

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	Grade	ACTION FOR BINIMETINIB[C]
Eye disorders[a,b]	Eye disorders – Other specify – any non-retinal events	Grade 3	Hold binimetinib and refer patient to ophthalmologist within 1 week: o If resolved to Grade ≤1 in ≤21 days, reduce 1 dose level of binimetinib o If not resolved to Grade ≤1 in ≤21 days, permanently discontinue binimetinib and close follow-up with ophthalmic monitoring until stabilization or resolution
		Grade 4	Permanently discontinue binimetinib and immediate follow-up with ophthalmic monitoring until stabilization or resolution
Gastrointestinal disorders	Diarrhea	Grade 1-2 Uncomplicated	Consider temporary hold of binimetinib until resolved to Grade ≤1 Resume binimetinib at current dose level
		Grade 1-2 Complicated	Temporarily hold binimetinib until resolved to Grade ≤1 Resume binimetinib at 1 reduced dose level
		Grade 3	Temporarily hold binimetinib until resolved to Grade ≤1 Resume binimetinib at 1 reduced dose level
		Grade 4	Temporarily hold binimetinib until resolved to Grade ≤1 Resume binimetinib at 1 reduced dose level
Investigations	Alanine aminotransferase increased (ALT) OR Aspartate aminotransferase increased (AST)	Grade 1	Maintain dose level of binimetinib
	Alanine aminotransferase increased (ALT) OR Aspartate aminotransferase increased (AST) AND Blood bilirubin increased	Grade 2 *For patients with Baseline ALT/AST values ≤ULN:* ALT or AST >3.0 to 5.0 × ULN and blood bilirubin (total) ≤2.0 × ULN	Hold binimetinib until resolved to Grade ≤1, then: o If resolved in ≤14 days, maintain dose level of binimetinib o If not resolved in ≤14 days, reduce 1 dose level of binimetinib

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	Grade	ACTION FOR BINIMETINIB[C]
Investigations	Alanine aminotransferase increased (ALT) OR Aspartate aminotransferase increased (AST) AND Blood bilirubin increased	Grade 2 *For patients with liver metastases or ALT/AST Baseline values >ULN:* ALT or AST 3 × Baseline value to 5.0 × ULN and blood bilirubin (total) ≤2.0 × ULN	Hold binimetinib until resolved to Grade ≤2, then: o If resolved in ≤14 days, maintain dose level of binimetinib o If not resolved in ≤14 days, reduce 1 dose level of binimetinib
		Grade 2 *For all patients:* ALT or AST >3.0 to 5.0 × ULN and blood bilirubin (total) >2.0 × ULN	Hold binimetinib until resolved to Grade ≤1, then: o If resolved in ≤7 days, reduce 1 dose level of binimetinib o If not resolved in ≤7 days, permanently discontinue binimetinib
	Alanine aminotransferase increased (ALT) OR Aspartate aminotransferase increased (AST) AND Blood bilirubin increased	Grade 3 ALT or AST >5.0 to 8.0 × ULN and blood bilirubin (total) ≤2.0 × ULN	Hold binimetinib until resolved to Grade ≤1 (Grade ≤2 in case of liver metastases) then: o If resolved in ≤14 days, maintain dose level of binimetinib o If not resolved in ≤14 days, reduce 1 dose level of binimetinib
		Grade 3 ALT or AST >8.0 ×ULN and blood bilirubin (total) ≤2.0 × ULN	Permanently discontinue binimetinib

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	Grade	ACTION FOR BINIMETINIB[C]
Investigations	Alanine aminotransferase increased (ALT) OR Aspartate aminotransferase increased (AST) AND Blood bilirubin increased	Grade 3 ALT or AST >5.0 ×ULN and blood bilirubin (total) >2.0 × ULN	Permanently discontinue binimetinib
	Alanine aminotransferase increased (ALT) OR Aspartate aminotransferase increased (AST)	Grade 4 >20.0 × ULN	Permanently discontinue binimetinib
	CPK increased	Grade 1-2	Maintain dose level of binimetinib o If total CK ≥3 × ULN, measure CK, CK isoenzymes and myoglobin in blood or urine weekly for 3 weeks and if total CK remains ≤Grade 2, continue to assess CK, CK isoenzymes and myoglobin along with regularly scheduled clinical chemistry assessments
		Grade 3 >5.0 to 10.0 × ULN	If asymptomatic, maintain dose of binimetinib and monitor closely o Measure CK, CK isoenzymes and myoglobin in blood or urine weekly for 3 weeks and if total CK remains ≤Grade 3, continue to assess CK, CK isoenzymes and myoglobin along with regularly scheduled clinical chemistry assessments If symptomatic (muscle pain/spasms), interrupt binimetinib until resolved to Grade ≤1 and monitor closely, then: o If resolved in ≤21 days, reduce 1 dose level of binimetinib o If not resolved in ≤21 days, permanently discontinue binimetinib

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	Grade	ACTION FOR BINIMETINIB[C]
Investigations	CPK increased	Grade 4	If asymptomatic, interrupt binimetinib until resolved to Grade ≤1 and monitor closely, then: o If resolved in ≤21 days, reduce 1 dose level of binimetinib o If not resolved in ≤21 days, permanently discontinue binimetinib If symptomatic, permanently discontinue binimetinib
	Electrocardiogram QT corrected interval prolonged	Grade 3 mean triplicate QTcF≥501 msec (confirmed by a separate mean triplicate ECG)	First Occurrence: o Interrupt binimetinib. Electrolyte abnormalities (if applicable) should be corrected and any concomitant medication that could potentially prolong QT should be discontinued o Monitor patient until resolution of the AE. Include a consultation with a cardiologist, if indicated o Once resolved to Grade ≤1, resume binimetinib at 1 reduced dose level Second Occurrence: o If second occurrence is attributed to binimetinib, permanently discontinue binimetinib No dose re-escalation after dose reduction due to QTcF>500msec
Skin and subcutaneous tissue disorders	Rash acneiform or Rash maculo-papular	Grade 1	Maintain dose level of binimetinib Initiate Initial Rash Treatment Regimen (Section 9.9f) if it was not already started and rash should be closely monitored
		Grade 2	First Occurrence: o Maintain dose level of binimetinib and rash should be closely monitored o Initiate Initial Rash Treatment if it was not already started o Reassess within ≤14 days. If rash worsens or does not improve, interrupt binimetinib until resolved to Grade ≤1. Resume binimetinib at current dose level Second Occurrence: o Reassess within ≤14 days. If rash worsens or does not improve, interrupt binimetinib until resolved to Grade ≤1. Resume binimetinib at 1 reduced dose level

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	Grade	ACTION FOR BINIMETINIB[C]
Skin and subcutaneous tissue disorders	Rash acneiform or Rash maculo-papular	Grade 3	First Occurrence: o Interrupt binimetinib until resolved to Grade ≤1 Reassess weekly; Resume binimetinib at current dose level o Consider referral to dermatologist and manage rash per dermatologist's recommendation Second Occurrence: o Interrupt binimetinib until resolved to Grade ≤1 Reassess weekly; Resume binimetinib at 1 reduced dose level o Consider referral to dermatologist and manage rash per dermatologist's recommendation
		Grade 4	Permanently discontinue binimetinib
Vascular disorders	Thromboembolic event	Grade 3	Withhold binimetinib for up to 3 weeks. • If improved to Grade 0 or 1, resume at reduced dose. • If not improved, permanently discontinue
		Grade 4	Permanently discontinue binimetinib
All other events	Related to binimetinib treatment	Grade 1-2	• If the event is Grade 1 or non-persistent Grade 2, maintain dose level of binimetinib and monitor until stabilization or resolution • If the event is a persistent Grade 2 AE not responsive to a specific therapy, consider binimetinib dose interruption or reduction
		Grade 3	Interrupt binimetinib until resolved to ≤Grade 1 or to pretreatment/Baseline level If the event resolves ≤21 days, then binimetinib may be resumed at 1 reduced dose level based upon the Investigator's discretion
		Grade 4	Permanently discontinue binimetinib

[a] Further evaluation with specialized retinal imaging (e.g., OCT [spectral domain OCT recommended] of the macula for non-vascular abnormalities; and color fundus photography of the central 30 degrees and/or fluorescein angiography for vascular abnormalities) is recommended.

[b] Images/results of the ophthalmic examinations (at a minimum, OCT, color fundus photography and/or fluorescein angiography) must be made available upon Sponsor request.

[c] If binimetinib is discontinued, patient can continue on single-agent pembrolizumab.

8.3 Dose Modifications for Pembrolizumab

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per the Table below. See Section 9.0 for supportive care guidelines, including use of corticosteroids.

Table 8.31 Dose Modification Guidelines for Drug-Related Adverse Events for Pembrolizumab

CTCAE System/Organ/Class (SOC)	Adverse Event	Hold Treatment for Grade	Timing for Restarting Treatment	Treatment Discontinuation
Gastrointestinal disorders	Diarrhea or Colitis	2-3	AE resolves to Grade 0-1	AE does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10mg or less of prednisone or equivalent per day within 12 weeks
		4	Permanently discontinue	Permanently discontinue
Investigations	AST, or ALT, or Blood bilirubin increased	2	AE resolves to Grade 0-1	AE does not resolve within 12 weeks of last dose.
		3-4	Permanently discontinue (see exception below)[a]	Permanently discontinue
Metabolism and nutrition disorders	Glucose intolerance (Type 1 diabetes mellitus [if new onset]) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure	Resume pembrolizumab when patients are clinically and metabolically stable.
Endocrine disorders	Endocrine disorders – Other, specify: Hypophysitis	2-4	AE resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	AE does not resolve within 12 weeks of last dose or inability to reduce cortico-steroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
Endocrine disorders	Hyperthyroidism	3	AE resolves to Grade 0-1	AE does not resolve within 12 weeks of last dose or inability to reduce cortico-steroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
		4	Permanently discontinue	Permanently discontinue
Endocrine disorders	Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted

CTCAE System/Organ/Class (SOC)	Adverse Event	Hold Treatment for Grade	Timing for Restarting Treatment	Treatment Discontinuation
General disorders and administration site conditions	Infusion related reaction	2[b]	AE resolves to Grade 0-1	Permanently discontinue if AE develops despite adequate premedication
		3-4	Permanently discontinue	Permanently discontinue
Respiratory, thoracic and mediastinal disorders	Pneumonitis	2	AE resolves to Grade 0-1	AE does not resolve within 12 weeks of last dose or inability to reduce cortico-steroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
		3-4	Permanently discontinue	Permanently discontinue
Renal and urinary disorders	Acute kidney injury or Chronic kidney disease (e g Renal failure or Nephritis)	2	AE resolves to Grade 0-1	AE does not resolve within 12 weeks of last dose or inability to reduce cortico-steroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
		3-4	Permanently discontinue	Permanently discontinue
	All Other Drug-Related Adverse Events[c]	3 or severe	AE resolves to Grade 0-1	AE does not resolve within 12 weeks of last dose or inability to reduce cortico-steroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
		4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.

[a] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.

[b] If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose.

[c] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

8.32 Other instructions for pembrolizumab

If pembrolizumab-related toxicity does not resolve to Grade 0-1 within 12 weeks after last administration of study drug, study therapy discontinuation is recommended. With Investigator agreement, patients with a laboratory adverse event still at Grade 2 may continue in the study only if asymptomatic and controlled.

In patients who continue on study therapy after experiencing an Adverse Event warranting potential dose modification, if considered drug-related by the investigator, once the patient has recovered to Grade 0-1 the dosing interval in

subsequent cycles will be increased by 1 week (e.g., to 3 weeks in patients who were on an every 2-week schedule). Following each such dose delay due to toxicity, the dosing interval should increase by an additional week. For example, patients who began the study on a 3-week dosing schedule, and have stopped drug twice for due to a drug-related toxicity that meets the above criteria, should now be dosing every 5 weeks.

For patients who experience a recurrence of the same severe AEs listed above with rechallenge of pembrolizumab, a consultation with the Investigator will occur to determine whether the patient should continue in the study. A patient who experiences the same SAE of the same NCI CTCAE grade or higher with rechallenge of pembrolizumab must discontinue pembrolizumab immediately.

Reduced dose of pembrolizumab dose (ie, below 200 mg) will not be administered.

9.0 Ancillary Treatment/Supportive Care

9.1 Full supportive care

Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti - inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 8.2 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

9.2 Blood products and growth factors

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology (ASCO) Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline. J Clin Oncol 2006; 24:3187-3205, 2006.

9.21 Neutropenia

Prophylactic use of colony-stimulating factors including Granulocyte Colony-Stimulating Factor (G-CSF), pegylated G-CSF or Granulocyte Macrophage Colony-Stimulating Factor GM-CSF is not allowed in this study. Therapeutic use of G-CSF is allowed in patients with Grade 3-4 febrile neutropenia.

9.22 Anemia

Transfusions and/or erythropoietin may be utilized as clinically indicated for the treatment of anemia, but should be clearly noted as concurrent medications.

9.23 Thrombocytopenia

Transfusion of platelets may be used if clinically indicated. ITP should be ruled out before initiation of platelet transfusion.

9.3 Antiemetics

Antiemetics may be used at the discretion of the attending physician. Nausea and vomiting should be treated aggressively, and consideration should be given to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake. Volume depletion should be corrected before initiation of study drug.

9.4 Anti-Diarrheals

Patients should be monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered. (See Section 9.5 and 9.9a for management of treatment-related enterocolitis)

All patients who experience diarrhea 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.

NOTE: Loperamide/diphenoxylate/atropines should NOT be used for diarrhea symptoms unless: (1) it is believed that pembrolizumab-related enterocolitis is unlikely to be present after detailed evaluation by gastroenterology, including endoscopy; PLUS (2) approval is documented by a gastroenterology specialist.

9.5 Management of treatment related enterocolitis

In patients with severe enterocolitis, pembrolizumab will be held and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.

In patients with moderate enterocolitis, pembrolizumab should be withheld and antidiarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (e.g., 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.

9.6 Anti-infectives

Patients with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating Investigator for a given infectious condition, according to standard institutional practice.

9.7 Corticosteroids

Patients requiring chronic steroid administration (excluding inhaled steroids).are excluded from the trial. Patients may continue on inhalation therapy. Corticosteroids are known immunosuppressive agents that can mitigate the effects of pembrolizumab. Steroids should be generally reserved to treat side effects of pembrolizumab. Steroids can be used as primary prevention of nausea per institutional guidelines, but steroid doses should be reduced in subsequent cycles if nausea/vomiting is absent or very mild (see Section 9.3).

9.8 Concomitant medications

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

9.81 Acceptable concomitant medications

All treatments that the investigator considers necessary for a subject’s welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the baseline case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If

changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded in the patient medical record. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs.

9.82 Permitted concomitant medications requiring caution for binimetinib

Binimetinib potently inhibits CYP2B6 (Ki of 1.67 μM). Based on these in vitro findings, binimetinib may inhibit the metabolic clearance of co-medications metabolized by CYP2B6, if sufficiently high concentrations are achieved in vivo. At 45 mg BID, the maximum concentrations achieved in plasma are normally <1.5 μM so the risk of drug interaction is limited. Caution should be used in patients receiving concomitant treatment with other drugs that are substrates of this enzyme.

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

Binimetinib has been identified to be primarily metabolized by UGT1A1 in vitro. It is advised that inhibitors and inducers of UGT1A1 should be taken with caution when co-administered with binimetinib. Patients should be closely monitored for the occurrence of adverse events. Please refer to the table below for a list of these known drugs but this list may not be exhaustive.

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

The solubility of binimetinib is pH dependent and a 10-fold decrease in solubility is observed between pH 1 and 2. Patients receiving concomitant treatments that could potentially modify the gastric pH (i.e. PPI) should be instructed to take them at least two hours after the administration of binimetinib.

Drugs with a conditional, possible, or known risk to induce Torsade de Pointes (TdP) should be used with caution. Patients receiving such medications must be carefully monitored for potentiating of toxicity due to any individual concomitant medication, and may require dose titration of the drug substance. Investigators should use caution when prescribing co-medications, as clinical experience with these compounds in patients with cancer is often limited.

See Appendix III for list of medications to be used with caution with used with binimetinib.

9.83 Prohibited concomitant medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab

- Radiation therapy
  - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids (e.g. equivalent to or less than oral prednisone 10 mg daily) is allowed and do not require Sponsor approval.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

The exclusion criteria describe other medications, which are prohibited in this trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

9.9 a Immunotherapy-related toxicities

Patients should be monitored for signs and symptoms of immunotherapy-related toxicities, which include but are not limited to the following:

- **Pneumonitis**
  - For Grade 2 events, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
  - For Grade 3-4 events, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
  - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

- **Diarrhea/colitis**
  Patients should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).
  - All patients who experience 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. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
  - For Grade 2 diarrhea/colitis, administer oral corticosteroids.
  - For Grade 3 or 4 diarrhea/colitis, treat with intravenous steroids followed by high dose oral steroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 Diabetes Mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
  For **T1DM** or **Grade 3-4** Hyperglycemia:

- Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
- Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis (Autoimmune disorder affecting pituitary gland)**
  - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hyperthyroidism or hypothyroidism**
  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism
    - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hepatic**
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

- **Renal failure or nephritis**
  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3-4** events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

9.9b Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

For this trial, male patients will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female patients will be considered of non-reproductive potential if they are either:

(1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women <45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

(2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

(3) has a congenital or acquired condition that prevents childbearing.

Female and male patients of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:

(1) practice abstinence† from heterosexual activity;

OR

(2) use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for patients participating at sites in this country/region.

Patients should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study patients of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a patient of childbearing potential will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

9.9c Use in Pregnancy

If a patient inadvertently becomes pregnant while on treatment with pembrolizumab, the patient will immediately be removed from the study. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Mayo Clinic and to Merck without delay and within 24 hours to Mayo Clinic and within 2 working days to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to Mayo Clinic and to Merck and followed as described above.

9.9d Use in Nursing Women

Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, patients who are breast-feeding are not eligible for enrollment. Specific additional information follows for individual agents used in this trial.

9.9d1 Pembrolizumab

It is unknown whether pembrolizumab is excreted in human milk.

9.9d2 Binimetinib

It is unknown whether binimetinib is excreted in human milk.

9.9e Hypertension Management

Patients that will receive binimetinib must monitor their blood pressure at home on Days 10 and 30 after treatment initiation if they meet the following criteria:

- Patients with history of hypertension and/or
- Patient receiving antihypertensive drugs before onset of study treatment and/or
- Patients with a screening systolic blood pressure ≥140 mmHg and/or
- Patients with a screening diastolic blood pressure of ≥90 mmHg

The investigator is to educate the patient on the signs and symptoms of hypertension and use of the home blood pressure monitor (if not already in place). More frequent assessments during the study drug treatment period may also be performed at the discretion of the investigator and if medically indicated.

Measurements are to be taken at the same time on Study Days 10 and 30 after taking any hypertensive medications and after being at rest for 5 minutes in a sitting position. If SBP ≥160 mmHg, or DBP ≥100 mmHg, the patient should contact their investigator to have an unscheduled visit. At this unscheduled visit, the patient's blood pressure should be assessed and these measurements must be documented in the patient record. Early

initiation of treatment and aggressive management of emergent hypertension must be implemented after its diagnosis.

For patients monitoring their blood pressure at home, it is suggested to develop a patient diary to record their self-assessed blood pressure measurements and present the collected data to the investigator for evaluation and appropriate management. This diary must be maintained in the patient's source documentation

9.9f Skin disorders/care

Initial Rash Treatment Regimen

Clinical judgment and experience of the treating physician should guide the management plan of each patient. In general, the following interventions are in addition to the rash dosing guidelines in Table 8.2:

- Prophylaxis of skin events to be initiated 24 hours prior to the first treatment with study drug or later as needed
- Application of topical agents to the most commonly affected skin areas such as face, scalp, neck, upper chest and upper back

Topical agents include non-oily sunscreen (PABA free, SPF ≥30, UVA/UVB protection), topical steroids (preferably mometasone cream i.e. Elocon®) and topical erythromycin evening (i.e. Eryaknen® or topical pimocrolimus)

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

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

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

The treatment algorithm based on CTCAE grade is as follows:

Mild rash (CTCAE Grade 1)

- Consider prophylactic rash treatment if not already started
- Topical or other topical corticosteroid (i.e. mometasone cream) and/or topical antibiotic (i.e. erythromycin 2%) are recommended.
- The patient should be reassessed within a maximum of 2 weeks or as per investigator opinion.

Moderate rash (CTCAE Grade 2)

- Use of topical erythromycin or clindamycin (1%) plus topical mometasone or pimecrolimus cream (1%) plus oral antibiotics such as: lymecycline (408 mg QD), doxycycline (100 mg BID) or minocycline (50 to 100 mg QD).
- Although there has been no evidence of phototoxicity or photosensitivity in patients being treated with MEK162, doxycycline (or minocycline as second-line) should be used with thorough UV protection (i.e., avoidance of direct exposure to sunlight, use of sunscreen and sunglasses, etc.).
- Use of acitretin is not recommended

Severe rash (CTCAE Grade 3-4)
CTCAE Grade 3

- In addition to the interventions recommended for moderate rash, consider oral prednisolone at a dose of 0.5 mg/kg. Upon improvement, taper the dose in a stepwise manner (25 mg for 7 days, subsequently decreasing the dose by 5 mg/day every day).

- Alternatively, in addition to the interventions recommended for moderate rash, consider oral isotretinoin (low doses, i.e. 0.3 to 0.5 mg/kg) (Lacouture et al 2011)
- Use of acitretin is not recommended

CTCAE Grade 4

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

Symptomatic treatment:

- It is strongly recommended that patients who develop rash/skin toxicities receive symptomatic treatment:
- For pruritic lesions, use cool compresses and oral antihistaminic agents
- For fissuring, use Monsel's solution, silver nitrate, or zinc oxide cream. If not sufficient use mild steroid ointments or combinations of steroids and antibiotics such as Fucicort®
- For desquamation, use emollients with mild pH 5/neutral (best containing urea 10%)
- For paronychia, antiseptic bath and local potent corticosteroids, use oral antibiotics and if no improvement is seen, refer to a dermatologist or surgeon
- For infected lesions, obtain bacterial and fungal cultures and treat with topical or systemic antibiotics based on sensitivity of culture

10.0 Adverse Event (AE) Reporting and Monitoring

The site principal investigator is responsible for reporting any/all serious adverse events to the sponsor as described within the protocol, regardless of attribution to study agent or treatment procedure.

The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug
- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).

Summary of SAE Reporting for this study
(please read entire section for specific instructions):

WHO:	WHAT form:	WHERE to send:
All sites	Pregnancy Reporting http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportFormUpdated.pdf	Mayo Sites – attach to MCCC Electronic SAE Reporting Form Non Mayo sites – complete and forward to [redacted]
Mayo Clinic Sites	Mayo Clinic Cancer Center SAE Reporting Form: [redacted] ND attach MedWatch 3500A: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf	Will automatically be sent to [redacted]

Definitions

Adverse Event
Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction
Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting
Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting
Events reported to sponsor via case report forms

Events of Interest

Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

Unanticipated Adverse Device Event (UADE)
Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

a. Identify the grade and severity of the event using the CTCAE version 4.0.
b. Determine whether the event is expected or unexpected (see Section 10.2).
c. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).
d. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).
e. Determine if other reporting is required (see Section 10.5).
f. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

NOTE: A severe AE is NOT the same as a serious AE, which is defined in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.

An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.

NOTE: *The consent form may contain study specific information at the discretion of the Principal Investigator; it is possible that this information may NOT be included in the protocol or the investigator brochure. Refer to protocol or IB for reporting needs.

10.3 Attribution to agent(s) or procedure

When assessing whether an adverse event (AE) is related to a medical agent(s) medical or procedure, the following attribution categories are utilized:

Definite - The AE *is clearly related* to the agent(s)/procedure.
Probable - The AE *is likely related* to the agent(s)/procedure.
Possible - The AE *may be related* to the agent(s)/procedure.
Unlikely - The AE *is doubtfully related* to the agent(s)/procedure.
Unrelated - The AE *is clearly NOT related* to the agent(s)/procedure.

10.31 **EXPECTED Serious Adverse Events: Protocol Specific Exceptions to Expedited Reporting**

For this protocol only, the following Adverse Events/Grades are expected to occur within this population and do not require Expedited Reporting. These events must still be reported via Routine Reporting (see Section 10.6).*

*Report any clinically important increase in the rate of a serious suspected adverse reaction (at your study site) over that which is listed in the protocol or investigator brochure as an expedited event.

*Report an expected event that is greater in severity or specificity than expected as an expedited event.

System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be reported in an expedited manner[1]
Blood and lymphatic system disorders	Anemia	≤Grade 4
Gastrointestinal disorders	Vomiting	≤Grade 3
	Nausea	≤Grade 3
	Diarrhea	≤Grade 3
General disorders and administrations site conditions	Fatigue	≤Grade 3
	Malaise	≤Grade 3
Investigations	Neutrophil count decreased	≤Grade 4
	White blood cell count decreased	≤Grade 4
	Lymphocyte count decreased	≤Grade 4
	Platelet count decreased	≤Grade 4
Skin and subcutaneous tissue disorders	Alopecia	≤Grade 4
	Rash (acneiform or maculo-papular)	≤Grade 4

[1] These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.
Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (*i.e.*, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for elective procedures unrelated to the current disease and/or treatment on this trial
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (*e.g.*, battery replacement) that was in place before study entry
- Hospitalization, or other serious outcomes for signs and symptoms of progression of the cancer.

10.4 Expedited Reporting Requirements for IND/IDE Agents

10.41 Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1,2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the sponsor within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥24 hrs	7 Calendar Days	24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥24 hrs	Not required	

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

NOTE: Refer to Section 10.31 for exceptions to Expedited Reporting

10.42 General reporting instructions

The Mayo IND Coordinator will assist the sponsor-investigator in the processing of expedited adverse events and forwarding of suspected unexpected serious adverse reactions (SUSARs) to the FDA and IRB.

Binimetinib expedited reports must be submitted to the FDA using MedWatch 3500A.

Commercial agent (eg pembrolizumab) expedited reports must be submitted to the FDA via MedWatch 3500A for Health Professionals (complete all three pages of the form).

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

or

http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/ListFormsAlphabetically/default.htm

Instructions for completing the MedWatch 3500A:
http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/UCM387002.pdf

Submit SAEs to Industry Partner Contacts:

[redacted] for investigational agents or commercial/investigational agents on the same arm and attach MedWatch 3500A.

10.43 Reporting of re-occurring SAEs

ALL SERIOUS adverse events that meet the criteria outlined in Table 10.41 MUST be immediately reported to the sponsor within the timeframes detailed in the corresponding table. This reporting includes, but is not limited to SAEs that re-occur again after resolution.

10.5 Other Required Reporting

10.51 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS)

Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the

IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

Note: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects should not get pregnant/impregnate others, then any pregnancy in a subject/patient or a male patient's partner (spontaneously reported) which occurs during the study or within 120 days of completing the study should be reported as a UPIRTSO.

Mayo Clinic Cancer Center (MCCC) Institutions:

If the event meets the criteria for IRB submission as a Reportable Event/UPIRTSO, provide appropriate documentation using Mayo Expedited Event Report form [redacted] he Mayo Regulatory Affairs Office will review and process the submission to the Mayo Clinic IRB.

10.52 Death

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Reportable categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

- Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (including cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.53 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
- All secondary malignancies that occur following treatment with an agent under an IND/IDE will be reported. Three options are available to describe the event:
  - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])
  - Myelodysplastic syndrome (MDS)
  - Treatment-related secondary malignancy
- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.54 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting unless otherwise specified.

10.55 Pregnancy, Fetal Death, and Death Neonatal

If a female subject (or female partner of a male subject) taking investigational product becomes pregnant, the subject taking should notify the Investigator, and the pregnant female should be advised to call her healthcare provider immediately. The patient should have appropriate follow-up as deemed necessary by her physician. If the baby is born with a birth defect or anomaly, a second expedited report is required.

Prior to obtaining private information about a pregnant woman and her infant, the investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian before any data collection can occur. A consent form will need to be submitted to the IRB for these subjects if a pregnancy occurs. If informed consent is not obtained, no information may be collected.

In cases of fetal death, miscarriage or abortion, the mother is the patient. In cases where the child/fetus experiences a serious adverse event other than fetal death, the child/fetus is the patient.

NOTE: When submitting Mayo Expedited Adverse Event Report reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section. Include any available medical documentation. Include this form:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportFormUpdated.pdf

Attach copy to automated Mayo Clinic Cancer Center Adverse Event Reporting Form [redacted]

10.551 Pregnancy

Pregnancy should be reported in an expedited manner as **Grade 3 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy)"** under the Pregnancy, puerperium and perinatal conditions SOC. Pregnancy should be followed until the outcome is known.

10.552 Fetal Death

Fetal death is defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation."

Any fetal death should be reported expeditiously, as **Grade 4 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy loss)"** under the Pregnancy, puerperium and perinatal conditions SOC.

10.553 Death Neonatal

Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention, should be reported expeditiously.

A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration - Other (neonatal loss)"** under the General disorders and administration SOC.

10.6 Required Routine Reporting

10.61 Baseline and Adverse Events Evaluations

Pretreatment symptoms/conditions to be graded at baseline and adverse events to be graded at each evaluation. (Grading is per CTCAE v4.0 **unless** alternate grading is indicated in the table below):

CTCAE SYSTEM ORGAN CLASS	Adverse event/Symptoms	Baseline	Each evaluation
Blood and lymphatic system disorders	Febrile neutropenia	X	X
Eye disorders	Retinal detachment	X	X
	Retinal vascular disorder (RVO)	X	X
General disorders and administration site conditions	Fatigue	X	X
Gastrointestinal disorders	Nausea	X	X
	Vomiting	X	X

CTCAE SYSTEM ORGAN CLASS	Adverse event/Symptoms	Baseline	Each evaluation
	# of Stools	X	
	Diarrhea		X
	Constipation	X	X
Infections and infestations	Sepsis	X	X
Investigations	CPK (CK) increased	X	X
	Creatinine increased	X	X
	Neutrophil count decreased	X	X
	Platelet count decreased	X	X
Nervous system disorders	Peripheral sensory neuropathy	X	X
	Peripheral motor neuropathy	X	X
Skin and subcutaneous tissue disorders	Rash, acneiform	X	X
	Rash, maculo-papular	X	X
Vascular disorders	Hypertension	X	X

10.62 All other AEs

Submit via appropriate MCCC Case Report Forms (i.e., paper electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.6:

10.621 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.622 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.623 Grade 5 AEs (Deaths)

10.6231 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.6232 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.7 Late Occurring Adverse Events

Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

10.8 Additional Event Reporting Instructions

10.81 Additional Instructions for AE Reporting to Merck
A serious adverse event is any adverse event occurring at any dose or during any use of Merck's product that:

- Results in death;

- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event
- Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject must be reported within 24 hours to the Sponsor (Mayo Clinic) and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study whether or not related to the Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck Global Safety.

All patients with serious adverse events must be followed up for outcome.

SAE reports and any other relevant safety information are to be forwarded to the **Merck Global Safety facsimile number:** [redacted]

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to Merck & Co., Inc. [redacted] at the time of submission to FDA.

10.82 Additional Instructions for AE Reporting to Pfizer

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided main informed consent and until at least 30 days

after the patient has stopped study treatment must be reported to Pfizer within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 days period should only be reported to Pfizer if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the Pfizer Drug Safety department.

Pfizer Drug Safety

[redacted]

[redacted]

The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the site.

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure and is thought to be related to the Pfizer study treatment, an Pfizer Drug Safety associate may urgently require further information from the investigator for Health Authority reporting. Pfizer may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

10.821 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Pfizer within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to Pfizer Drug Safety. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Women of childbearing potential should be advised to use highly effective contraception methods while they are receiving study treatment and up to 8 weeks after treatment has been stopped.

If a pregnancy occurs while on study treatment, the newborn will be followed for at least 3 months following the expected delivery date

10.822 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided Investigator Brochure. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

11.0 Treatment Evaluation

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1) and by the ESMO 2014 Adaptation of the Immune-Related Response Criteria: irRECIST {Bohnsack 2014}. RECIST version 1.1 will be used for assessment of tumor response for the primary endpoint. **irRECIST will be used to make patient management decisions during the trial.**

Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST 1.1 and irRECIST guidelines. **In RECIST 1.1, the appearance of new lesions automatically signifies progressive disease (PD), while in irRECIST new measurable lesions are factored into the total tumor burden.** The specifics are presented below.

NOTE: This study uses protocol RECIST v1.1 template dated 2/16/2011. See the footnote for the table regarding measureable disease in Section 11.44, as it pertains to data collection and analysis.

11.1 Schedule of Evaluations

For the purposes of this study, patients should be reevaluated every 6 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 4 weeks following initial documentation of objective response.

11.2 Definitions of Measurable and Non-Measurable Disease (same definitions for RECIST 1.1 and irRECIST)

11.21 Measurable Disease

11.211 A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥2.0 cm with chest x-ray, or as ≥1.0 cm with CT scan, , or MRI.

11.212 A superficial non-nodal lesion is measurable if its longest diameter is ≥1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.213 A malignant lymph node is considered measurable if its short axis is >1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

NOTE: Tumor lesions in a previously irradiated area are not considered measurable disease.

11.22 Non-Measurable Disease

11.221 All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥1.0 to <1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/ pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.

Note: ‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred

for selection as target lesions. In addition, lymph nodes that have a short axis <1.0 cm are considered non- pathological (i.e., normal) and should not be recorded or followed.

11.3 Guidelines for Evaluation of Measurable Disease

11.31 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.32 Acceptable Modalities for Measurable Disease:

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

- As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.
- PET-CT: If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST and irRECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.
- Chest X-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT scans are preferable.
- Physical Examination: For superficial non-nodal lesions, physical examination is acceptable, but imaging is preferable, if both can be done. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.33 Measurement at Follow-up Evaluation:
A subsequent scan must be obtained a minimum of 4 weeks following initial documentation of an objective status of either complete response (irCR) or partial response (irPR).

In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks (see Section 11.44).

NOTE: Once patient has had SD for ≥6 months, scanning can be reduced to every 3 months.

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

11.4 Measurement of Effect

11.41 Target Lesions & Target Lymph Nodes

- Measurable lesions (as defined in Section 11.21) up to a maximum of 5 lesions, representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. <u>These lesions can be non-nodal or nodal (as defined in 11.21)</u>, where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

  Note: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.
- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.
- Baseline Sum of Dimensions (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.
- Post-Baseline Sum of the Dimensions (PBSD, or irPBSD for irRECIST): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes (and for irRECIST, plus the sum of new measurable lesions) will be calculated and reported as the post-baseline sum of dimensions (PBSD, or irPBSD for irRECIST). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.
- The minimum sum of the dimensions (MSD, or irMSD for irRECIST) is the minimum of the BSD and the PBSD (or the irPBSD for irRECIST)

11.42 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease (Section 11.22) are classified as non-target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with Section 11.443.

11.43 irRECIST Response Criteria

11.431 All target lesions and target lymph nodes followed by CT/MRI/PET-CT/Chest X-ray/physical examination must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either irPR or irCR cannot be done without re-measuring target lesions and target lymph nodes.

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

11.432 irRECIST Overall Tumor Assessments

11.4321 irRECIST Complete Response (irCR):

a. Complete disappearance of all measurable and non-measurable lesions, and
b. Each target lymph node must have reduction in short axis to <1.0 cm.

11.4322 irRECIST Partial Response (irPR):

a. At least a 30% decrease in irPBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation, plus the measurements of new measurable lesions) taking as reference the BSD (see Section 11.41), and
b. Non-target lesions are irNN (no target disease was identified at baseline and at follow-up the patient fails to meet criteria for irCR and irPD), and
c. No unequivocal progression of new non-measurable lesions.

11.4323 irRECIST Stable Disease (irSD):

a. Failure to meet criteria for irCR or irPR in the absence of irPD.

11.4324 irRECIST Progression (irPD):

a. At least a 20% increase in irPBSD taking as reference the irMSD (see Section 11.41) with an absolute increase of at least 0.5 cm from the irMSD, or
b. Unequivocal irPD for non-target or new non-measurable lesions.

11.44 RECIST 1.1 Response Criteria

11.441 All target lesions and target lymph nodes followed by CT/MRI/PET-CT/Chest X-ray/physical examination must be measured on re-

evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

11.442 Evaluation of Target Lesions

Complete Response (CR): All of the following must be true:

a. Disappearance of all target lesions.

b. Each target lymph node must have reduction in short axis to <1.0 cm.

Partial Response (PR): At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (*see* Section 11.41).

Progression (PD): At least one of the following must be true:

c. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (<1.0 cm short axis) and increased to ≥1.0 cm short axis during follow-up.

d. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.41). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.

e. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

11.443 Evaluation of Non-Target Lesions & Non-target Lymph Nodes

Complete Response (CR):	All of the following must be true: a. Disappearance of all non-target lesions. b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.
Non-CR/Non-PD:	Persistence of one or more non-target lesions or non-target lymph nodes.
Progression (PD):	At least one of the following must be true: a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (<1.0 cm short axis) and increased to ≥1.0 cm short axis during follow-up.

b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)

c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

11.45 RECIST 1.1 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following tables:

11.451 For Patients with Measurable Disease

Target Lesions & Target Lymph Nodes	**Non-Target Lesions & Non-Target Lymph Nodes**	**New Sites of Disease**	**RECIST 1.1 Overall Objective Status**
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR**
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

*See Section 11.441

** NOTE: This study uses the protocol RECIST v1.1 template dated 2/16/2011. For data collection and analysis purposes the objective status changed from SD to PR in the MCCC protocol RECIST v1.1 template as of 2/16/2011 and to match RECIST v1.1 requirements.

11.46 Symptomatic Deterioration

Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD and irPD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration. A patient is classified as having PD and irPD due

to “symptomatic deterioration” if any of the following occur that are not either related to study treatment or other medical conditions:

- Unintentional weight loss >10% of body weight
- Decline in performance status of >1 level on ECOG scale

12.0 Descriptive Factors

12.1 Prior treatment: 1 vs 2 vs 3+

12.2 Phase I dose level: 0 vs -1

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Continuation of treatment

Patients who are irCR, irPR, or irSD will continue treatment per protocol.

13.2 Progressive disease (PD/irPD)

Patients who develop irPD while receiving therapy will go to the event-monitoring phase.

13.3 Off protocol treatment

Patients who go off protocol treatment for reasons other than irPD will go to the event-monitoring phase per Section 18.0.

13.4 Duration of therapy for irCR

Patients who achieve irCR will receive treatment for a maximum of 2 years, then they will go to event monitoring

13.5 Duration of therapy for irPR or irSD

Patients who are in irPR or irSD will continue on therapy for a total of 2 years. After 2 years, then they will go to event monitoring (see 13.4 above). Subsequent treatment is at the discretion of their attending physician

13.6 Retreatment

Patients who achieve SD, PR, CR may be eligible for retreatment for up to 1 year if their disease progresses after stopping treatment. (See Section 7.5 for criteria.)

13.7 Inevaluable patients

Phase I only: If a patient fails to complete the first two cycles (Cycles 1 and 2) of treatment for reasons other than toxicity, the patient will be regarded as inevaluable and will be replaced.

13.8 Ineligible

A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly to the event-monitoring phase of the study (or off study, if applicable).

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.
- If the patient never received treatment, on-study material must be submitted. Event monitoring will be required per Section 18.0 of the protocol.

13.9 a Major violation

A patient is deemed a *major violation*, if protocol requirements regarding treatment in the first two cycles (Cycles 1-2) of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the event-monitoring phase of the study. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. Event monitoring will be required per Section 18.0 of the protocol.

13.9b Cancel

A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

14.0 Body Fluid Biospecimens

14.1 Summary Table of Research Blood and Body Fluid Specimens to be Collected for this Protocol

Correlative Study (Section for more information)	Mandatory[1] or Optional	Blood or Body Fluid being Collected	Type of Collection Tube (color of tube top)	Volume to collect per tube (# of tubes to be collected)	Baseline B0	End of Cycle 1 Prior to pembro B1	C3, D1 After 1 cycle of bini and pembro B2	C9, D1 Only after objective response or SD >6mos B3	End of Tx for any reason B4	Process at site? (Yes or No)	Temperature Conditions for Storage /Shipping
Immunoregulatory cell quantification (Section 14.21)	Mandatory	PBMCs and plasma	Mononuclear (CPT) sodium citrate (lt blue/black)	8 mL (1)	X	X	X	X	X	No	Ambient
Cytokine profiling (Section 14.21)	Mandatory	PBMCs and plasma	Mononuclear (CPT) sodium citrate (lt blue/black)	8 mL (1)	X	X	X	X	X	No	Ambient
Circulating Tumor Cells (CTC) (Section 14.22)	Mandatory	Whole Blood	CellSave	10 mL (2)	X	X	X	X	X	No	Ambient

1. Samples are required at baseline and requested at all other timepoints.

14.2 Collection and Processing

All samples should be labeled with the study number [redacted] the patient's study ID, treatment phase (I or II), dose level (-1 or 0), and the designated specimen timepoint in Section 14.1 (i.e. B0/B1/B2/B3/B4). The samples should *not* contain patients' identifying information.

14.21 Immunoregulatory cell quantification and cytokine profiling

Collect two 8 ml, BD Vacutainer® Mononuclear Cell Preparation Tubes (CPT) with sodium citrate and ship overnight within 24 hours of collection.

14.22 Circulating tumor cells

Collect two 10 mL CellSave Preservative vacutainers and ship overnight within 24 hours of collection per Section 14.32.

14.3 Shipping and Handling

14.31 Kits will be provided for Minnesota only.

14.311 Kits will be supplied by the Mayo Florida Biospecimen Acessioning and Processing Shared Resource (BAP).

14.312 The kit contains supplies and instructions for collecting, processing, and shipping specimens.

14.313 Participating institutions may obtain kits by submitting the supply order form to [redacted] Because we are charged for all outgoing kits, a small, but sufficient, supply of the specimen collection kits should be ordered prior to patient entry. Supply Order Forms must be filled in completely and legibly for quick processing.

14.314 Kits will be sent via Fed Ex® Ground at no additional cost to the participating institutions. **Allow at least two weeks to receive the kits.**

14.315 Kits will not be sent via rush delivery service unless the participating institution provides their own Fed Ex® account number or alternate billing number for express mail. **Cost for rush delivery of kits will not be covered by the study.**

14.316 For Jacksonville:

Immunoregulatory cell quantification and cytokine profiling should be hand carried to [redacted]

14.317 For Rochester samples:

Immunoregulatory cell quantification and cytokine profiling must be shipped overnight within 24 hours of draw to [redacted] laboratory.

14.318 For all sites: CTCs must be shipped **overnight within 24 hours of draw** (see Section 14.323)

14.319 All specimens must be collected and shipped Monday – Thursday ONLY.

14.32 Shipping Specimens

14.321 Immunoregulatory cell quantification and cytokine profiling must be shipped **OVERNIGHT within 24 hours** to:

[redacted] PRIOR to shipping.

14.323 Circulating Tumor Cells

Two 10 mL blood collection CellSave Preservative vacutainers will be collected for this purpose. After collection, samples should be labeled as previously described and shipped **OVERNIGHT within 24 hours** to:

[redacted] PRIOR to shipping.

14.4 Background and Methodology

14.41 Immunoregulatory cell quanitification

Several subtypes of circulating immunoregulatory cells (IRC) (CD8, CD4, Treg, MDSC, NK cells) will be evaluated in the peripheral blood of patients treated with pembrolizumab and binimetinib as previously described {Thomas 2014}. These subsets of IRC include CD4, CD8, regulatory T cells, myeloid derived suppressor cells, and NK cells.

14.42 Cytokine profiling

Luminex Multianalyte assay is a multiplex assay that allows simultaneous quantification of multiple cytokines in a single sample. A panel of 17 cytokines and chemokines will be analyzed using a multiplexed approach with commercially available human 17-plex kits. The following cytokines will be assessed: IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, CXCL8 (IL-8), IL-10, IL-12, IL-13, IL-17A, IFN-γ, TNF-α, CCL2 (MCP-1), CCL4 (MIP-1β), G-CSF, and GM-CSF. Cytokine concentrations will be determined based on a standard curve generated on each plate using the manufacturer-supplied reagents.

14.43 Circulating Tumor Cells

Circulating tumor cells (CTC) will be isolated by Creatv MicroTech, Inc. using CellSeive microfiltration technique as previously described {Adams 2014}. Using a standard CTC fluorescent stain, we identify, quantify and score these cells according to their Cytokeratin, CD14 and CD45 positivity. The filtered samples are then processed by the QUAS-R technique, whereby the fluorescent CTC stain is “Quenched-Underivatized- Amine Striped” removing all fluorescence while leaving the cells intact and unaltered. The samples are “Restained” for subtyping of additional biomarker panels against biological targets (i.e. p-ERK, PD-L1, etc.) as well as circulating cancer-associated macrophage-like cells (CAMLs). The same previously identified CTC and CStC are reimaged with the new immuno-targets, the markers are quantified and

scored. The process is repeated with up to 12 biomarkers identified, quantified and scored using the initially identified CStC and CTC.

15.0 Drug Information

15.1 Binimetinib (MEK162, ARRY-438162, ONO-7703)

15.11 **Background**: Binimetinib is an orally bioavailable, selective and potent MEK1 and MEK 2 inhibitor. As a MEK inhibitor, this compound has the potential to benefit patients with advanced cancers by inhibiting the MAPK (mitogen-activated protein kinases) pathway.

15.12 **Formulation**: Binimetinib drug product is supplied as film-coated tablets in a dose 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.

Binimetinib tablets can be constituted in 3:1 (v/v) Ora Sweet®/water at 1 mg/mL binimetinib concentration to provide an easy to swallow oral suspension.

15.13 **Preparation and storage**: 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.

Binimetinib oral suspension prepared from 15 mg binimetinib tablets should not be stored above 25°C and should not be refrigerated. The suspension should be used within 30 days after preparation.

15.14 **Administration:** Binimetinib is administered twice daily with water, approximately 12 hours apart with or without meals. Tablets should be swallowed whole and should not be chewed.

Binimetinib oral suspension is intended for oral administration as prepared.

15.15 **Pharmacokinetic information**:

Absorption: The pharmacokinetics of binimetinib are characterized by moderate to high variability, accumulation of approximately 1.5-fold, and steady state concentrations reached within 15 days. The human ADME study indicated that approximately 50% of binimetinib dose was absorbed.

Distribution: Binimetinib is more distributed in plasma than blood. The blood-to-plasma concentration ratio of binimetinib in humans is 0.718. It is highly bound to plasma proteins (humans: 97.2%)

Metabolism: The primary metabolic pathways include glucuronidation (up to 61.2% via UGT1A1), N-dealkylation (up to 17.8% via CYP1A2 and CYP2C19) and amide hydrolysis.

Excretion: The excretion route was 31.7% of unchanged binimetinib in feces and 18.4% in urine. Estimated renal clearance of unchanged binimetinib was 6.3% of total dose.

15.16 **Potential Drug Interactions**:

Overall, the risk for binimetinib to be a cause of or be affected by significant drug-drug interactions is predicted to be low. However, given the predominant role of UGT1A1 in the metabolism of binimetinib, special consideration should

be taken for co-administration of drugs that are UGT1A1 inhibitors or inducers, and administration of binimetinib to patients with low UGT1A1 activity.

Binimetinib has been shown to be a substrate for P-gp and BCRP in vitro. The impact of P-gp/BCRP inhibitors on the PK of binimetinib in vivo is unknown; therefore, it is recommended that P-gp and BCRP inhibitors are dosed with caution.

15.17 **Known potential toxicities**:

Very Common (≥10%) - Anemia, abdominal pain, constipation, diarrhea, nausea, vomiting, fatigue, peripheral edema, increased AST, increased ALT, increased blood creatine phosphokinase (CPK), dyspnea, dermatitis acneiform, pruritus, rash, hypertension

Common (≥1% - <10%) – Left ventricular dysfunction, tachycardia, chorioretinopathy, eye edema, macular edema, retinal detachment, retinopathy, blurred vision, visual impairment, dry mouth, gastritis, gastrointestinal obstruction, stomatitis, asthenia, facial edema, general physical health deterioration, generalized edema, malaise, mucosal inflammation, pyrexia, cellulitis, pneumonia, infection, decreased ejection fraction, increased GGT, increased INR, increased troponin T, dehydration, hyponatremia, arthralgia, muscular weakness, myalgia, cough, epistaxis, hypoxia, pulmonary embolism, alopecia, maculo-papular rash, skin fissures, hypotension

Uncommon (≥0.1 - <1%) - Left ventricular failure, retinal vein occlusion, retinal vein thrombosis, reduced visual acuity, enteritis, gastroenteritis, gastrointestinal hemorrhage, acute hepatic failure, irregular heart rate, increased troponin I, increased troponin T, hypoglycemia, myositis, dropped head syndrome, renal failure, atelectasis, lung infiltration, pneumonitis, pneumothorax, wheezing, angioedema, erythema nodosum/panniculitis, palmar-plantar dysesthesia syndrome, macular rash, deep vein thrombosis, hematoma

15.18 Drug procurement:

Binimetinib is supplied by Pfizer Inc. (formerly Array Biopharma LLC and Array Biopharma Inc.), Inc

15.19 Nursing guidelines

15.191 Instruct patient to take binimetinib twice daily approximately 12 hours apart. Agent may be taking with or without food.

15.192 MEK inhibitors can have significant cardiac side effects; including cardiac failure, tachycardia, myocarditis, and decreased ejection fraction. Instruct patients to report any side effects concerning for heart failure (SOB, peripheral edema, chest, pain, etc) to the study team immediately.

15.193 Warn patient of eye disorders, which can be severe and lead to permanent loss of eyesight. Instruct patient to report any eye pain, dryness, itching, etc. to study team. Refer patient to ophthalmologist for treatment.

15.194 Binimetinib may cause gastrointestinal side effects (diarrhea, nausea, vomiting, GI bleeding, etc). Treat symptomatically and/or premedicate as necessary and monitor for effectiveness.

15.195 Monitor LFTs. Patients have experienced acute hepatic failure. Instruct patients to report any acute and or worsening RUQ pain and/or any jaundice to study team immediately.

15.196 Patients may experience pruritus and/or rash. Manage symptomatically and monitor for effectiveness.

15.197 Patients may experience generalized edema, including the face and the limbs. Instruct patient to report any edema and rule out any allergic and/or cardiac component.

15.198 Monitor creatinine levels.

15.199a Patients may experience myositis or rarely rhabdomyolysis. Patients should be instructed to report generalized muscle pain to the study team.

15.199b Agent may cause pneumonitis. Instruct patients to report any cough, SOB, or chest pain to study team.

15.199c Monitor any new skin lesions. Patients may develop secondary skin cancer or cysts. Refer to dermatology as necessary.

15.199d Patients may experience palma-plantar erythrodysesthesia (hand-foot syndrome). Instruct patients to report any redness, pain or skin changes of the hands or feet to the study team immediately. Encourage good hand and foot care and use of moisturizers.

15.2 Pembrolizumab (MK-3475, SCH 900475, Keytruda™)

15.21 **Background**: Pembrolizumab is a potent humanized IgG4 monoclonal antibody with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical *in vitro* data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1.

15.22 **Formulation**:
Pembrolizumab is available as a liquid 25 mg/mL, 100 mg/vial.

15.23 **Preparation and storage**:
Vials should be stored in the refrigerator at temperatures between 2-8°C.

Drug concentrate is further diluted with normal saline (or 5% dextrose) in the concentration range of 1 to 10 mg/mL. The infusion solution in the IV bag should be immediately administered. Diluted pembrolizumab solutions may be stored at room temperature for a cumulative period of up to 6 hours. This includes room temperature storage of admixture solutions in the IV bags and the duration of infusion. In addition, IV bags can be stored at 2-8 °C for up to a cumulative time of 2 hours. This 24-hour total hold time from dilution may include up to 6 hours at room temperature. IV bags must be allowed to come to room temperature before use.

15.24 **Administration:** Pembrolizumab is administered by intravenous infusion over 30 minutes via a 0.22 micron in-line filter. The final infusion volume must be between 1 and 10 mg/mL. Maximum rate of infusion should not exceed 6.7 mL/minute through a peripheral or indwelling catheter. Flush the line with 0.9% NaCL following the completion of the infusion.

15.25 **Pharmacokinetic information**:

a) Absorption – Because pembrolizumab is administered intravenously, it is immediately and completely bioavailable. Steady-state concentrations of pembrolizumab are reached by 16 weeks of repeated dosing with a Q3W regimen and the systemic accumulation is 2.1-fold. The peak concentration, trough concentration, and area under the plasma concentration versus time curve at steady state of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg Q3W.

b) Distribution – Pembrolizumab has a limited volume of distribution.

c) Excretion – CL is approximately 23% lower after achieving maximal change at steady state compared with the first dose. The terminal elimination half-life($t_{½}$) is estimated to be 22 days at steady state.

d) Metabolism – Pembrolizumab is catabolized through non-specific pathways; metabolism does not contribute to its CL.

15.26 **Potential Drug Interactions:** There are no known significant drug interactions.

15.27 **Known potential toxicities**:
Very common known potential toxicities, ≥ 10%:
Gastrointestinal disorders: diarrhea, nausea, abdominal pain
Skin and subcutaneous tissue disorders: rash, pruritis
General disorders and administration site conditions: fatigue

Common known potential toxicities, ≥1% to <10%:
Blood and lymphatic system disorders: anemia
Immune system disorders: infusion related reaction
Endocrine disorders: hyperthyroidism, hypothyroidism
Metabolism and nutrition disorders: decreased appetite
Nervous system disorders: headache, dizziness, dysgeusia
Respiratory, thoracic, and mediastinal disorders: pneumonitis, dyspnea, cough
Gastrointestinal disorders: colitis, vomiting, constipation, dry mouth
Skin and subcutaneous tissue disorders: severe skin reactions, vitiligo, dry skin, erythema
Musculoskeletal and connective tissue disorders: arthralgia, myositis, musculoskeletal pain, arthritis, pain in extremity

General disorders and administration site conditions: asthenia, edema, pyrexia, influenza like illness, chills
Investigations: alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatinine increased

Uncommon known potential toxicities, ≥0.1% to <1%:
Infusion related reactions
Blood and lymphatic system disorders: neutropenia, thrombocytopenia, leukopenia, lymphopenia, eosinophilia

Endocrine disorders: hypophysitis, adrenal insufficiency, Thyroiditis, hypopituitarism
Metabolism and nutrition disorders: type I diabetes mellitus, hyponatremia, hypokalemia, hypocalcemia
Psychiatric disorders: insomnia, confusional state
Nervous system disorders: epilepsy, lethargy, peripheral neuropathy
Eye disorders: uveitis, dry eye
Cardiac disorders: myocarditis, atrial fibrillation
Vascular disorders: hypertension
Gastrointestinal disorders: pancreatitis
Hepatobiliary disorders: hepatitis
Skin and subcutaneous tissue disorders: lichenoid keratosis, psoriasis, alopecia, dermatitis, dermatitis acneiform, eczema, hair color changes, papule
Musculoskeletal and connective tissue disorders: tenosynovitis
Renal and urinary disorders: nephritis, acute kidney injury
Investigations: blood bilirubin increased, amylase increased, hypercalcemia

Rare known potential toxicities, <0.1% (Limited to important or life-threatening):
Blood and lymphatic system disorders: immune thrombocytopenic

purpura, hemolytic anemia

Immune system disorders: sarcoidosis
Nervous system disorders: Guillain-Barre syndrome, myasthenic syndrome
Gastrointestinal disorders: small intestinal perforation
Skin and subcutaneous tissue disorders: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema nodosum
The risk profile for pembrolizumab also includes two important potential risks: a) myasthenic syndrome, and b) an increased risk of severe complications (such as early severe graft versus host disease and veno-occlusive disease) of allogeneic transplant in patients with hematologic malignancies who have previously been treated with PD-1 inhibitors.

Patients with multiple myeloma who were treated with pembrolizumab in combination with either pomalidomide or lenalidomide and dexamethasone, had an increased number of serious side effects and deaths as compared to patients who received only dexamethasone and either pomalidomide or lenalidomide. The benefit-risk profile is unfavorable for the combination of pembrolizumab, pomalidomide, and dexamethasone in relapsed refractory multiple myeloma, and the combination of pembrolizumab, lenalidomide, and dexamethasone in newly diagnosed treatment-naive multiple myeloma.

Post marketing reports identified Vogt-Koyanagi-Harada syndrome and hemophagocytic lymphohistiocytosis.

15.28 **Drug procurement:** Pembrolizumab will be provided free of charge to study participants by Merck.

15.29 Nursing Guidelines

15.291 Pembrolizumab side effects vary greatly from those of traditional chemotherapy and can vary in severity from mild to life threatening. Instruct patients to report any side effects to the study team immediately. Side effects may be immediate or delayed up to months after discontinuation of therapy. Most side effects are reversible with prompt intervention of corticosteroids.

15.292 Diarrhea can be seen however it is less common than that seen with anti-CTLA-4 agents. However it can be severe, leading to colonic perforation. Instruct patients to report ANY increase in the number of stools and/or change in baseline, blood in the stool, abdominal pain to the study team immediately.

15.293 Rash/pruritis/dermatitis is seen. Patients should report any rash to the study team. Treat per section 9.0 and monitor for effectiveness.

15.294 Monitor LFTs closely as elevations in these levels could indicate early onset autoimmune hepatitis. Patients should also be instructed to report any jaundice, or right upper quadrant pain to the study team immediately.

15.295 Pneumonitis can be seen and may be mild (only seen on imaging) to severe. Patients should be instructed to report any SOB, dyspnea, cough, chest pain, etc. to the study team immediately. Patients reporting these symptoms should have a pulse ox checked and consider immediate imaging per the treating MD.

15.296 Endocrinopathies (including hypopituitarism, hypothyroidism, hypophysitis, and adrenal insufficiency) are seen with this agent. Patients may present only with the vague sense of fatigue and "not feeling well." Additional symptoms may be that of nausea, sweating and decreased activity tolerance. Instruct patients to report these signs or symptoms immediately and obtain appropriate labs as ordered by MD.

15.297 Patients who are started on steroid therapy for any side effects of pembrolizumab toxicity should be instructed to take the steroids as ordered, and not to discontinue abruptly as symptoms may return and be severe. Patients may be on steroid therapy for weeks. Instruct patients to report any increase or change in side effects with any dosage decrease as patients may need a slower taper.

15.298 Fatigue is common and may or may not be associated with immune related side effects. Assess patient's fatigue level prior to each cycle of therapy and report any changes to the study team.

15.299 Patients should avoid receiving live vaccines within 30 days of study drug administration or per other study guidelines.

15.299a Patients who have undergone an allogenic bone marrow transplant, have an increased risk of severe complications including early GVHD, and venoocclusive disease, if they have previously been treated with pembrolizumab

15.299b Myocarditis has been reported and associated with pembrolizumab. Instruct patients to report chest pain, SOB, or dyspnea to study team immediately and/or seek emergency medical attention.

15.299c Autoimmune hematologic disorders including ITP and hemolytic anemia have been reported. Monitor blood counts closely and report any abnormalities to the study team.

15.299d Rare neurologic disorders including Guillian-Barre syndrome and myasthenia gravis have been reported. Instruct patients to report any neurologic symptoms including weakness, parasthesias or numbness, tingling to the study team immediately.

16.0 Statistical Considerations and Methodology

16.1 Overview

This is a Phase I/II, single-arm, open-labeled, multi-center study of pembrolizumab in combination with binimetinib in women with unresectable locally advanced or metastatic triple negative breast cancer. The main objective of this study is to assess the safety and efficacy of the combination of pembrolizumab and binimetinib.

The phase I part will be a dose-finding study, utilizing the classic 3+3 study design. The primary objectives are to determine the DLTs, to evaluate the safety of this combination, and to establish the recommended dose for the phase II part. There are a total of 2 dose levels as defined in the treatment section. The number of participants enrolled in the phase I of this study will range from 6-12 participants.

16.11 Primary Endpoint

16.111 Phase I

The primary endpoint in the phase I portion is to determine the maximum tolerated dose of this combination.

16.112 Phase II

The primary endpoint in the phase II portion is confirmed objective response rate (ORR) by RECIST criteria with pembrolizumab and binimetinib.

We will utilize Simon's Two-Stage Optimal Design to test the null hypothesis that this two-drug combination has an ORR of at most 15% versus the alternative hypothesis that it has an ORR of at least 35%. Patients in the phase I part who are treated with the recommended dose of phase II and are evaluable for response will be included in the phase II analysis. The first stage will require 9 evaluable patients. With this design, if $\leq$1 of the first 9 patients has objective response (i.e. CR or PR), the study will be closed since there is sufficient evidence that the therapy is not promising. Otherwise, an additional 14 patients will be enrolled. In total, if >5 patients of 23 patients have objective response, this combination will be considered promising. This design has 80% power while controlling the type I error at 10%. Under the null hypothesis (when the true objective response rate is 15%), this design has a 60% chance of stopping the trial early. A minimum of 9 and a maximum of 23 evaluable patients are required to evaluate the primary endpoint. To account for cases that are ineligible or non-evaluable, we will accrue an additional 3 patients for a maximum accrual of 26 patients in this phase. The secondary endpoints in part II include objective response rate by irRECIST, progression free survival, and overall survival.

16.2 Sample size and accrual rate

For phase I, the study will require 6-12 patients to complete, allowing for 6 patients per dose level and 2 predefined dose levels. In phase II, the study will require 9-26 patients to complete. Therefore, the total sample size for this study is 15-38 patients. At an anticipated accrual rate of 10-12 patients/year, we expect that this trial will need to accrue patients for anywhere from 15 to 32 months.

16.3 Statistical Analysis Plan

The objective of the phase I portion of the study is to estimate the maximum tolerated dose (MTD) using the standard 3+3 design. Safety/adverse events data will be tabulated, including adverse events of all grades.

For the phase II portion of the study, the overall response rate by RECIST will be estimated using the approach of Jung and Kim [On the estimation of the binomial probability in multistage clinical trials. Stat Med 23:881-96, 2004]. The 90% lower confidence bound will be calculated using the approach of Koyama and Chen [Proper inference from Simon's two-stage designs. Stat Med 27:3145-54, 2008]. Secondary efficacy endpoints include objective response rate by immune-related response criteria (irRECIST), progression-free survival (PFS) and overall survival (OS). Objective response rate by irRECIST will be estimated as a binomial proportion with a 2-sided 95% CI. PFS will be defined as the time from study enrollment to date of progression. Patients who have not progressed (including those lost to follow-up) at the time of data analysis will be censored at the date last known to be free of progression. OS will be defined as the time from study enrollment to death attributable to any cause (i.e. death from breast cancer, non-breast cancer cause, or from unknown cause). Patients who are alive (including those lost to follow-up) at the time of data analysis will be censored at the last known alive date. A Kaplan-Meier curve will be used to summarize the PFS and OS experience of this patient cohort.

Baseline TILs and percent change in TILs from baseline will be summarized. Logistic regression models will be used to assess the correlation between these biomarkers and ORR in order to assess their prognostic significance. Cox Proportional Hazard models will be used to assess their correlation with time-to-event endpoints such as PFS and OS. Similar analyses will be performed for other exploratory biomarkers such as immune related gene signature, PDJ amplification, etc. These analyses will be exploratory in nature. As such, no adjustment for multiple comparisons will be made; all hypothesis tests will be based on 2-sided alpha = 0.05 level.

16.4 Phase I

This portion of the study is designed to determine the MTD and toxicity profile of binimetinib in combination pembrolizumab.

16.41 MTD Definition: MTD is defined as the dose level below the lowest dose that induces dose-limiting toxicity (DLT) in at least one-third of patients (at least 2 of a maximum of 6 new patients). A total of 6 patients treated at the MTD will be sufficient to identify common toxicities at the MTD.

Refer to Section 7.52 for definition of dose-limiting toxicity (DLT). The focus of this study is to establish the DLT of the combination of binimetinib and pembrolizumab. Therefore, only adverse events that occur during the first cycle of treatment with the combination (Cycle 2) will be considered when evaluating for dose-limiting toxicity.

16.42 MTD Determination

The phase I portion of this study will utilize a standard cohort of three design. The dose levels to which patients will be assigned in sequential cohorts are described in Section 7.51. The first cohort of three patients will be treated at dose level 0. Decisions on when and how to dose escalate are described below.

16.421 Three patients will be treated at a given dose level combination and observed for one cycle of the combination (Cycle 2) from start of treatment to assess toxicity.

16.422 If DLT is not seen in any of the 3 patients, 3 new patients will be accrued and treated at the next higher dose level. If DLT is seen in 2 or 3 of 3 patients treated at a given dose level, then the next 3 patients will be treated at the next lower dose level, if only 3 patients were enrolled and treated at this lower dose level.

16.423 If DLT is seen in 1 of 3 patients treated at a given dose level, up to 3 additional patients will be enrolled and treated at the same dose level. If DLT is seen in at least one of these additional three patients (≥2 of 6), the MTD will have been exceeded and further accrual will cease to this cohort. If dose-limiting toxicity (DLT) is not seen in any of the three additional patients, 3 new patients will be accrued and treated at the next higher dose level.

16.424 After enrolling 6 patients on a specific dose level, if DLT is observed in at least 2 of 6 patients, then the MTD will have been exceeded and defined as the previous dose unless only 3 patients were treated at the lower dose level. In that case, 3 additional patients will be treated at this lower dose level such that a total of 6 patients are treated at the MTD to more fully assess the toxicities associated with the MTD.

16.426 If a patient fails to complete the first combined cycle (Cycle 2) of therapy for reasons other than dose-limiting toxicity defined adverse events, the patient will be regarded as uninformative in regard to the primary study goal (i.e. MTD determination) and will be replaced.

16.427 Operating Characteristics for standard cohort of 3 design: The following table gives the probability of dose escalation at a single dose level as a function of the true probability of DLT at that level using the cohorts of 3 design described above.

True Rate of DLT (%)	Probability of Dose Escalation
10	0.91
20	0.71
30	0.49
40	0.31
50	0.17

16.5 Data & Safety Monitoring

16.51 The principal investigator(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.52 Adverse Event Stopping Rules:

The stopping rules specified below are based on the knowledge available at study development. We note that the rules may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatments under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rules below.

Phase I (Includes all dose levels in phase I):

By the nature of the "cohorts of three" phase I study design, toxicity (i.e., adverse events that are possibly, probably or definitely related to study treatment) stopping rules are in place for each dose level. Specifically, if 2 or more dose-limiting toxicities (DLTs) are observed during Cycle 2 at any given dose level, accrual to that dose level will be stopped, and patients will be accrued to the next lower dose level until a maximum of 6 patients are treated at the lower level. Note that a DLT that affects dose escalation is only that which is observed in the second cycle of treatment. However, all cycles will be reviewed and the study team will determine whether the dose level needs to be adjusted for future patients if ≥1 in the first 3 patients OR ≥2 in the first 6 patients experience a Grade 4 or higher adverse event at least possibly related to treatment over all cycles at any given dose level.

Phase II (includes all phase II patients including phase I patients treated at the MTD:

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as "possible," "probable," or "definite") that satisfy either of the following:

- If 3 or more patients in the first 9 treated patients experience a Grade 4 or higher adverse event at least possibly related to treatment.
- If after the first 9 patients have been treated, 25% of all patients experience a Grade 4 or higher adverse event at least possibly related to treatment.

We note that we will review Grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse events.

16.6 Inclusion of Women and Minorities

16.61 This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.

16.62 There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.63 The geographical region served by MCCC has a population which includes approximately 3% minorities. Based on prior MCCC studies involving similar disease sites, we expect about 3-5% of patients will be classified as minorities by

race and about 100% of patients will be women. Expected sizes of racial by gender subsets are shown in the following table:

16.64 Table of Accrual by Ethnicity/Race/Gender

Accrual Targets			
	Sex/Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	1	0	1
Not Hispanic or Latino	37	0	37
Ethnic Category: Total of all subjects	38	0	38
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	1	0	1
Black or African American	1	0	1
Native Hawaiian or other Pacific Islander	0	0	0
White	36	0	36
Racial Category: Total of all subjects	38	0	38

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens

17.1 Summary Table of Research Tissue Specimens to be Collected for this Protocol

Correlative Study (Section for more information)	Type of Tissue to Collect	Block, Slides, Core, etc. (# of each to submit)	Baseline	End of Cycle 1 (prior to pembro)	End of Tx for any reason	Process at site? (Yes or No)	Temperature Conditions for Storage /Shipping
Tumor infiltrating lymphocytes (Section 17.41	FFPE	H&E slide and 5 unstained slides of 5 microns.	Mandatory	Optional	Optional	Yes	Ambient
Immunohistochemistry for PD-L1 (Section 17.42)	FFPE	2 unstained slides of 5 microns	Mandatory	Optional	Optional	Yes	Ambient
Gene expression analysis (Section 17.43)	FFPE	10 unstained slides of 5 microns	Mandatory	Optional	Optional	Yes	Ambient
PDJ amplification (Section 17.44)	FFPE	2 unstained slides of 5 microns	Mandatory	Optional	Optional	Yes	Ambient

NOTE: First biopsy* is mandatory, second and third are optional. (*Unless adequate tissue is available from biopsy obtained ≤90 days prior to registration)

NOTE: Tests are listed in order of priority. If insufficient material to do all items, start with top and work down.

17.2 Diagnostic Slides from Original and /or Recurrent Tissue

Please see the number of required unstained slides for each test in the table. Slides should be sent to BAP lab in Jacksonville

Along with original diagnostic slides, include pathology reporting form, surgical pathology report and operative report.

17.3 Correlative Tissue Collection

17.31 Tissue Kits will not be provided for this protocol. Kits will be supplied by the Mayo Florida Biospecimen Acessioning and Processing Shared Resource (BAP). See section 14.31 on how to order kits.

17.32 Paraffin Embedded Tissue

17.321 Submit H&E as well as uncharged, unstained slides – see table. Do not use coverslips, do not bake. 5 micron thick sections on uncharged slides at ambient temperature.

17.322 

17.33 Correlative Tissue will be sent to:

17.4 Background and Methodology

17.41 Tumor infiltrating lymphocytes

Given that tumor infiltrating lymphocytes (TILs) have been shown to correlate with patients' outcome in several tumor types, we plan to evaluate both stromal and intraepithelial TILs in patient samples from this trial. Besides H&E, more comprehensive evaluation of TILs will be performed using immunohistochemistry (IHC) staining for CD4, CD8, CD25, and FOXP3 as we previously published {Knutson 2015}.

17.42 Immunohistochemistry for PD-L1

Since PD-L1 expression had been shown to correlate with response to anti-PD1 therapy in the past20, we also plan to evaluate PD-L1 expression by immunohistochemistry {Topalian 2012}

17.43 Gene expression analysis

Global assessment of immune-related gene expression in pre- and post-treatment tumors will be assessed to potentially identify baseline gene expression signature and/or changes in gene expression that may predict response to this combination.

Gene expression analysis will be performed using NanoString platform with the nCounter GX Human ImmunologyV2 panel comprised of 594 immune-related and 15 reference genes.

17.44 PDJ amplification

We have recently reported that approximately 30% of patients with TNBC harbor PDJ amplification {Barrett 2015}. Locating at chromosome 9p24.1, this amplicon encompasses JAK2, PD-L1, and PD-L2 genes. TNBC patients with PDJ amplification had worse disease free (25.0% vs. 66.0%, p = 0.005) and overall survival (25.0% vs. 69.0%, p = 0.004). This amplicon has been previously described in the majority of Hodgkin's lymphoma, which has been reported to have remarkable response to nivolumab (86% clinical benefit rate in heavily pretreated patients) {Ansell 2015}. Based on these intriguing results, we plan to correlate PDJ amplification and clinical outcome of patients in this trial.

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18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Data submission instructions for this study can be found in the Case Report Form packet.

18.2 Event monitoring

See Section 4.2 and data submission table in the case report form packet for the event monitoring schedule.

18.3 CRF completion

This study will use Medidata Rave for remote data capture (rdc) of all study data.

18.4 Site responsibilities

Each site will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.5 Supporting documentation

This study requires supporting documentation for evidence of response to study therapy and progression after study therapy.

For Phase II patients only, attach a copy of documentation of response or progression in RAVE on the Supporting Documentation Form

18.6 Labelling of materials

Each site will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.7 Incomplete materials

Any materials deemed incomplete by the MCCC Operations Office will be considered "not received" and will not be edited or otherwise processed until the missing information is received. A list of the missing documents will be made available to the appropriate co-sponsor/participant.

18.8 Overdue lists

A list of overdue materials and forms for study patients will be generated monthly. The listings will be sorted by location and will include the patient study registration number. The appropriate co-sponsor/participant will be responsible to obtain the overdue material.

18.9 Corrections forms

If a correction is necessary the QAS will query the site. The query will be sent to the appropriate site to make the correction and return the query and documentation of correction back to the QAS.

19.0 Budget

19.1 Costs charged to patient: routine clinical care

19.2 Tests to be research funded: biopsies and research testing on blood and tissue specimens

19.3 Other budget concerns:

19.31 Binimetinib will be supplied by Pfizer Inc. (formerly Array Biopharma LLC and Array Biopharma Inc.)

19.32 Pembrolizumab will be supplied by Merck.

19.33 Merck, Inc. will provide funding to support this study.

20.0 References

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Appendix I ECOG Performance Status

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

*As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

From http://www.ecog.org/general/perf_stat.html

Appendix II Patient Medication Diary

Name _____ Study ID Number _____

Please complete this diary on a daily basis. Write in the amount of the dose of binimetinib that you took in the appropriate "Day" box. Binimetinib can be taken with or without food and should be taken twice a day approximately 12 hours apart.

On the days that you do not take any study drug, please write in "0". If you forget to take your dose, please write in "0", but remember to take your prescribed dose at the next regularly scheduled time.

Please drink at least 6 to 8 cups of liquid per day to help drug absorption. Swallow pills whole, with water, and do not to break, chew, crush or open the pills.

If you experience any health/medical complaints or take any **NEW** medication other than your regular medications and binimetinib, please record this information.

Week of:

Binimetinib	***Day 1***	***Day 2***	***Day 3***	***Day 4***	***Day 5***	***Day 6***	***Day 7***
Morning dose							
Evening dose							

Week of:

Binimetinib	***Day 8***	***Day 9***	***Day 10***	***Day 11***	***Day 12***	***Day 13***	***Day 14***
Morning dose							
Evening dose							

Week of:

Binimetinib	***Day 15***	***Day 16***	***Day 17***	***Day 18***	***Day 19***	***Day 20***	***Day 21***
Morning dose							
Evening dose							

Patient signature:_____Date: _____

Health or medical complaints during this time:

Other NEW medications or supplements (not previously reported) taken during this time:

Name of NEW medication or supplement	How much did you take? (example: Two 500mg pills)	When did you take it (examples: Every day Or Day 19 and Day 20)

Use a separate sheet of paper if more space is needed.

If you've been instructed by the study team to monitor your Blood Pressure please record your blood pressure readings in the space below. You should take your blood pressure at the same time after taking any hypertensive medications and after being at rest for 5 minutes in a sitting position 10 days & 30 days after starting binimetinib

DAY 10 ( ): _____

DAY 30 ( ): _____

If the systolic reading (top number) is ≥160 mmHg, or diastolic reading (bottom number) is ≥100 mmHg, contact your study team.

My next scheduled visit is: _____
If you have any questions, please call: _____
Bring all bottles and any unused study medication along with this diary when you return for your next appointment.

Study Coordinator Use Only

Number of pills returned _____ Number of bottles returned: _____
Discrepancy Yes____/No____ Verified by _____ Date_____

Appendix III List of medications to be used with caution with binimetinib

List of CYP2B6, CYP2C9 and CYP3A substrates to be used with caution

CYP Enzymes	Substrates
CYP2B6	**Alkylating Agents (anticancer):** cyclophosphamide, ifosfamide, thiotepa **Others:** bupropion[1], efavirenz[1], methadone
CYP2C9	**Angiotensin II Blockers:** losartan, irbesartan **NSAIDs:** diclofenac, ibuprofen, piroxicam **Oral Hypoglycemics:** tolbutamide, glipizide **Others:** acenocoumarol, celecoxib[1], phenytoin[2], sulfamethoxazole, tolbutamide, torsemide, warfarin[2]
CYP3A4,5,7	**Antiarrhythmics:** quinidine→3-OH (not CYP3A5)[2], dronedarone[1] **Antihistamines:** astemizole[2], ebastine[1], [terfenadine][1,2] **Benzodiazepines (CNS agents):** alprazolam, brotizolam[1], diazepam→3OH, midazolam[1], triazolam[1] **Calcium Channel Blockers:** amlodipine, diltiazem, felodipine[1], nifedipine, nisoldipine[1], nitrendipine, verapamil **Protease Inhibitors:** boceprevir, brecanavir[1], capravirine[1], darunavir[1], indinavir[1], lopinavir[1], ritonavir, saquinavir[1], telaprevir, tipranavir[1] **HMG CoA Reductase Inhibitors:** atorvastatin[1], lovastatin[1], simvastatin[1] **Immune Modulators:** cyclosporine[2], everolimus[1], sirolimus[1,2], tacrolimus[1,2] **Antibiotics:** clarithromycin, erythromycin (not CYP3A5), telithromycin **Antipsychotics:** aripiprazole, haloperidol, lurasidone[1], perospirone[1], pimozide[2], quetiapine[1] **Tyrosine Kinase Inhibitors (anticancer):** dasatinib[1], imatinib, neratinib[1], nilotinib **Opioids:** alfentanil[1,2], fentanyl[2], methadone, levomethadyl[1] **Ergot derivatives (for migraines):** diergotamine (dihydroergotamine)[2], ergotamine[2] **Corticosteroids:** budesonide[1], fluticasone[1] **Erectile Dysfunction Agents:** sildenafil[1], vardenafil[1] **Antiemetics:** aprepitant[1], casopitant[1] **Others:** alpha-dihydroergocryptine[1], aplaviroc[1], buspirone[1], cisapride[2], conivaptan[1], darifenacin[1], eletriptan[1], eplerenone[1], lumefantrine[1], maraviroc[1], quinine, ridaforolimus[1], tamoxifen, ticagrelor[1], tolvaptan[1], trazodone, vicriviroc[1], vincristine
This database of CYP substrates was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table; from the FDA's "Guidance for Industry, Drug Interaction Studies" and from the University of Washington's Drug Interaction Database. **1** Sensitive substrates: Drugs that exhibit an AUC ratio (AUCi/AUC) of 5-fold or more when co-administered with a known potent inhibitor. **2** Substrates with narrow therapeutic index (NTI): Drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).	

List of strong CYP3A inhibitors to be used with caution

Strong Inhibitors – AUC substrate increased by ≥ 5 fold
Boceprevir, clarithromycin, cobicistat, conivaptan, elivegravir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir, troleandomycin, voriconazole

List of P-gp inhibitors and dual P-gp/CYP3A inhibitors to be used with caution

Inhibitor* (P-gp probe substrate is **digoxin** unless otherwise specified; CYP3A probe substrate is **midazolam** unless otherwise specified)	**P-gp** **Maximum AUC Ratio (AUC_i/AUC)****	**CYP3A4,5,7** **Inhibition Coding**
Calcium Channel Blockers:		
felodipine	1.5	
verapamil	1.5	2
diltiazem	1.4	2
mibefradil	1.3	3
nifedipine	1.2	
nitrendipine	1.2	
Protease Inhibitors:		
indinavir/ritonavir	4.8[a]	3[d]
indinavir	3.3[a]	3
lopinavir/ritonavir	1.8	3[e]
telaprevir	1.8	3
saquinavir/ritonavir	1.7	3
tipranavir/ritonavir	1.6	3
nelfinavir	1.3	3
ritonavir	1.2	3
Antibiotics:		
fexofenadine	1.7[a]	
clarithromycin	1.7	3
azithromycin	1.7[a]	1
erythromycin	1.5[b]	2
rifampin	1.5	
Antiarrhythmics:		
quinidine	2.7	
dronedarone	2.3	
amiodarone	1.7	
α/β Adrenergic Antagonists:		
carvedilol	1.6	
talinolol	1.2	
Herbal Medications:		
Schisandra chinensis	1.5[b]	
St John's wort (hypericum perforatum)	1.3[a]	
milk thistle (silybum marianum)	1.3[b]	
ginkgo (ginkgo biloba)	1.2[b]	

Inhibitor* (P-gp probe substrate is **digoxin** unless otherwise specified; CYP3A probe substrate is **midazolam** unless otherwise specified)	**P-gp** **Maximum AUC Ratio (AUC_i/AUC)****	**CYP3A4,5,7** **Inhibition Coding**
Others:		
valspodar (PSC 833)	3	
elacridar (GF120918)	2.4[c]	
ranolazine	1.9	
fluvoxamine	1.8[a]	1
amiodarone	1.7	
itraconazole	1.7	
quercetin	1.6[a]	
captopril	1.4	
conivaptan	1.4	
paroxetine	1.4[a]	
ticagrelor	1.3	
telmisartan	1.2	
tolvaptan	1.2	1

*This database of P-gp and CYP3A inhibitors was compiled from the FDA's "Guidance for Industry, Drug Interaction Studies;" and from the University of Washington (UW)'s Drug Interaction Database.
**Maximum AUC ratios are provided from UW Database.
X = 3 for strong inhibitors, which result in substrate AUC ratio (AUCi/AUC) of ≥ 5-fold.
X = 2 for moderate inhibitors, which result in substrate AUC ratio (AUCi/AUC) of ≥ 2-fold and < 5-fold.
X = 1 for weak inhibitors, which result in substrate AUC ratio (AUCi/AUC) of ≥ 1.25-fold and < 2-fold.
X = BLANK for inhibitors whose level of inhibition is unknown or results in an AUC ratio (AUCi/AUC) of < 1.25-fold.
[a] P-gp probe substrate is fexofenadine. [b] P-gp probe substrate is talinolol. [c] P-gp probe substrate is topotecan. [d] CYP3A probe substrate is alfentanil. [e] CYP3A probe substrate is aplaviroc.

List of substrates and inhibitors/inducers of human transporters to be used with caution

Transporter	**Substrates**	**Inhibitors**	**Inducers**
P-gp*		See previous table	rifampin (rifampicin), St-John's worth (hypericum perforatum)
BCRP	daunorubicin, doxorubicin, topotecan, rosuvastatin, sulfasalazine	elacridar (GF120918)	

Transporter	Substrates	Inhibitors	Inducers
OATP1B1*	atrasentan, atorvastatin, bosentan, ezetimibe, fluvastatin, glyburide, SN-38, rosuvastatin, simvastatin acid, pitavastatin, pravastatin, repaglinide, rifampin, valsartan, olmesartan		
OATP1B3*	atorvastatin, rosuvastatin, pitavastatin, telmisartan, valsartan, olmesartan		

* This database was compiled from the FDA's "Guidance for Industry, Drug Interaction Studies-study design, data analysis, implications for dosing, and labeling recommendations" published in February 2012

List of drugs with known risk for causing Torsades de Pointes to be used with caution
Substantial evidence supports the conclusion that these drugs, when used as directed in labeling, can prolong the QT interval and can have a risk of Torsades de pointes (TdP) in some patients.

Generic Name	Brand Name	Class/Clinical Use	Comments
Amiodarone	Cordarone®	Anti-arrhythmic / abnormal heart rhythm	Females>Males,TdP risk regarded as low
Amiodarone	Pacerone®	Anti-arrhythmic / abnormal heart rhythm	Females>Males,TdP risk regarded as low
Arsenic trioxide	Trisenox®	Anti-cancer / Leukemia	
Astemizole	Hismanal®	Antihistamine / Allergic rhinitis	No Longer available in U.S.
Azithromycin	Zithromax®	Antibiotic / bacterial infection	
Bepridil	Vascor®	Anti-anginal / heart pain	Females>Males
Chloroquine	Aralen®	Anti-malarial / malaria infection	
Chlorpromazine	Thorazine®	Anti-psychotic/ Anti-emetic / schizophrenia/ nausea	
Cisapride	Propulsid®	GI stimulant / heartburn	No longer available in U.S.
Citalopram	Celexa®	Anti-depressant / depression	
Clarithromycin	Biaxin®	Antibiotic / bacterial infection	

Generic Name	Brand Name	Class/Clinical Use	Comments
Disopyramide	Norpace®	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Dofetilide	Tikosyn®	Anti-arrhythmic / abnormal heart rhythm	Females > Males
Domperidone	Motilium®	Anti-nausea / nausea	Not available in U.S.
Droperidol	Inapsine®	Sedative;Anti-nausea / anesthesia adjunct, nausea	
Erythromycin	E.E.S.®	Antibiotic;GI stimulant / bacterial infection; increase GI motility	Females>Males
Erythromycin	Erythrocin®	Antibiotic;GI stimulant / bacterial infection; increase GI motility	Females>Males
Escitalopram	Cipralex®	Anti-depressant / Major depression/ Anxiety disorders	
Escitalopram	Lexapro®	Anti-depressant / Major depression/ Anxiety disorders	
Flecainide	Tambocor®	Anti-arrhythmic / abnormal heart rhythm	
Halofantrine	Halfan®	Anti-malarial / malaria infection	Females>Males
Haloperidol	Haldol®	Anti-psychotic / schizophrenia, agitation	TdP risk with I.V. or excess dosage
Ibutilide	Corvert®	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Levomethadyl	Orlaam®	Opiate agonist / pain control, narcotic dependence	Not available in U.S.
Mesoridazine	Serentil®	Anti-psychotic / schizophrenia	Removed from US market in 2004
Methadone	Dolophine®	Opiate agonist / pain control, narcotic dependence	Females>Males
Methadone	Methadose®	Opiate agonist / pain control, narcotic dependence	Females>Males
Moxifloxacin	Avelox®	Antibiotic / bacterial infection	
Pentamidine	NebuPent®	Anti-infective / pneumocystis	Females>Males

Generic Name	Brand Name	Class/Clinical Use	Comments
		pneumonia	
Pentamidine	Pentam®	Anti-infective / pneumocystis pneumonia	Females>Males
Pimozide	Orap®	Anti-psychotic / Tourette's tics	Females>Males
Probucol	Lorelco®	Antilipemic / Hypercholesterolemia	No longer available in U.S.
Procainamide	Pronestyl®	Anti-arrhythmic / abnormal heart rhythm	
Procainamide	Procan®	Anti-arrhythmic / abnormal heart rhythm	
Quinidine	Quinaglute®	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Quinidine	Cardioquin®	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Sevoflurane	Ulane®	Anesthetic, general / anesthesia	Label warning for patients with congenital long QT or patients taking QT prolonging drugs
Sevoflurane	Sojourn®	Anesthetic, general / anesthesia	Label warning for patients with congenital long QT or patients taking QT prolonging drugs
Sotalol	Betapace®	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Sparfloxacin	Zagam®	Antibiotic / bacterial infection	No longer available in U.S.
Terfenadine	Seldane®	Antihistamine / Allergic rhinitis	No longer available in U.S.
Thioridazine	Mellaril®	Anti-psychotic / schizophrenia	
Vandetanib	Caprelsa®	Anti-cancer / Thyroid cancer	

List of drugs with possible risk for causing Torsades de Pointes to be used with caution
Substantial evidence supports the conclusion that these drugs, when used as directed in labeling, can cause QT prolongation but there is insufficient evidence at this time that they have a risk of causing TdP.

Generic Name	Brand Name	Class/Clinical Use	Comments
Alfuzosin	Uroxatral®	Alpha1-blocker / Benign prostatic hyperplasia	
Amantadine	Symmetrel®	Dopaminergic/Anti-viral / Anti-infective/ Parkinson's Disease	
Artenimol+piperaquine	Eurartesim®	Anti-malarial /	Not available in U.S.
Atazanavir	Reyataz®	Protease inhibitor / HIV	
Bedaquiline	Sirturo®	Anti-infective / Drug-resistant Tuberculosis	Black Box for QT
Chloral hydrate	Noctec®	Sedative / sedation/ insomnia	
Clozapine	Clozaril®	Anti-psychotic / schizophrenia	
Dolasetron	Anzemet®	Anti-nausea / nausea, vomiting	
Dronedarone	Multaq®	Anti-arrhythmic / Atrial Fibrillation	
Eribulin	Halaven®	Anti-cancer / metastatic breast neoplasias	
Famotidine	Pepcid®	H2-receptor antagonist / Peptic ulcer/ GERD	
Felbamate	Felbatol®	Anti-convulsant / seizure	
Fingolimod	Gilenya®	Immunosuppressant / Multiple Sclerosis	
Foscarnet	Foscavir®	Anti-viral / HIV infection	
Fosphenytoin	Cerebyx®	Anti-convulsant / seizure	
Gatifloxacin	Tequin®	Antibiotic / bacterial infection	Oral/I.V. forms no longer available in U.S. and Canada, only ophthalmic
Gemifloxacin	Factive®	Antibiotic / bacterial infection	
Granisetron	Kytril®	Anti-nausea / nausea and vomiting	
Iloperidone	Fanapt®	Antipsychotic, atypical / Schizophrenia	

Generic Name	Brand Name	Class/Clinical Use	Comments
Indapamide	Lozol®	Diuretic / stimulate urine & salt loss	
Isradipine	Dynacirc®	Anti-hypertensive / high blood pressure	
Lapatinib	Tykerb®	Anti-cancer / breast cancer, metastatic	
Lapatinib	Tyverb®	Anti-cancer / breast cancer, metastatic	
Levofloxacin	Levaquin®	Antibiotic / bacterial infection	
Lithium	Eskalith®	Anti-mania / bipolar disorder	
Lithium	Lithobid®	Anti-mania / bipolar disorder	
Mirtazapine	Remeron	Anti-depressant /	
Moexipril/HCTZ	Uniretic®	Anti-hypertensive / high blood pressure	
Nicardipine	Cardene®	Anti-hypertensive / high blood pressure	
Nilotinib	Tasigna®	Anti-cancer / Leukemia	
Octreotide	Sandostatin®	Endocrine / acromegaly, carcinoid diarrhea	
Ofloxacin	Floxin®	Antibiotic / bacterial infection	
Olanzapine	Zyprexa®	Antipsychotic, atypical / Schizophrenia, bipolar	Combo c fluoxetine: Symbyax
Ondansetron	Zofran®	Anti-emetic / nausea and vomiting	
Oxytocin	Pitocin®	Oxytocic / Labor stimulation	
Paliperidone	Invega®	Antipsychotic, atypical / Schizophrenia	
Perflutren lipid microspheres	Definity®	Imaging contrast agent / Echocardiography	
Quetiapine	Seroquel®	Anti-psychotic / schizophrenia	
Ranolazine	Ranexa®	Anti-anginal / chronic angina	
Risperidone	Risperdal®	Anti-psychotic / schizophrenia	

Generic Name	Brand Name	Class/Clinical Use	Comments
Roxithromycin*	Rulide®	Antibiotic / bacterial infection	*Not available in U.S.
Sertindole	Serdolect®	Antipsychotic, atypical / Anxiety, Schizophrenia	Not available in U.S.
Sertindole	Serlect®	Antipsychotic, atypical / Anxiety, Schizophrenia	Not available in U.S.
Sunitinib	Sutent®	Anti-cancer / RCC, GIST	
Tacrolimus	Prograf®	Immunosuppressant / Immune suppression	
Tamoxifen	Nolvadex®	Anti-cancer / breast cancer	
Telithromycin	Ketek®	Antibiotic / bacterial infection	
Tizanidine	Zanaflex®	Muscle relaxant /	
Vardenafil	Levitra®	phosphodiesterase inhibitor / vasodilator	
Venlafaxine	Effexor®	Anti-depressant / depression	
Voriconazole	VFend®	Anti-fungal / anti-fungal	
Ziprasidone	Geodon®	Anti-psychotic / schizophrenia	

List of drugs with conditional risk for causing Torsades de Pointes to be used with caution
Substantial evidence supports the conclusion that these drugs can prolong QT and therefore have a risk of TdP but only under certain known conditions (e.g. excessive dose, drug interaction, etc.).

Generic Name	Brand Name	Class/Clinical Use	Comments
Amisulpride	Solian® and others	Antipsychotic, atypical /	Risk of TdP with overdose - not available in US
Amitriptyline	Elavil®	Tricyclic Antidepressant / depression	Risk of TdP with overdosage
Ciprofloxacin	Cipro®	Antibiotic / bacterial infection	Drug interaction risk - metabolic inhibitor
Clomipramine	Anafranil®	Tricyclic Antidepressant / depression	
Desipramine	Pertofrane®	Tricyclic Antidepressant / depression	Risk of TdP with overdosage
Diphenhydramine	Benadryl®	Antihistamine / Allergic rhinitis, insomnia	Risk of QT increase/TdP in overdosages

Generic Name	Brand Name	Class/Clinical Use	Comments
Diphenhydramine	Nytol®	Antihistamine / Allergic rhinitis, insomnia	Risk of QT increase/TdP in overdosages
Doxepin	Sinequan®	Tricyclic Antidepressant / depression	
Fluconazole	Diflucan®	Anti-fungal / fungal infection	Drug interaction risk-metabolic inhibitor. Can also increase QT at high doses - 800 mg/day
Fluoxetine	Sarafem®	Anti-depressant / depression	
Fluoxetine	Prozac®	Anti-depressant / depression	
Galantamine	Reminyl®	Cholinesterase inhibitor / Dementia, Alzheimer's	
Imipramine	Norfranil®	Tricyclic Antidepressant / depression	TdP risk with excess dosage
Itraconazole	Sporanox®	Anti-fungal / fungal infection	Drug interaction risk - metabolic inhibitor
Ketoconazole	Nizoral®	Anti-fungal / fungal infection	Prolongs QT & Drug interaction risk - metabolic inhibitor.
Nortriptyline	Pamelor®	Tricyclic Antidepressant / depression	
Paroxetine	Paxil®	Anti-depressant / depression	
Protriptyline	Vivactil®	Tricyclic Antidepressant / depression	
Quinine sulfate	Qualaquin®	Anti-malarial / Malaria or leg cramps	TdP with overdose or drug-drug or drug food interaction
Ritonavir	Norvir®	Protease inhibitor / HIV	
Sertraline	Zoloft®	Anti-depressant / depression	
Solifenacin	VESIcare®	muscarinic receptor anatagonist / treatment of overactive bladder	
Trazodone	Desyrel®	Anti-depressant / Depression, insomnia	
Trimethoprim-Sulfa	Septra® or Bactrim®	Antibiotic / bacterial infection	Also available in DS (double strength)

Generic Name	Brand Name	Class/Clinical Use	Comments
Trimipramine	Surmontil®	Tricyclic Antidepressant / depression	

Appendix IV Biospecimen Accessioning Processing Requisition Form

MAYO CLINIC [redacted]	**Patient Initials:** ☐ ☐ ☐ F M L **Other Subject ID #:** ☐☐☐☐ **Date of Birth:** ☐☐-☐☐☐-☐☐☐☐ Day Month Year **Gender:** ☐ **Male** ☐ **Female**
Study Name: MC1632 **Study Contact**: **Collection Site Contact: (Please write/print legibly)** Name: _____ Phone: _____ Email: _____ **Place Patient Label below:**	**Visit Description:** Please check box and include label time point ☐ Visit: Blood Draw Label _____ ☐ Visit: Tissue Label _____ **Specimen collection** **Date:** ☐☐☐-☐☐-☐☐☐☐ (M-D-Y) **Time:** ☐☐ : ☐☐ (24-hour clock) **FedEx Tracking Number: Please fill in prior to shipping** ☐☐☐☐☐☐☐☐☐☐☐☐ **Notes: Send package – Priority Overnightt** [redacted]

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