Version: November 11, 2016

SPONSOR: M.D. Anderson Cancer Center
SUPPORTERS: Merck, BiolineRx.

TITLE: A Phase IIb Pilot study to assess the efficacy, safety and pharmacodynamics effects of Pembrolizumab and BL-8040 in Patients with Metastatic Pancreatic Cancer.

IND NUMBER: 131, 637

Principal Investigator:

David Fogelman, MD, Assistant Professor,

1515 Holcombe Blvd, Unit 426, Department of GI Medical Oncology, Houston, TX 77030,

Phone: 713-792-2828

Email : dfogelman@mdanderson.org

Statistician: J. Jack Lee, MS, PhD
Professor, Quantitative Research, Biostatistics
MD Anderson Cancer Center
T. Boone Pickens Academic Towe (FCT4.6018)
1515 Holcombe Blvd., Unit 1411
Houston, TX 77030
Phone (713) 794-4158 office

CONTENTS

LIST OF TABLES

LIST OF FIGURES

1.0 TRIAL ABSTRACT

Abbreviated Title	Pembrolizumab and BL8040 in Pancreatic Cancer
Trial Phase	Phase II study
Clinical Indication	Metastatic Pancreatic cancer
Trial Type	IIb, Pilot Study
Type of control	None
Route of administration	Pembrolizumab IV; Bioline 8040 Subcutaneous (SC)
Trial Blinding	None
Treatment Groups	Single arm
Number of trial subjects	15
Estimated enrollment period	6 months
Estimated duration of trial	24 months Each subject will participate in the trial from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening phase of up to 28 days, patients are treated based on three week cycles. In cycle 1, a daily dose of BL-8040 will be administered subcutaneously on days 1-5 and 8-12 (e.g. Mon-Fri for the first two weeks), week three will be free of treatment. No pembrolizumab will be administered during cycle 1. Cycles two and beyond will include pembrolizumab, administered on day 1 of the cycle, and BL-8040, administered BIW on weeks 1 and 2 (e.g. days 1,4, 8, and 11 of the 21 day cycle). In week three there will be no dosing. Dose Selection/Modification Treatment will continue until progressive disease, unacceptable adverse events, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdrawal of consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, subject receives 17 treatments (approximately 1 year) of pembrolizumab, or administrative reasons requiring cessation of treatment. Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up visits for monitoring disease status until progressive disease, initiating a non-study cancer treatment, withdrawing consent from study participation, or becoming lost to follow-up. All subjects will be followed (by telephone or visit) for overall survival until death, withdrawal of consent from study participation, or the end of the study. After the end of study treatment, each subject will be followed for 30 days for adverse event monitoring. Serious adverse events will be collected for 30 days after the end of treatment.
Duration of Participation	12 months
Estimated average length of treatment per patient	4 months

Statisical Analysis Plan	Simon's 2-stage design will be used. The null hypothesis that the true response rate is 10% will be tested against a one-sided alternative. In this treatment arm, 15 patients will be accrued. If there is </= 1 response in these 15 patients, research into this combination will be halted. If we see significant activity, we will plan to study (in a subsequent protocol) an additional 26 patients, for a total of 41. The null hypothesis will be rejected if 8 or more responses are observed in 41 patients. This design yields a type I error rate of 5% and power of 80% when the true response rate is 25%. The 15 patients needed for this analysis will be enrolled as one cohort. Patients who do not receive study drug, and patients who receive BL only (cycle 1) and who withdraw from the study for reasons unrelated to safety or efficacy may be replaced in the cohort at the discretion of the investigator.
Correlative Studies	Biomarker research to identify factors important for pembrolizumab therapy will be pursued. Tumor and blood samples (including serum and plasma) from this study may undergo proteomic, genomic, metabolomic, and transcriptional analyses. Additional research may evaluate factors important for predicting responsiveness or resistance to pembrolizumab therapy and other immunologic targets. We will avail ourselves of the services of the M.D. Anderson Tissue Molecular Pathology laboratory – in particular, the immunoprofiling lab (TMPIL) directed by Ignacio Wistuba. Some correlative studies may be performed at Merck Research Labs. Assays may include but are not be limited to: • Tumor PD-L1 Expression by IHC • Immune-related Gene Expression Profile (GEP) by Nanostring and HTG–Edge analysis • Transcriptional Analyses by global messenger RNA profiling • Proteomic Analysis by liquid chromatography/mass spectrometry. • Gene Analyses by next generation sequencing • Planned Genetic Analysis • Whole ExoBlood Analysis - Serum Cytokine Analysis; Liquid Biopsy Analysis; Flow cytometry

2.0 TRIAL DESIGN

2.1 Trial Design

This will be a pilot study investigating combinations of Pembrolizumab (Keytruda) with BL-8040 (CXCR4) in patients with metastatic pancreatic cancer. It will be a single arm trial of 15 patients and is designed to test the response rate and biological impact of their combination.

Patients will initially receive BL-8040 as a single agent, followed by the addition of Pembrolizumab. A biopsy will be performed, preferably from a metastatic site, prior to treatment. An additional biopsy will be performed during the third week of cycle 1. A third, optional biopsy will be requested during the third week of cycle 3.

In order to be eligible, subjects must have at least one measurable lesion per RECIST 1.1 criteria. Although subjects will be enrolled regardless of PD-L1 status, the pre- and post-treatment biopsis will be assessed for PD-L1 expression by IHC.

Beginning with screening, all imaging assessments will be determined by the investigator's institution using RECIST 1.1 criteria. Images will be transferred to Merck for data analysis. On-study imaging assessments will be performed every 9 weeks (63±7 days) calculated from the date of enrollment and independent of treatment delays. RECIST 1.1 will be used by the site for treatment decisions until the first radiologic evidence of progressive disease (PD). Following the first radiologic evidence of PD by RECIST 1.1, treatment decisions may be made by the adaptation of RECIST 1.1 as described in Sections 4.2.3.2 and 7.1.6.4.1.5 termed immune-related RECIST (irRECIST) to accommodate the tumor response patterns seen with pembrolizumab treatment (e.g., tumor flare). This was first described by Nishino, et al. 2013[1], but is further modified for the PD-1 program. For a clinically stable subject with first radiologic evidence of PD, it will be at the discretion of the investigator to continue treating the subject with pembrolizumab until PD is confirmed at least 4 weeks from the date of the first tumor imaging suggesting PD. If radiologic PD is confirmed, the subject should be discontinued from treatment unless, in the opinion of the investigator, the subject is achieving a clinically meaningful benefit; an exception for continued treatment may be considered following consultation with Merck.

Subjects may continue to be treated with pembrolizumab until PD is confirmed by modified RECIST, unacceptable adverse events (AEs), intercurrent illness that prevents further administration of treatment, investigator decides to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, administrative reasons, or the subject has received 17 trial treatments (approximately 1 year) with pembrolizumab. Subjects who discontinue trial treatment will move into the Follow-Up Phase and should be assessed every 9 weeks (±3 weeks) by radiologic imaging to monitor disease status for up to 12 months calculated from the date of treatment and independent of treatment delays and then every 12 weeks (±3 weeks) thereafter. The follow-up phase imaging does not apply to patients who terminate treatment for disease progression. Disease status will continue to be monitored until whichever of the following occurs first: The start of new anti-cancer treatment, disease progression, death, or the end of the study. All subjects, once progressed, will be followed every 12 weeks for OS until death, withdrawal of consent from participation in the study, or the end of the study, whichever comes first.

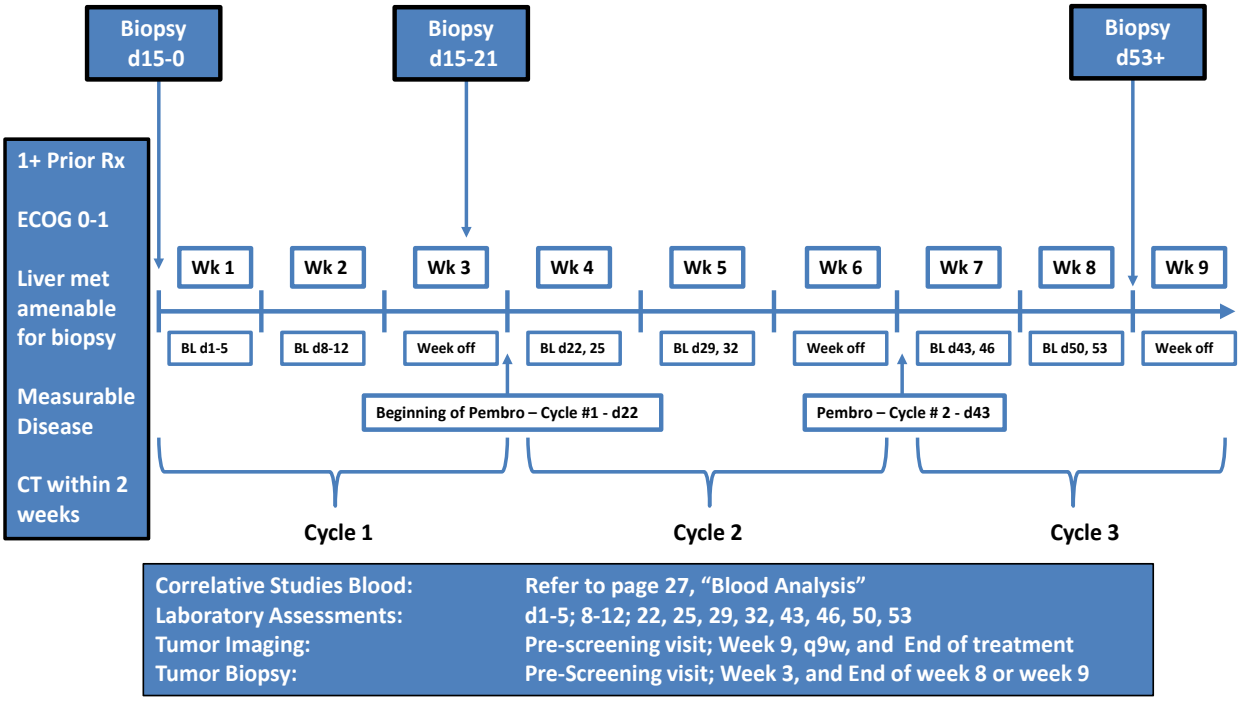
Subjects who attain a complete response (CR) by 2 tumor imaging assessments at least 4 weeks apart and who have received at least 8 treatments (approximately 6 months of therapy) with pembrolizumab may discontinue treatment at the discretion of the investigator after receiving at least 2 treatments beyond the initial determination of a CR. Such patients would thereafter be allowed to resume treatment at the discretion of the investigator in the event of a recurrence.

Adverse events will be monitored throughout the trial and graded in severity according to the guidelines outlined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (Section 12.11). After the end of treatment, each subject will be followed for 30 days for AE monitoring. Serious adverse events (SAEs) will be collected for 30 days after the end of treatment.

This study will be conducted in conformance with Good Clinical Practices (GCP).

2.2 Trial Diagram

Figure 1. Trial Design:



3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective:** To assess the overall response rate (complete response, partial response) after treatment with BL-8040 and Pembrolizumab.

Hypothesis: The increase in immune cell infiltration into pancreatic cancers will slow disease growth, and may result in regression of disease.

3.2 Secondary Objective(s) & Hypothesis(es)

(1) **Objective**: To determine the ability of BL-8040 by itself and in combination with pembrolizumab to increase T cell infiltration into the tumor.

Hypothesis: One of the anticipated effects of BL-8040 is the mobilization of immune cells from the bone marrow and peripheral blood. Another anticipated effects are a reduction of stroma, an increased infiltration of immune cells into tumor and a decrease of the Myeloderived suppressor cells in the tumor microenvironment. If so, we should be able to measure these changes both after single agent BL-8040 administration, as well as after combined treatment with BL-8040 and Pembrolizumab.

(2) **Objective:** To determine if BL-8040 treatment results in increases in circulating immune cells.

Hypothesis: A putative mechanism of BL-8040 is an increase in the release of immune cells from the bone marrow environment. If so, this should be simple to demonstrate through serial blood sampling.

(3) **Objective:** To estimate the safety and tolerability of intravenous administration of pembrolizumab in combination with sub-cutaneously injected BL-8040 in subjects with advanced pancreatic cancer.

Hypothesis: That pembrolizumab and BL-8040 are safe and effective in subjects with advanced pancreatic cancer.

3.3 Exploratory Objectives

(1) **Objective:** To evaluate Overall response rate (ORR) per irRECIST and duration of response (DOR), disease control rate (DCR), time to progression (TTP), progression free survivial (PFS), and Overall survivial (OS) per RECIST and irRECIST assessed by MD Anderson investigators.

(2) **Objective:** To explore the association between PD-L1 expression by immunohistochemistry, shed PD-L1 level, somatic gene expression profiling and antitumor efficacy of pembrolizumab based on RECIST 1.1 imaging criteria as well as overall survival.

(3) **Objective:** To explore the relationship between genomic variation and response to the treatment administered. Variation across the human genome may be analyzed for association with clinical data collected in this study.

(4) **Objective:** Tissue and blood immune monitoring will be conducted through our immune platform group as detailed per the biomarker section based on 3 biopsies done at the following time points: 1) pre-treatment, 2) during the third week of cycle 1, and 3) during the third week of cycle 3.

4.0 BACKGROUND & RATIONALE

4.1 Background

Immunotherapeutic agents such as anti-CTLA4 antibodies and anti-PD-L1 antibodies enhance the immune system's response to cancer. They are effective in a number of tumor types – for example, melanoma and non-small cell lung cancer. However, these agents have been shown to be ineffective against pancreatic ductal adenocarcinoma (PDA). In one early example, BMS-936559, an anti-PD-L1 antibody, was administered to a group of patients with advanced cancer. While responses were seen in patients with melanoma, non-small cell lung cancer, renal cell cancer, and ovarian cancer, none of the 14 patients with pancreatic adenocarcinoma demonstrated a radiologic response[2]. In a later study, investigators at Johns Hopkins treated PDA patients with either ipilimumab alone or in combination with the GVAX vaccine.[3] Again, disappointingly, while some patients demonstrated transient stable disease, there were no objective responses to the combination. One potential mechanism for an absence of efficacy in PDA patients is an ability of these cancers to exclude immune cells from the tumor

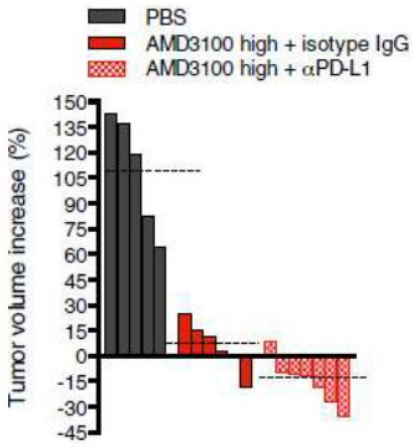
stroma. Accordingly, this study will address whether BL-8040 can overcome this barrier to immunotherapy.

4.1.1 Pharmaceutical and Therapeutic Background – BL-8040

Please refer to the Investigator's Brochure for updated BL-8040 information

BL-8040 is a 14 residue synthetic peptide capped with an aromatic ring. It binds and inhibits the CXCR4 chemokine receptor with high affinity. BL-8040 was shown to be a specific antagonist of CXCR4 and to have a slow dissociation rate from the receptor, with receptor occupancy extending over 24 hours.

There are four potential mechanisms by which BL-8040 may improve the activity of immunotherapy in PDA. First, BL-8040 has demonstrated accelerated mobilization of adult white blood cells (neutrophils, monocytes, lymphocytes) from the bone marrow to the peripheral blood[4]. A single dose in adult healthy volunteers resulted in a substantial increase in T cells, B cells, NK cells, and dendritic cells into the peripheral blood. These include both naïve and effector memory T lymphocyte subsets. One hope is that cells mobilized by this agent may then be available to infiltrate into tumor.



A second potential mechanism includes distraction of stromal barriers to immune cell entry into the tumor. The tumor microenvironment of pancreatic ductal adenocarcinomas (PDA) actively suppresses infiltration of immune cells by secretion of SDF-1/CXCL12, which restrains immune cells from penetrating into the interior of the tumor. CXCR4 inhibition allows T-cell infiltration into the interior of the tumor, allowing for a potential synergistic effect with PD-L1 antibodies.[5] Carcinoma Associated Fibroblasts (CAFs) secrete CXCL12/SDF-1, which in turn coats cancer cells in the tumor. CXCL12 bound to tumor cells suppresses the ability of immune cells to enter the tumor and exert an immunological effect. The application of an exogenous CXCR4 antagonist (AMD3100) to tumor cells in vitro blocks CXCL12 and allows for increased immune suppression. In a mouse model, combination of this exogenous CXCR4 antagonist with PD-L1 antibody was synergistic in inducing T-cell infiltration into the tumor, resulting in tumor shrinkage. FACS analysis confirmed increases in CD45, CD11c, GR1, and CD3, among other T cell markers.

In addition to allowing effector T cells into the tumor, disruption of the CXCR4/CXCL12 interaction may also reduce T suppressor cells from entering the tumor. Righi[6] and others have demonstrated this effect in ovarian cancer model, noting a reduction of FoxP3 T suppressor cells. As this appears to be distinct from the impact on effector cells, this may be considered a third mechanism of action of BL-8040.

A fourth potential mechanism of action of BL-8040 is through upregulation of CCL20, a chemoattractant for dendritic cells (DCs). Prior work with colon cancer and melanoma cell lines has demonstrated that tumor associated DCs reside at the periphery of the tumor and may fail to effectively

stimulate local T cells from a naïve state to an effector state.[7] Stimulation of dendritic cells may result in mature, primed cells that are more capable of inducing an immune response.[8,9] CCL-20/macrophage inflammatory protein-3a (MIP-3a) is a chemoattractant for dendritic cells, and may increase the number of DCs in tumor.[10] BL-8040 has been shown to increase CCL20 production by PDA tumor cells. One goal of this study is to assess whether such an increase may be found in PDA patients treated with this agent.

4.1.2 Pharmaceutical and Therapeutic Background – Pembrolizunab

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-3475

Pembrolizumab (Keytruda, MK-3475) 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) is a programmed death receptor-1 (PD-1)-blocking antibody indicated for the treatment of:

1. Patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

2. Patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA

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.

4.1.3 Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure for Preclinical and Clinical data.

Therapeutic studies in mouse models have shown that the administration of antibodies blocking the PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor rejection, either as a monotherapy or in combination with other treatment modalities. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumor responses as a monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, and colorectal carcinoma. Blockade of the PD-1 pathway effectively promotes CD8+ T-cell infiltration into the tumor and the presence of IFN-γ, granzyme B and perforin, indicating that the mechanism of action involves local infiltration and activation of effector T-cell function in vivo [11-16]. Experiments have confirmed the in vivo efficacy of PD-1 blockade as a monotherapy as well as in combination with chemotherapy in syngeneic mouse tumor models (see the Investigator's Brochure [IB]).

Clinical trials have demonstrated efficacy using pembrolizumab in subjects with advanced melanoma, non-small cell lung cancer, head and neck cancer, bladder cancer, Hodgkin's lymphoma, triple-negative breast cancer, and gastric adenocarcinoma. In addition, recent data demonstrates emerging evidence of single-agent activity in additional tumor types such as mesothelioma, urothelial cancer, ovarian cancer, neuroendocrine carcinoma, and small cell lung cancer.

4.1.4 Ongoing Clinical Trials

Ongoing clinical trials of pembrolizumab are being conducted in advanced melanoma, non- small cell lung cancer, and a number of other advanced solid tumor indications and hematologic malignancies. For study details refer to the IB.

4.2 Rationale

Cancer immunotherapy is a novel and rapidly growing field of research investigating the use of therapies that harness the body's own immune system in the fight against the tumor. Tumors utilize a variety of mechanisms to evade host immune detection. Cancer cells, as well as infiltrating monocytic cells, including dendritic cells and macrophages—express PD-L1, which suppresses the proliferative and effector responses of T cells by engaging the inhibitory PD-1 receptor on these cells. In addition, there is mounting evidence that some tumor-infiltrating immune cells such as MDSCs, T-regulatory cells (Tregs) and tumor-associated macrophages, actively modulate the tumor microenvironment to suppress the effector arms of this response. The aim of cancer immunotherapy is to prevent the tumor's ability to suppress its own detection and elimination by the host immune system. The therapeutic effect of blocking antibodies to the immune checkpoint regulators cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) and the programmed cell death protein 1 (PD-1)/PD-L1 receptor-ligand pair is considered a major breakthrough in the treatment of several solid tumors. Nevertheless, it has become apparent that even if these T cell checkpoint antagonists overcome some of the immune-suppressive effects of the tumor microenvironment, other, more fundamental inhibitory reactions in the tumor microenvironment may constitute the underlying reason for the fact that many subjects— especially those with microsatellite stable colorectal cancer, ovarian cancer, prostate cancer, and pancreatic ductal adenocarcinoma — rarely exhibit objective responses to these therapies.

It was found that activated fibroblasts in the tumor stroma mediate immune suppression in several mouse models of cancer. The basis of the immune suppression involves the production of the chemokine, CXCL12, by cancer associated fibroblasts. Binding of this CXCL12 by T cells leads to their exclusion from the vicinity of the cancer cells. T cell exclusion causes antagonists of T cell checkpoints to be ineffective, despite the presence of cancer-specific CD8+ T cells. The exclusion of CD8+ T cells from the vicinity of cancer cells in CRC was shown to correlate with a poor long-term clinical outcome[17,18]. Exclusion of T cells from the vicinity of cancer cells was also found in ovarian cancer[19,20] and PDA[5]. Thus, the tumor microenvironment can limit the capacity of T cells to accumulate among cancer cells. This immune suppression is interrupted by administering inhibitors of CXCR4, the receptor for CXCL12, which leads to the rapid accumulation of T cells among cancer cells, thereby uncovering the efficacy of immune checkpoints inhibitors[5,21].

BL-8040 (BKT-140) is a 14-residue, cyclic, synthetic peptide capped with an aromatic ring. BL-8040 was shown in vitro and in vivo to be a specific antagonist of CXCR4 with high affinity to the CXCR4 receptor (0.54-5.4 nM) and long receptor occupancy (>48hrs). BL-8040 is considered the most active CXCR4 peptide antagonist among inhibitors of the same class. In vitro and in vivo preclinical studies have shown that in addition to its activity as a mobilizer of hematopoietic cells, BL-8040 exhibits a CXCR4-dependent preferential anti-tumor effect against malignant cells overexpressing CXCR4[22-24]. The efficacy of BL-8040 and its analogues for blocking CXCR4 in vitro and in vivo has been

documented in numerous preclinical studies, including in vitro and in vivo models for small cell lung carcinoma, breast cancer, malignant melanoma, neuroblastoma and pancreatic cancer[25,26] (and unpublished). As a CXCR4 antagonist, BL-8040 affects the trafficking of immune cells to the tumor microenvironment. It was found that administration of BL-8040 induces the mobilization of NK cells, T cells and B-cells from the BM and lymph nodes into the periphery. Using a syngeneic cancer model in mice it was demonstrated that BL-8040 may eliminate the immunological barrier and allow the accumulation of immune cells within the tumor microenvironment (further details are available in the BL-8040 IB).

These findings raise the possibility that increasing the proportion of cancer-specific T cells may be more effective if immunotherapy is combined with a CXCR4 antagonist that alters the immune-suppressive tumor microenvironment. The aim of this study is to examine the effectiveness of combining BL-8040, a CXCR4 antagonist, with pembrolizumab, a PD-1 monoclonal antibody, in pancreatic ductal adenocarcinoma patients.

Blood samples taken throughout the study (baseline, weekly through week 6, end of study) will be investigated specifically for carbohydrate antigen 19-9 (CA 19-9) expressed on the surface of cancer cells as a glycolipid and as an O-linked glycoprotein. CA 19-9 has been identified in the tissue and sera of subjects with gastrointestinal tumors including esophageal, gastric, biliary and pancreatic cancer. CA 19-9 is the most extensively studied and validated serum biomarker for the diagnosis of pancreatic cancer in symptomatic subjects. The CA 19-9 serum level can provide important information with regards to prognosis, overall survival, and response to chemotherapy as well as predict post-operative recurrence.

Blood samples will also be characterized by flow cytometric immunophenotyping to study the kinetics and identity of immune cells enriched in the blood of treated subjects following treatment with the study drugs (baseline, weekly for the first six weeks). Flow cytometric immunophenotyping will evaluate individual cells in suspension for the presence and absence of specific antigens (including but not limited to: CD45, CD3, CD4, CD8, CD56, CD11b, CD86, CD25 and Foxp3) to determine which immune cells are enriched in the blood circulation following the treatment. In addition, the expression and receptors' occupancy by the study drugs will be assessed by means of flow cytometry analysis using specific antibodies against the two targeted proteins, PD-1 and CXCR4.

Biopsy samples from tumor tissue (liver metastasis) will be evaluated for immune cells infiltration by immunohistochemistry and/or immunofluorescence. Using specific markers against specific antigens (including but not limited to: CD45, CD3, CD4, CD8, CD56, CD11b, CD86, CD25 and Foxp3). This study will provide qualitative information with regards to the kinetics and identity of immune cells enriched in the tumor tissue following treatment with the study drugs. Biopsy samples will also be characterized for expression of specific proteins by immunohistochemistry and/or immunofluorescence (including but not limited to: PDL-1, FAP, CCL20, CXCL12 and apoptotic markers) to better understand the molecular signaling affected by treatment with the study drugs and its correlation with response to the treatment under evaluation.

4.2.1 Rationale for the Trial and Selected Subject Population

As a pilot study, we are seeking both an objective response rate to the combination, as well as sufficient numbers of patients who will be amenable for serial biopsies which might inform us as to changes in tumor biology and immune infiltrates after both BL-8040 as a single agent and in combination with pembrolizumab.

4.2.2 Rationale for Dose Selection/Regimen/Modification

4.2.2.1 Pembrolizumab (MK-3475)

The dose of pembrolizumab planned to be studied in this trial is 200 mg Q3W. The dose recently approved in the United States and several other countries for treatment of melanoma subjects is 2 mg/kg Q3W. Information on the rationale for selecting 200 mg Q3W is summarized below.

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent MK-3475. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

4.2.2.2 BL-8040

Dose Selection

In the Phase I/IIa study BKTSC001 (NCT01010880), a dose escalation study to assess the safety of BL-8040 for induction of mobilization of progenitor and stem cells from the BM to the PB in subjects with multiple myeloma, a total of 18 subjects were exposed to escalating doses according to the following scheme:

Group dose	BL-8040 mg/kg [free base]	N
1	0.006 [0.0048]	2
2	0.03 [0.024]	4
3	0.1 [0.08]	4
4	0.3 [0.24]	4
5	0.9 [0.72]	4

In Phase I study, BL-8040.02 (NCT02073019), the safety, tolerability, pharmacodynamic and PK effect of ascending doses of BL-8040 were assessed in healthy subjects. The study had two phases, escalation and expansion. A total of 26 subjects were exposed to escalating doses of BL-8040 according to the following scheme:

Group dose	BL-8040 mg/kg (free base)	N (escalation)	N (expansion)
1	0.5	8 (6 active)	-
2	0.75	8 (6 active)	-

3	1.0	8 (6 active)	8

In addition, ascending doses of BL-8040 were assessed in the BL-8040.01 (NCT01838395) study, a phase IIa study to assess the safety and efficacy of BL-8040 in subjects with relapsed/refractory acute myeloid leukemia. A total of 25 subjects were exposed to seven days of BL-8040 according to the protocol's escalation scheme and three additional subjects received compassionate use therapy according to the scheme below. All doses were found to be safe and well tolerated and the 1.5 mg/kg was selected for the currently ongoing expansion phase.

Group dose	BL-8040 mg/kg (free	N (escalation)	Compassionate use
1	0.5	3	-
2	0.75	3	-
3	1.0	6	-
4	1.25	4	2
5	1.5	6	1
6	2.0	3	-

The maximum tolerated dose (MTD) in humans for BL-8040 has not been reached. A similar PK profile was observed across different clinical studies showing similar exposure between healthy volunteers, multiple myeloma subjects and AML subjects. Adequate receptor occupancy was confirmed from the 1.0 mg/kg dose and higher. The rationale for the suggested combination relies on the ability of BL-8040 as a CXCR4 antagonist to mobilize immune cells from the BM and the lymph nodes to the PB. Rapid and dose-dependent mobilization of WBCs was seen in both, preclinical studies (mice) and humans treated with BL-8040. BL-8040 induces rapid (2-4 hrs), dose-dependent and transient mobilization of WBCs, including monocytes, B-cells, T cells and NK cells. The mobilization effect of BL-8040 was observed at doses of 0.5-2.0mg/kg in all conducted clinical trials. In addition, immune suppression by the tumor microenvironment involves the production of the chemokine, CXCL12 the ligand of CXCR4, by the fibroblastic stromal cells. Binding of CXCL12 by T cells results in their exclusion from the vicinity of the cancer cells. T cell exclusion occurs in several types of human adenocarcinomas, causes antagonists of T cell checkpoints to be ineffective, despite the presence of cancer-specific CD8+ T cells. This immune suppression may be interrupted by administering BL-8040, an inhibitor of CXCR4, the receptor for CXCL12, which leads to the rapid accumulation of T cells among cancer cells, thereby uncovering the efficacy of the anti-PD-1 and eliminating cancer cells. The effect was seen in mice at a dose range of 10-20 mg/kg, equivalent to 0.83-1.66 mg/kg, respectively, in humans.

Although the higher dose tested in the BL-8040.01 study (1.5 mg/kg) in combination with cytarabine was found to be safe and well tolerated and MTD was not achieved, our policy with new combinations is to leave safety margins and use a dose lower than the highest tested exposure in humans. In general, BL-8040 at the dose of 1.25 mg/kg was observed to be associated with a favorable safety profile with

the most common AEs being injection site irritation, flushing, and itching, and systemic reactions that were successfully managed with pre-medication.

Based on the above safety, mobilization and preclinical effect on the tumor microenvironment the 1.25 mg/kg dose was selected for the combination study.

Regimen Selection

The considerations for the proposed regimen (BL-8040 monotherapy at days 1-5 and 8-12 followed by BL-8040 two times a week [BIW] in combination with pembrolizumab 200 mg every three weeks [Q3W] fixed-dose regimen) are as follows:

1. The aim of the BL-8040 monotherapy at days 1-5 and 8-12 is to enable the identification of a single agent effect of BL-8040 on increased T cell infiltration.
2. For the combination cycles, the long receptor occupancy of BL-8040 (48-72 hrs) supports a BIW administration that will ensure continuous CXCR4 inhibition in order to facilitate T effector cell infiltration.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

4.2.3.1.1 Primary Efficacy Endpoints

Objective response rate by RECIST will be the primary endpoint. Immunotherapy has so far been disappointing in pancreatic cancer patients, with little response observed among patients treated with immune checkpoint inhibitors. Observed responses would suggest a synergistic relationship between the two medications. If the combination of pembrolizumab and BL-8040 does have clinical efficacy, we would hope to show this in at least a small number of patients enrolled in our study (see statistical design, section 8).

4.2.3.1.2 Secondary efficacy endpoints

Secondary efficacy endpoints will include among others, progression free survival and overall survival. Secondary endpoints are defined as follow:

1) ORR (overall response rate) , defined as the proportion of subjects who have a CR or PR using irRECIST 1.1 and with confirmatory assessment as required per irRECIST at any time during the trial. Observed responses would suggest a synergistic relationship between the two medications. Subjects with unknown or missing response information will be treated as non-responders.

2) DCR (disease control rate), defined as the proportion of subjects who have a CR, PR, or SD (stable disease) using RECIST 1.1 and with confirmatory assessment as required by

irRECIST at any time during the trial. Subjects with unknown or missing response information will be as not meeting this definition.

3) DOR (duration of response), defined in the subset of subjects with a CR or PR, based on RECIST 1.1 and with confirmatory assessment as required per irRECIST, as the time from first documented evidence of CR or PR until the first documented sign of disease progression or death due to any cause, whichever occurs first. Subjects who are alive, have not progressed, have not initiated new anti-cancer treatment, and have not been determined to be lost to follow-up are considered ongoing responders at the time of analysis.

4) PFS (preogression free survivial), defined as the time from the 1st dose of study treatment to the first documented disease progression according to RECIST 1.1 and with confirmatory assessment as required per irRECIST, or death due to any cause, whichever occurs first. If a subject does not have a documented date of progression or death, PFS will be censored at the date of the last adequate assessment.

5) OS (overall survivial), defined as the time from the date of the 1st dose of study to the date of death due to any cause. Censoring will be performed using the date of last known contact for those who are alive at the time of analysis.

Toxicity endpoints will include treatment emergent adverse events.

4.2.3.1.3 Exploratory Efficacy Endpoints

Tissue and blood immune monitoring will be conducted through our immune platform group as detailed per the biomarker section based on 3 biopsies done at the following time points: 1) pre-treatment, 2) during the third week of cycle 1, and 3) during the third week of cycle 3. Exploratory efficacy objectives of this study are to explore the association between biomarkers including PD-L1 protein expression by IHC, CXCR4 expression, MSI status, mutation burden, cytokine profile, and gene expression profiling, and antitumor efficacy and survival outcome of pembrolizumab based on RECIST 1.1 as assessed by MD Anderson investigators in subjects with pancreatic cancer; and to evaluate ORR, DOR, TTP and PFS per irRECIST assessed by MD Anderson investigators.

4.2.3.2 Immune-related RECIST (irRECIST) measurements

RECIST 1.1 will be the imaging criteria we will use for response assessment. In addition we will us a modified RECIST 1.1 criteria adapted to account for the unique tumor response characteristics seen with pembrolizumab treatment. Immunotherapeutic agents such as pembrolizumab may produce anti-tumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of

new lesions. Standard RECIST 1.1 thus, may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab.

Based on an analysis of patients with melanoma enrolled in Keynote 001, 7% of evaluable patients experienced delayed or early tumor pseudoprogression. Of note, patients who had progressive disease by RECIST 1.1 but not by immune-related response criteria had longer OS than patients with progressive disease by both criteria. Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab in approximately 15% of patients. These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique patterns of atypical response in immunotherapy and enable treatment beyond initial radiographic progression.

irRECIST is RECIST 1.1 adapted to account for the unique tumor response seen with immuno-therapeutics as described in Nishino et al.[1]. The assessment of unidimensional target lesions and response categories per irRECIST are identical to RECIST 1.1. However, Merck has implemented an adaptation related to new lesions, non-target and tumor burden assessment in order to confirm radiographic progression. irRECIST will be used by the investigators to assess tumor response and progression, and make treatment decisions as well as by MD Anderson investigators in support of all secondary and exploratory response endpoints. Confirmation of PD for irRECIST endpoints will be taken from central imaging retrospectively, according to irRECIST definition.

4.2.3.3 Safety Endpoints

The safety objective of this trial is to characterize the safety and tolerability of pembrolizumab in combination with BL-8040 in subjects with previously systemically treated pancreatic cancer. The primary safety analysis will be based on subjects who have toxicities as defined by CTCAE, v4.03.

The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded on case report forms or electronically using PDMS/CORe and DMI. AEs will be analyzed including, but not limited to, all AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, specific events will be collected and designated as events of clinical interest (ECIs) as described in Section 7.2.3.2

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-neoplastic treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade >1 will be followed until the resolution or stabilization of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 30 days following cessation of treatment should be followed and recorded.

4.2.3.4 Biomarker Research

Biomarker research to identify factors important for pembrolizumab therapy will be pursued. Tumor and blood samples (including serum and plasma) from this study may undergo proteomic, genomic, metabolomic, and transcriptional analyses. Additional research may evaluate factors important for predicting responsiveness or resistance to pembrolizumab therapy and other immunologic targets.

We will avail ourselves of the services of the M.D. Anderson Tissue Molecular Pathology laboratory – in particular, the immunoprofiling lab (TMPIL) directed by Ignacio Wistuba. Some of the research may be conducted at Merck Researh Labs and affiliates. Assays may include but are not be limited to:

Tumor PD-L1 Expression

In the pembrolizumab PN001 and PN012 studies, PD-L1 immunohistochemistry (IHC) has successfully been used as a biomarker in the NSCLC and head and neck cancer cohort, respectively, to enrich for a subpopulation with high response to pembrolizumab[27]. Therefore, the relationship between PD-L1 expression in pancreatic tumor tissue and response to treatment with pembrolizumab will be evaluated. PD-L1 expression in tumor cells and inflammatory cells within pre-treatment tumor tissue samples will be characterized by IHC and retrospectively tested for association with response to pembrolizumab. The range of PD-L1 staining in a population of pancreatic tumors may also be used to identify a cut-off, above which a tissue is scored as biomarker positive.

Multiplex Immunofluorescence Analysis (mIF) may be performed on tumor core samples. Three panels will be utilized. Currently, there are two Vectra panels optimized: Panel #1, CD3, CD4, CD8, CD68, PD-L1, pan-cytokeratin and DAPI; Panel #2, PD-1, CD45RO, FOXP3, Granzyme B, CD57, pan-cytokeratin and DAPI. We will optimize a modified Panel #1 and Panel #2 according to Merck request including TIM-3, PD-1 (provided by Merck) and LAG-3. A new Myeloid Panel will be developed and optimized for the study: Myeloid Panel #3, includes CD68, CD163, CD11b, CD33, CD14, Cd66b, pan-cytokeratin and DAPI. These three modified panels will be classified as Panels 6-8, respectively in the IHC lab. For muliplex IF analysis, we will use the Opal chemistry and multispectral microscopy Vectra system (Perkin-Elmer) which includes the Nuance software; analysis will be performed using the InForm software.

The appropriate cellular localization of the markers and the type of cells that express the markers will be taken into account when scoring them. For quantification of PD-1 and other immune markers (immune cells infiltrates, immune checkpoints and other proteins) whole tissue sections or five randomly selected one-mm square areas within the tumor region will be selected for analysis. In selected cases, peritumoral and intratumoral areas will be examined. The expression of markers in malignant cells will be evaluated using image analysis to determine the percentage of positive cells (0 to 100) and intensity (0 to 3+), with a total score ranging from 0 to 300 (H-score system). The intensity is classified as 0 (absent), 1 (weak apparently only on 100x magnification), 2 (moderate apparent on 50x magnification), and 3 (strong apparent on 16x magnification). This scoring system provides criteria that can be reproduced more consistently by pathologists.

The expression of protein markers and inflammatory cells will be examined using an infiltrate density score established by the number of cells expressing a determined marker by tissue area. The data and digital images will be deposited in a central database for review by pathologists. Among other markers, we will study the expression of the following CD3, CD4, CD8, PD-L1, PD-1, FOXP3, CD45RO, CD57, CD68, and Granzyme B; additional markers will be selected according to the PI's decision.

Immune-related Gene Expression Profile (GEP)

Intratumoral expression levels of select genes will be analyzed using an analytically validated platform, such as the NanoString nCounter Analysis System. Association between the immune-related GEP and response to pembrolizumab has been established using these genes in melanoma and in cancers from clinical studies KN012 (head and neck, bladder, and gastric cancers) and KN028 (ovarian, esophageal, and other cancers) [28-30]. Data from these cohorts has been used to derive a GEP which combines the expression levels of several key genes into a single scalar score. The pattern of association in the esophageal cohort of KN028 using a prototype GEP suggested the ability to identify patients who may not respond to pembrolizumab by identifying tumors that have low values of the GEP. The GEP includes genes from immune-regulatory pathways and a GEP score will be tested for association with response to pembrolizumab in retrospective fashion. The relationship between GEP and the probability of response will be used to develop cut-offs that may have high clinical utility.

The immune-gene related panels available range from 100 to 800 genes. Alternatively, if very limited tissue sections are available tumor tissue scraped from one or two histology sections will be placed in the RNA lysate and examined for gene expression using the HTG Edge-Seq™ platform and their immune-oncology panel (IOP) composed of 550 genes. These Nanostring and HTG–Edge analyses will be performed using FFPE tissue from the CNB specimens in the TMPIL.

Transcriptional Analyses

In addition to examining an immune-related GEP described above, global messenger RNA profiling will also be pursued. Expression of individual genes related to the immune system may also be evaluated such as immune signatures and critical cytokines (e.g., IL-10). MicroRNA profiling may also be pursued in serum samples.

Proteomic Analysis

In addition to expression on the tumor tissue, PD-L1 can be shed from tumor and released into the blood. Enzyme-linked immunoassay can measure PD-L1 in serum and correlate this expression with response to pembrolizumab (MK-3475) therapy, as well as levels of PD-L1 IHC or protein in the tumor. Blood would be a less invasive compartment compared to tumor from which to measure PD-L1 protein biomarker. In addition to this specific protein biomarker, both tissue and blood derivatives can be subjected to proteomic profiling studies using a variety of platforms that could include but are not limited to immunoassay, or liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for pembrolizumab (MK-3475) therapy.

Gene Analyses

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to define certain tumor types at the genetic level as being ‘hypermutated’ or it can detect the presence of specific t-cell clones within the tumor microenvironment. There is a potential that this hypermutated state and the detection of increased T-cell clonality may correlate with response to pembrolizumab therapy, and/or that the converse, ‘hypomutated’ state or lack of T-cells clones may correlate with non-response.

Planned Genetic Analysis

Understanding genetic determinants of drug response is an important endeavor during medical research. This research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or adverse events, the data might identify optimal use of therapies in the patient population. This research contributes to understanding genetic determinants of efficacy and safety associated with the treatments in this study.

Whole Exome Sequencing

Flash freezing of biopsy cores in liquid nitrogen may allow for RNA-squencing and Whole Exome Sequencing of tumor. This analysis will be performed using fresh frozen tissue specimens from both CNB and resected tumor tissues at MD Anderson Sequencing Facilities.

Blood Analysis

Patients will have peripheral blood collected at weeks 1, 4, 7, 16, at the time of a confirmed response, and on discontinuation of treatment.

Flow cytometry: High order flow cytometry panels will be designed with input from the investigators at the time of analysis. The panels may include but not be limited to: 1) delineation of major immune cell types (T cells, B cells, NK cells, DCs, MDSCs), 2) determination of T cell differentiation status and limited functionality (IFNg, TNFa, GB) and 3) defining the expression level of costimulatory and coinhibitory molecules on T cells and myeloid cells. The proposed studies will be conducted on cryopreserved PBMCs. All time points belonging to a patient will be stained and acquired at the same time to avoid any technical variation (sample at time of progression will be omitted for responders if analysis needs to be completed when patient is still responding). Briefly, up to 40 cc of peripheral blood from pancreatic cancer patients prior to the initiation of treatment, and at up to7 time points throughout treatment will be processed fresh (within 24h of being drawn) for PBMC isolation. PBMCs will be cryopreserved and stored in Liquid Nitrogen until use. Plasma will be frozen at -80C until use. For flow cytometric analysis cells will be thawed and stained right away. Samples will be stained for surface and/or intracellular markers using standard procedures. Stained samples will be fixed and acquired on a flow cytometer (Fortessa) within one week. Single color controls will be used to adjust compensation and Fluorescence minus one (FMO) controls will be used to set positive gates for markers where the negative and positive population do not clearly separate. Fixable viability dye will be included in all panels to discriminate dead cells.

Liquid Biopsy Analysis: Using plasma specimens, genotyping analysis of circulating free DNA (cfDNA), circulating tumor cells (CTCs), and exosome (exo)-DNA will be perfomed to monitor tumor response and progression at the Molecular Testing Developmental Laboratory (MTDL; Ignacio Wistuba and Raja Luthra) housed in TMP. For cfDNA, both ultra-deep next-generation sequencing (NGS) mutation analysis of a panel of 50 genes (CMS50) (Ion Torrent PGM and Ion Proton), as well as uniplex or multiplex digital droplet PCR (ddPCR, BioRad and Raindance) are available (Raja Luthra, MTDL), using 40-50 ng of DNA extracted from 4-5 ml of plasma (blood, purple top). For CTC analysis, isolation of cells will be performed using the Cynvenio or CellSearch platforms using 10 ml of blood (1 tube

purple top), followed by NGS or ddPCR analysis of gene mutations (Beverly Handy, MTDL). For exo-DNA analysis, at least 5 ml of plasma will be used for exosome isolation utilizing a ultracentrifugation-based method followed by NGS (WES, targeted-sequencing, RNA-sequencing). Liquid biopsy has a total ~20 ml blood requirement, using 2 purple top tubes (EDTA).

Serum Cytokine Analysis: Serum cytokines to be measured include IFN-γ, granzyme B, perforin, IL-10, CCL20/MIP3α, CXCL12/SDF-1. Standard pancreatic cancer markers will also be assessed (e.g. CA 19-9, CEA). Additional cytokines may be selected at the discretion of the investigators based on emerging literature.

4.2.3.5 Future Biomedical Research

As an optional procedure for willing patients, the M.D. Anderson and Merck will retain specimens for Future Biomedical Research during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes.

4.3 Benefit/Risk

Subjects in clinical trials may not receive direct benefit from treatment during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine. Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying IB and Informed Consent documents.

5.0 METHODOLOGY

5.1 Entry Criteria

Selected patients will have a diagnosis of a pancreatic adenocarcinoma, and will have received at least one prior regimen of therapy for metasatic disease. Patients may have had an unlimited number of treatments in the neoadjuvant or adjuvant setting prior to the appearance of metastatic disease.

5.1.1 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Have histologically or cytologically confirmed diagnosis of pancreatic adenocarcinoma based on pathology report

2. Be willing and able to provide written informed consent for the trial.

3. Be ≥ 18 years of age on day of signing informed consent.

4. Have measurable disease based on RECIST 1.1 Target lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

5. Have had prior treatment with first-line therapy

   Note: the same image acquisition and processing parameters should be used throughout the study for a given subject.

6. Be willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion from a metastatic site. *Newly-obtained is defined as a specimen obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1. Subjects for whom newly-obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived specimen only upon agreement from Merck . The specimen must be from a biopsy site that would be accessible for at least one subsequent biopsy after initiation on the trial.*

7. Have a performance status of 0 or 1 on the ECOG Performance Scale.

8. Have a predicted life expectancy of greater than 3 months.

9. Demonstrate adequate organ function as defined in Table 1. All screening labs should be performed within 10 days of treatment initiation.

Table 1. Adequate Organ Function Laboratory Values:

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,000/mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 14 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > ULN
AST (SGOT) and ALT (SGPT)	≤ 1.5 X ULN
Albumin	≥3.3 mg/dL in the absence of dehydration
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

10. Have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication (Cycle 1, Day 1) (female subjects of childbearing potential). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
11. Be willing to use an adequate method of contraception for the course of the study through 120 days after the last dose of study medication (male and female subjects of childbearing potential.

    Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

    Acceptable methods of contraception are as follows:
    - 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

5.1.2 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Has pancreatic tumor other than adenocarcinoma, including: acinar cell carcinoma, pancreaticoblastoma, malignant cystic neoplasms, endocrine neoplasms, squamous cell carcinoma. Vater and periampullary duodenal or common bile duct malignancies.
2. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy, herbal/complementary oral or IV medicine, or used an investigation device within 4 weeks of the first dose of treatment.
3. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

4. Had a solid organ or hematologic transplant.
5. Has active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs). 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.
6. Has a diagnosed additional malignancy within 1 year prior to first dose of study treatment with the exception of curatively treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin and/or curatively resected in situ cervical and/or breast cancers.
7. Has radiographically detectable (even if asymptomatic and/or previously treated) central nervous system (CNS) metastases and/or carcinomatous meningitis as assessed by the investigator and radiology review.
8. Subjects excluded if there is a history of (non-infectious) pneumonitis that required steroids, evidence of interstitial lung disease, or active, non-infectious pneumonitis.
9. Has an active infection requiring systemic therapy.
10. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, 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, including dialysis.
11. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
12. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.
13. Has received prior immunotherapy including anti–PD-1, anti–PD-L1, or anti–PD-L2 agents, or if the subject has previously participated in Merck pembrolizumab clinical trials.
14. Has a known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies).
15. Has known Hepatitis B or Hepatitis C
16. Has received a live vaccine within 30 days of planned start of study therapy (Cycle 1, Day 1).
    a. Note: The killed virus vaccines used for seasonal influenza vaccines for injection are allowed; however intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.
17. Has a known history of active TB (Bacillus Tuberculosis)
18. Unable to tolerate a contrast enhanced CT or MRI for staging/restaging purposes
19. Hypersensitivity to pembrolizumab or any of its excipients.

20. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to such agents administered more than 4 weeks earlier.

21. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered small molecule agent.

    a. Note: Subjects with ≤ Grade 2 neuropathy or alopecia are an exception to this criterion and may qualify for the study.

    b. Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

22. Patients requiring beta blockade are disqualified from participating in this study.

23. Patients who, in the estimation of the treating physician or primary investigator, have had a clinical deterioration of their ECOG performance within the month prior to enrollment.

24. The use of natural or synthetic cannabinoids

25. Patients with unstable angina, new onset angina within the last 3 months, myocardial infarction within the last 6 months, and current congestive heart failure New York Heart Association Class III or higher.

5.2 Trial Treatments

The treatment to be used in this trial is outlined below in **Table 2**

Table 2. Trial Treatment:

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen / Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental
BL-8040	1.25 mg/kg	See chart	Subcutaneous	See chart	Experimental

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations

Treatment will be based on three week cycles. In cycle 1, a daily dose of BL-8040 will be administered subcutaneously on days 1-5 and 8-12 (e.g. Mon-Fri for the first two weeks). No pembrolizumab will be administered during cycle 1.

A pre-treatment biopsy is mandated prior to the start of cycle 1. A second biopsy is mandated during the third week of cycle 1. An optional biopsy will be requested during the third week of cycle 3.

Cycles two and beyond will include pembrolizumab, administered on day 1 of each 21 day cycle, and BL-8040, administered BIW on days 1, 4, 8, and 11 of each 21 day cycle.

5.2.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background and Rationale.

Details on preparation and administration of pembrolizumab (MK-3475) and BL-8040 are provided in the Investigator's Brochures.

5.2.2 Dose Modification (Escalation/Titration/Other)

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events 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 Table 3 below. See Section 5.5.2 for supportive care guidelines, including use of corticosteroids.

Table 3. Dose Modification Guidelines for Drug-Related Adverse Events:

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose
	3-4	Permanently discontinue (see exception below)[a]	Permanently discontinue
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
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
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
Infusion Reaction	2[b]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4 Or recurrent gr 2	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[c]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid 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; Refer to Table 4 – Infusion Treatment Guidelines for further management details.

[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.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Merck. The reason for interruption should be documented in the patient's study record.

For BL-8040, in case of clinical evidence of leukostasis or WBC >60,000/μL, BL-8040 will be skipped. Treatment with BL-8040 may be resumed when WBC ≤60,000/μl and/ or there are no signs of leukostasis. BL-8040 injections can be skipped for any reason as per Investigator judgment; however they must be skipped in case of a significant increase in WBC >60,000/μL, measured prior to administration of the next BL-8040 injection and/or evidence of leukostasis. In this case daily WBC assessment should be done, and BL-8040 treatment can be resumed provided the WBC counts decrease to ≤ 60,000/μL. Pre-dosing WBC monitoring should continue as long as the WBC count is ≥40,000/μL. For values <40,000/μL daily WBC monitoring can be stopped and further analysis should be done based on the Investigator's judgment.

In case more than two consecutive doses are skipped during the monotherapy period and more than three consecutive doses (a week of treatment) during the combination period, the primary investigator will assess the risk-benefit and decide whether there is a need for treatment sequence modification or whether the subject should discontinue the study participation.

During cycle 1, if fewer than 7 doses of BL-8040 can be administered during the first two weeks of therapy, it will be to the investigator's discretion whether to complete the remaining doses during week 3.

5.2.3 Timing of Dose Administration

Cycle 2 Day 1 treatment with pembrolizumab should begin on schedule, but a delay of up to 3 days is permitted.

Trial treatment should begin on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks.

BL-8040 will be administered as a single subcutaneous dose in the Ambulatory Treatment Center or CTRC. A delay of pembrolizumab does not necessarily require a delay of BL-8040 if the reason for delay is unlikely to be or unrelated to BL-8040.

The Investigators' Brochures contain specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution as well as the BL-80040 preparation and administration.

BL-8040 dosing may be adjusted by ± 1 day for either patient convenience or at the discretion of the investigator, with a maximum of one dose per day. The final dose of BL-8040 in each cycle may be deferred by up to three days. Missed doses of BL-8040 will otherwise not be replaced with the exception of cycle 1. During cycle 1, if fewer than 7 doses of BL-8040 can be administered during the first two weeks of therapy, it will be to the investigator's discretion whether to complete the remaining doses during week 3

Hydrocortisone 100 mg IV and diphenhydramine (25 mg PO or IV, each repeated once if necessary) may be given for systemic reactions to BL-8040 and may be used prophylactically for subsequent BL-8040 dose administration).

5.2.4 Trial Blinding/Masking

This is an open-label trial. All parties will know the treatment administered.

5.3 Treatment Assignment

All enrolled subjects will treated in a non-randomised fashion.

5.4 Stratification

No stratification based on age, sex or other characteristics will be used in this trial.

5.5 Concomitant Medications/Vaccinations (allowed & prohibited)

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 investigator should discuss any questions regarding this with the Merck Clinical team. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

5.5.1 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 in the DMI database 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 will 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. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2. Allowed Concomitant Medications.

- Premedication prior to BL-8040 injection with antihistamines in order to minimize the occurrence of BL-8040 related systemic reactions is recommended. Systemic steroids are allowed for the treatment of these reactions; they may be used as pre-medication for these reactions at the discretion of the investigator.
- Clinically appropriate measures in case of BL-8040-related local injection site reactions e.g., local corticosteroids, systemic and local painkillers, antihistamines, local treatments etc.
- Antiemetic drugs (e.g., Ondansetron) as required clinically based on local guidelines for subjects experiencing nausea.
- Prophylactic antibiotics when appropriate. (e.g., quinolone or cephalosporin), anti-fungals (e.g., voriconazole) and antivirals (e.g., valacyclovir).
- Blood products, commonly required in oncology subjects.
- Low-dose steroids are allowed as pre-medication for blood transfusion or with IV anti-fungals.

Additional medications/therapies to manage treatment or disease emergent conditions will be allowed at the discretion of the Investigator in consultation with Merck and BiolineRx, in advance where possible. In case there is a change in therapy related to an AE, the Investigator may decide to withdraw the subject

5.5.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase 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: Prior CNS radiation is a contraindication to enrollment as noted in the exclusion criteria. After enrollment, radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion. Such a radiated lesion must not be a RECIST 1.1 target lesion and the subject must have clear measurable disease outside the irradiated field.

- 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, BCG, and typhoid vaccine.

- Glucocorticoids (inhaled steroids as part of a stable regimen for the treatment of asthma/COPD are permitted) for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology or treatment of systemnic and local injection reaction secondary to BL-8040 treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the primary investigator and Merck.
- Chronic use of NSAIDs with a high risk of bleeding, for example, indomethacin, ibuprofen, naproxen, or similar agents. Chronic use of aspirin up to 325 mg/day is permitted.

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.

It is important for investigators to review each medication (prescription and non-prescription) the subject is taking before starting the study and at each study visit.

- At each visit, subjects should be questioned about any new drug they are taking.
- To minimize the risk of adverse drug interactions, every effort should be made to limit the number of concomitant drugs to those that are truly essential.
- Drugs known to be hepatotoxic (i.e., drugs with a warning of hepatotoxicity in the package insert) should be avoided during the dosing period. Investigators are encouraged to review each medication for potential hepatotoxicity by searching the www.livertox.nih.gov website.

Listed below are specific restrictions for concomitant therapy during the course of the trial.

The following medications/therapies are contraindicated during the dosing period and for 14 days thereafter:

Known hepatotoxic drugs, including but not limited to:

- Etifoxine
- Isoniazid
- Nitrofurantoin
- Ketoconazole
- Amiodarone
- Phenytoin
- Herbal supplements

The Exclusion Criteria describes other medications which are prohibited in this trial.

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

5.6 Rescue Medications & Supportive Care

5.6.1 Rescue Medications

No rescue medications are specified to be used in this trial.

5.6.2 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. 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 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 5.2.1 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.

- **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**:

  Subjects 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 subjects 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**:
  - 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. However, this will require discontinuation of study treatment.
- 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**:

  Refer to Section 7.2.4.2. for specific hepatic events of clinical interest

  Treatment interruption and discontinuation:

  Elevated transaminases and alkaline phosphatase may be seen during treatment. Treatment should be interrupted per dose modification table above. Evaluation of subjects with elevated transaminases, direct bilirubin, and alkaline phosphatase should involve a work-up to assess for infection (spontaneous bacterial peritonitis or other), viral reactivation (if relevant), vascular thrombosis, biliary obstruction, possible hepatotoxic medications, tumor progression, alcohol toxicity, and effects of pembrolizumab. In 1567 subjects with other cancers treated with pembrolizumab, rates of autoimmune hepatitis were 1%, so it is quite rare. However, it needs to be considered in the differential of elevated liver function tests.

- For **Grade 4** total bilirubin or PT/INR, study treatment should be permanently discontinued.
- **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.
- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

  Table 4 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 4. Infusion Reaction Treatment Guidelines:

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines,	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to:	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. 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. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	(MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

Patients who develop a reaction to BL-8040 may be treated with hydrocortisone (100 mg IV) and diphenhydramine (25 mg IV or PO, repeated if necessary).

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

5.7.2 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 subjects 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 subjects 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 first dose of study treatment;

screening;

OR

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

Female and male subjects 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 subjects participating at sites in this country/region.

Subjects 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 subjects 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 subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the primary investigator and Merck without delay and within 72 hours 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 to Merck. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to Merck and followed as described above and in Section 7.2.2.

5.7.4 Use in Nursing Women

It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.5 – Other Procedures.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression

  Note: For unconfirmed radiographic disease progression, please see Section 4.2.3.2

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section 4.2.3.2
- Unacceptable adverse experiences
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 12 months of uninterrupted treatment with pembrolizumab or 17 administrations of study medication, whichever is later.

  a. *Note: 17 treatments (approx. 1 year) are calculated from the first dose..*
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.6 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 30 days after the end of treatment as described in Section 7.2.3.1). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.8.1 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared.

5.8.2 Treatment after Initial Radiologic Progression (irRECIST-based Management)

Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest as a clinical response after an initial apparent increase in tumor burden (i.e., pseudoprogression) or even the appearance of new lesions. Standard RECIST-based assessment of disease progression may, thus, not provide an accurate assessment of response to immunotherapeutic agents such as pembrolizumab. For this reason, irRECIST has been developed to help guide treatment decisions during tumor immunotherapy.

For subjects who have initial radiological evidence of radiological PD by RECIST 1.1, the investigator may elect to continue a subject on study treatment until repeat imaging is obtained. This clinical judgment decision by the investigator should only be made if the subject is clinically stable, based on clinical factors including performance status, clinical symptoms, and laboratory data. Such subjects may continue to receive study treatment and an imaging-based tumor assessment should be repeated ≥ 4 weeks later in order to reassess PD per investigator assessment.

Clinical stability is defined by the following:

- Absence of signs and symptoms of clinically significant progression of disease, including worsening of laboratory values
- No decline in ECOG performancestatus
- Absence of rapid progression of disease (this is at the discretion of the investigator)
- Absence of tumor progression at critical anatomical sites that requires urgent alternative medical intervention (e.g., CNS metastasis with potential for cord compression)

NOTE: Any subject deemed **clinically unstable** should be discontinued from trial treatment at 1st radiologically assessed evidence of PD and is not required to have repeat imaging for PD confirmation.

In determining whether or not the tumor burden has increased or decreased per irRECIST, all target and non-target lesions as well as any incremental new lesion(s) should be considered.

Upon repeat imaging, PD will be confirmed if ANY of the following occur by irRECIST:

- Tumor burden remains increased by ≥ 20%, and at least 5 mm absolute increase compared to nadir
- Non-target disease resulting in initial diagnosis of PD is worse (qualitative assessment)
- New lesion resulting in initial diagnosis of PD is worse (qualitative assessment)
- Additional new lesion(s) since last evaluation

- Additional new non-target lesion progression since last evaluation

If repeat imaging confirms PD due to any of the scenarios listed above, subjects will be discontinued from trial therapy.

Upon repeat imaging, PD will have failed to be confirmed if ALL of the following occur by irRECIST:

- Tumor burden is increased by < 20 %, or < 5 mm absolute increase compared to nadir
- Non-target disease resulting in initial diagnosis of PD is stable or improved (qualitative assessment)
- New lesion resulting in initial diagnosis of PD is stable or improved (qualitative assessment)
- No incremental new lesion(s) since last evaluation
- No incremental new non-target progression since last evaluation

If repeat imaging fails to confirm PD by irRECIST and the subject continues to be clinically stable, treatment may continue and follow the regular imaging schedule.

When feasible, subjects should not be discontinued until PD is confirmed by radiology assessment. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. Subjects who are deemed clinically unstable are not required to have repeat tumor imaging for confirmation of PD. Tumor flares include any of the following scenarios:

- Worsening of existing target lesion(s)
- Worsening of existing non-target lesion(s)
- Development of new lesion(s)

Additional details about RECIST 1.1 and irRECIST are referenced in the appendices.

Table 5. Imaging and Treatment after First Radiologic Evidence of PD (irRECIST-based Management):

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
1st radiologic evidence of PD by RECIST 1.1	Repeat imaging at ≥4 weeks to confirm PD	May continue study treatment at the investigator's discretion while awaiting confirmatory tumor imaging by irRECIST.	Repeat imaging at ≥4 weeks to confirm PD per Physician discretion only	Discontinue treatment
Repeat tumor imaging	No additional Imaging required	Discontinue treatment (exception is possible upon	No additional imaging required	N/A

confirms PD by irRECIST		consultation with Merck)		
Repeat tumor imaging shows SD, PR or CR by irRECIST	Continue regularly scheduled imaging assessments	Continue study treatment at the investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion. Next tumor image should occur according to the regular imaging schedule outlined in the protocol

5.9 Subject Replacement Strategy

Patients who do not receive study drug, and patients who receive BL only (cycle 1) and who withdraw for reasons unrelated to safety or efficacy may be replaced in the cohort at the discretion of the investigator.

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last study-related phone-call or visit, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

5.11 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete

2. Poor adherence to protocol and regulatory requirements

3. Incidence or severity of adverse drug reaction in this or other studies that indicates a potential health hazard to subjects

4. Plans to modify or discontinue the development of the study drug

In the event of a pharmaceutical company decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made for patients.

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Table 6. Study Flow Chart:

Trial Period	**Screen**	**Treatment Week**									**End of Rx**	**Post Treatment**		
Treatment Cycle:	**Screenng Visit**	**1**	**2**	**3**	**4**	Repeated Every 3 Weeks,starting in Week 4 **5**	**6**	**7**	**8**	**9**	At D/C	Safety Follow Up	Follow Up Visit	Survival Follow Up
Scheduling Window (days)	-28 to -1		±3	±3	±3	±3	±3	±3	±3	±3	@D/C	30 d.	Q10w ±4¥	Q12 w ±3.©
Administrative Procedures														
Informed Consent	X													
Inclusion/Exclusion Criteria	X													
Demographics and Medical History; Medication Review	X													
Post-study anti-cancer therapy status												X	X	X
Survival Status												X	X	X
Clinical Procedures and Assessments														
Review Adverse Events			X		X	X		X	X		X	X		
Physical Examination incl. vital signs, weight and ECOG PS	X	X	X		X	X		X	X		X		X	
Laboratory Procedures														
Pregnancy Test (within 72h of d1)	X													
CBC with Differential†	X	X	X		X	X		X	X		X			
PT/PTT, Serum Chemistry, T3, FT4, TSH, UA	X				X			X						
Hep B, Hep C, EKG	X													
Efficacy Measurements and Correlative Science														
Tumor Imaging	X	"Week 9, then every 9 weeks, ±7d,"									X		X	
Tissue Collection	X			X						*				
Correlative Blood Collection		Weeks 1, 4, 7, 16, with confirmed response, and on discontinuation of treatment.												
Treatment Administration														
Pembrolizumab					X			X						
BL-8040 (doses/week)**		5	5		2	2		2	2					

† Prior to and within 24 hours of each dose of BL *Optional Biopsy week third week of cycle 3 **See text for allowed schedule variations © After disease progression or new anticancer treatment.. ¥ After discontinuation of treatment but before disease progression, new anticancer treatment, or death.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and/or Merck for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

If the subject has lost at least 15 lbs. (6.8 kg) over the 3 months prior to screening, “weight loss” should be entered as an active condition on the Medical History. As well, any autoimmune disorders, regardless of onset date, should be recorded.

Disease details regarding the subject’s pancreatic cancer will be recorded separately and not listed as medical history.

7.1.1.2 Disease Details

The investigator or qualified designee will obtain prior and current details regarding the subject’s pancreatic cancer.

7.1.1.3 Prior and Concomitant Medications Review

7.1.1.3.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record in the DMI database prior medication taken by the subject within 28 days before starting the trial. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

7.1.1.3.2 Concomitant Medications

The investigator or qualified designee will record medication in the DMI database, if any, taken by the subject during the trial from the time of signing the informed consent form until the Safety Follow-up Visit. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.4 Disease Details and Treatments

7.1.1.4.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status and will capture them within the CRF.

7.1.1.4.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries and will capture them within the CRF.

7.1.1.4.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up. Details on new anti-cancer therapy should be recorded within the CRF.

7.1.1.5 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to treatment. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 7.1.6.1.1

7.1.1.6 Assignment of Randomization Number

N/A; There will be no randomization.

A single subject cannot be assigned more than 1 identification number

7.1.1.7 Study Medication Administration

Trial Treatment:

Monotherapy: SC BL-8040 on week 1: days 1-5, week 2: days 8-12 and week 3 off.

Combination:

- Pembrolizumab 200mg IV Q3W.
- BL-8040 SC BIW on weeks 1 and 2 of each cycle (1.25mg/kg)
- Week 3 of each cycle off

In general, the window for each visit is ± 3 days unless otherwise noted. The first dose of the treatment is counted as Cycle 1 Day 1.

7.1.1.8 Survival Status

After the start of new anti-cancer treatment or documented disease progression, the subject should be contacted every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the trial, whichever occurs first.

7.1.1.9 Trial Compliance (Medication/Diet/Activity/Other)

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with Merck and/or BiolineRx. The reason for interruption should be documented in the patient's study record. BL-8040 and pembrolizumab can be delayed provided when it is resumed will continue to be given with the same schedule as defined within the protocol.

If pembrolizumab is held for reasons unrelated to BL-8040, the latter agent may be continued for up to three weeks as a single agent.

The total volume of pembrolizumab infused will be compared to the total volume prepared to determine compliance with each dose of pembrolizumab administered. The instructions for preparing and administering pembrolizumab are provided in the Investigator Brochures.

The number of BL-8040 doses provided will be compared to the total number of doses planned according to the schedule of treatment in order to determined compliance.

Administration of trial medication will be performed by MDA nursing staff; patients will be observed for 30 minutes after dosing.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse

experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.03 (see Section 11.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving treatment with pembrolizumab all AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs).

Please refer to section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 12-Lead Electrocardiogram

As specified in the Study Flow Chart (section 6.0), a standard 12-lead ECG will be performed once during the screening phase and then as clinically indicated. Clinically significant abnormal findings at screening phase should be recorded as medical history. After the first dose of trial treatment, new clinically significant abnormal findings should be recorded as AEs.

7.1.2.3 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening, After the first dose of trial treatment new clinically significant abnormal findings should be recorded as AEs.

7.1.2.4 Weight and Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate and blood pressure. Weight should be assessed at the beginning of each cycle for BL-8040 dose calculation.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status at screening and prior to each cycle of trial treatment as specified in the Trial Flow Chart.

7.1.2.6 Tumor Imaging and Assessment of Disease

Cross sectional imaging will be performed with either contrast enhanced CT or MRI. RECIST 1.1 criteria will be used to determine disease response[31].

See Section 4.2.3.1 and 7.1.4.1

7.1.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

See Section 4.2.3.4

A tumor tissue sample from a newly obtained core, incisional or excisional biopsy (preferably from a metastatic site) must be submitted for characterization of PD-L1 expression, GEP, and MSI. The submitted tumor tissue specimen must be of sufficient quality and quantity for assessment of all three of these primary biomarkers.

Submission of an both a frozen specimen and FFPE tumor tissue block is preferred, but tumor tissue from a new biopsy in formalin is also acceptable. If unstained slides are submitted, the slides must be freshly cut and submitted to the testing laboratory within 14 days from the slide sectioning date. All submitted slides must be cut from a single tumor tissue sample specimen. Tissue sample collection date and slide cut date will be are documented. Slides submitted more than 14 days after cutting or cut from more than one tissue specimen is not acceptable and a new specimen will be required.

In cases in which an adequate amount of tumor tissue has not been provided to allow for evaluation of all three primary biomarkers, additional tumor tissue must be provided. If additional tumor tissue from the same specimen is available, tumor tissue from that specimen of sufficient quantity and quality for assessment of the remaining required biomarkers must be submitted. If a sufficient amount of additional tumor tissue from the same specimen is NOT available, a different newly obtained tumor tissue specimen of sufficient quantity and quality for assessment of all three primary biomarkers must be submitted.
Future Biomedical Research

The following specimens are to be obtained as part of Future Biomedical Research:

- Remaining DNA for future use
- Remaining tumor tissue
- Remaining DNA and RNA from correlative samples
- Remaining plasma and serum from biomarker samples

CT-guided core biopsies will be performed prior to treatment, during the third week of cycle 1, and during the third week of cycle 3. Whenever possible the biopsies will be taken from the same metastatic site.

7.1.3 Laboratory Procedures/Assessments

Routine labs at screening are to be drawn as shown in table 7, below.

Refer to the Trial Flow Chart - Section 6.0 for the schedule of laboratory assessments.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 7.

Table 7. Laboratory Tests:

Hematology	Chemistry	Urinalysis	Other

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Total thriiodothyronine (T3)
Absolute Neutrophil Count	BUN	results are noted	Free tyroxine (T4)
Absolute Lymphocyte Count	Total Protein	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		Hepatitis B & C AB
	Calcium		Blood for correlative studies
	Chloride		
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Creatinine		

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

‡ If considered standard of care in your region.

After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing, except for CBC that need to be done within 24 before the BL-8040 dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.3.1.1 Pregnancy Tests

All women who are being considered for participation in the trial, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy within 72 hours of cycle 1 of trial treatment. If a urine test is positive or not evaluable a serum test will be required. Subjects must be excluded/discontinued from the study in the event of a positive or borderline-positive test result.

7.1.3.2 Central Laboratory Assessments

Sample collection timing, storage and shipment instructions for the Central Laboratory assessments will be provided in the laboratory SOP (submitted as a separate document).

7.1.3.3 Pharmacokinetic/Pharmacodynamic Evaluations

There will be no PK evaluation in this trial

7.1.3.3.1 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided in the lab SOP submitted as an attached document. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. If there is either a documented law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes, then this sample will not be collected at that site. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the subject agrees as to this as an optional procedure in the ICD.

7.1.4 Efficacy Measurements

7.1.4.1 Tumor Imaging and Assessment of Disease

Tumor imaging should be acquired by computed tomography (CT, strongly preferred). Magnetic resonance imaging (MRI) should be used when CT is contraindicated or for imaging in the brain. The same imaging technique regarding modality and use of contrast should be used in a subject throughout the trial to optimize the visualization of existing and new tumor burden.

Expedited confirmation of measurable disease based on RECIST 1.1 by MD Anderson radiology at screening will be used to determine subject eligibility. Confirmation of measurable disease by MD Anderson radiology per RECIST 1.1 is required prior to subject enrollment. Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, Merck allows a maximum of 10 target lesions in total and 5 per organ.

All scheduled images will be assessed by MD Anderson radiology for all study. In addition, additional imaging (including other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons but captures radiologic progression, should likewise be assessed.

7.1.4.1.1 Initial Tumor Imaging

Initial tumor imaging at screening must be performed within 28 days prior to the date of enrollment. The site study team must review screening images to confirm the subject has measurable disease per RECIST 1.1. Prior to enrollment, the screening images that have been done during during rutine management, must be submitted to MD Anderson radiology for confirmation of measurable disease per RECIST 1.1.

Scans performed as part of routine clinical management are acceptable for use as screening tumor imaging if they are of diagnostic quality, were performed within 28 days prior to the first date of treatment, and can be assessed by MD Anderson radiology.

Subjects with previously treated brain metastases may participate provided they have stable brain metastases, i.e. without evidence of progression by imaging (confirmed by magnetic resonance imaging [MRI] if MRI was used at prior imaging, or confirmed by computed tomography [CT] imaging if CT used at prior imaging) for at least 4 weeks prior to the first dose of trial treatment (Day 1). Any neurologic symptoms must have returned to baseline, there must be no evidence of new or enlarging brain metastases, and they must not have used steroids for brain metastases for at least 30 days prior to first dose as per local site assessment. This exception does not include carcinomatous meningitis, as subjects with carcinomatous meningitis are excluded regardless of clinical stability.

7.1.4.1.2 Tumor Imaging During the Trial

The first on-study imaging assessment should be performed at 9 weeks (63±7 days) from the date of enrollment. Subsequent tumor imaging should be performed Q9W (63±7 days) or more frequently if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression (unless site PI elects to continue treatment and follow irRECIST), the start of new anti-cancer treatment, withdrawal of consent, death, or notification by Merck, whichever occurs first. All supplemental imaging, done outside from MD Anderson, must be submitted to MD Anderson radiology for retrospective review.

Per RECIST 1.1, PR and CR should be confirmed by a repeat tumor imaging assessment ≥4 weeks from the date the response was first documented. The tumor imaging for confirmation of response may be performed ≥4 weeks after the first indication of response, or at the next scheduled scan (i.e., 9 weeks later), whichever is clinically indicated. Subjects will then return to regular scheduled imaging every 9 weeks (63±7 days) within the year of the study.. Subjects who obtain a local confirmation scan do not need to undergo the next scheduled tumor imaging if it is <4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

Per irRECIST, disease progression should be confirmed by the site at least 4 weeks after site-assessed 1st radiologic evidence of PD in clinically stable subjects. Subjects who have unconfirmed disease progression may continue on treatment at the discretion of the investigator until progression is confirmed on a subsequent study. Subjects who obtain a confirmation scan do not need to undergo the next scheduled tumor imaging if it is <4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point if clinically stable. Subjects who have confirmed disease progression as assessed by the site will discontinue the treatment.

7.1.4.1.3 End of Treatment and Follow-up Tumor Imaging

In subjects who discontinue trial treatment, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation is not mandatory. In subjects who discontinue trial treatment due to documented disease progression, this is the final required tumor imaging.

In subjects who discontinue trial treatment without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging at an interval of every 10 ± 4 weeks until (1) the start of new anti-cancer treatment, (2) disease progression, (3) death, or (4) the end of the study, whichever occurs first.

7.1.4.1.4 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be applied by MD Anderson investigators as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (e.g., discontinuation of study therapy). Confirmation of PR and CR for RECIST 1.1 will be taken from central imaging retrospectively.

7.1.4.1.5 irRECIST Assessment of Disease

irRECIST is RECIST 1.1 adapted as described below to account for the unique tumor response seen with immunotherapeutic drugs. irRECIST will be used by the investigator to assess tumor response and progression, and make treatment decisions. This data will be collected in the clinical database. Treatment efficacy based on irRECIST as assessed by MD Anderson radiology review will be evaluated retrospectively.

When feasible, subjects should not be discontinued until progression is confirmed by the investigator. This allowance to continue treatment despite initial radiologic progressive disease (PD) takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. Subjects that are deemed clinically unstable are not required to have repeat tumor imaging for confirmation of PD. Tumor flare includes any of the following scenarios:

- Worsening of existing target lesion(s)
- Worsening of existing non-target lesion(s)
- Development of new lesion(s)

In subjects who have initial evidence of radiological PD by RECIST 1.1 as determined by the site, it is at the discretion of the PI whether to continue a subject on study treatment until repeat imaging is obtained. This clinical judgment decision by the investigator should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive study treatment and tumor assessment should be repeated ≥4 weeks later to confirm PD by irRECIST per site assessment. Clinical stability is defined as the following:

1) Absence of symptoms and signs indicating clinically significant progression of disease, including worsening of laboratory values,

2) No decline in ECOG performance status,

3) Absence of rapid progression of disease, and

4) Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

Any subject deemed clinically unstable should be discontinued from trial treatment at site-assessed 1st radiologic evidence of PD and is not required to have repeat imaging for PD confirmation.

In determining whether or not the tumor burden has increased or decreased per irRECIST, the investigator should consider all target and non-target lesions as well as any incremental new lesion(s).

Scenarios where PD is not confirmed at repeat imaging if ALL of the following occur by irRECIST:

- Target lesion sum of diameters increased <20% or <5 mm absolute increase compared to nadir,
- Non-target disease resulting in initial PD is qualitatively stable or improved,
- New lesion resulting in initial PD is qualitatively stable or improved,
- No incremental new lesion(s) since last evaluation, and
- No incremental new non-target lesion progression since last evaluation.

If repeat imaging does not confirm PD by irRECIST as assessed by the investigator and the subject continues to be clinically stable, treatment may continue and follow the regular imaging schedule.

Scenarios where PD is confirmed at repeat imaging if ANY of the following occur by irRECIST:

- Target lesion sum of diameters remains increased by ≥20% and at least 5 mm absolute increase compared to nadir,
- Non-target disease resulting in initial PD is qualitatively worse,
- New lesion resulting in initial PD is qualitatively worse,
- Additional new lesion(s) since last evaluation, or
- Additional new non-target lesion progression since last evaluation.

If repeat imaging confirms PD by irRECIST as assessed by the investigator and the subject continues to be clinically stable, treatment may continue and follow the regular imaging schedule.

NOTE: If a subject has confirmed radiographic progression (i.e., 2 scans at least 4 weeks apart demonstrating progressive disease) per irRECIST, but the subject is achieving a clinically meaningful benefit and there is no further increase in the tumor burden at the confirmatory tumor imaging, an exception to continue treatment may be considered following consultation with Merck. In this case, if treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Trial Flow Chart.

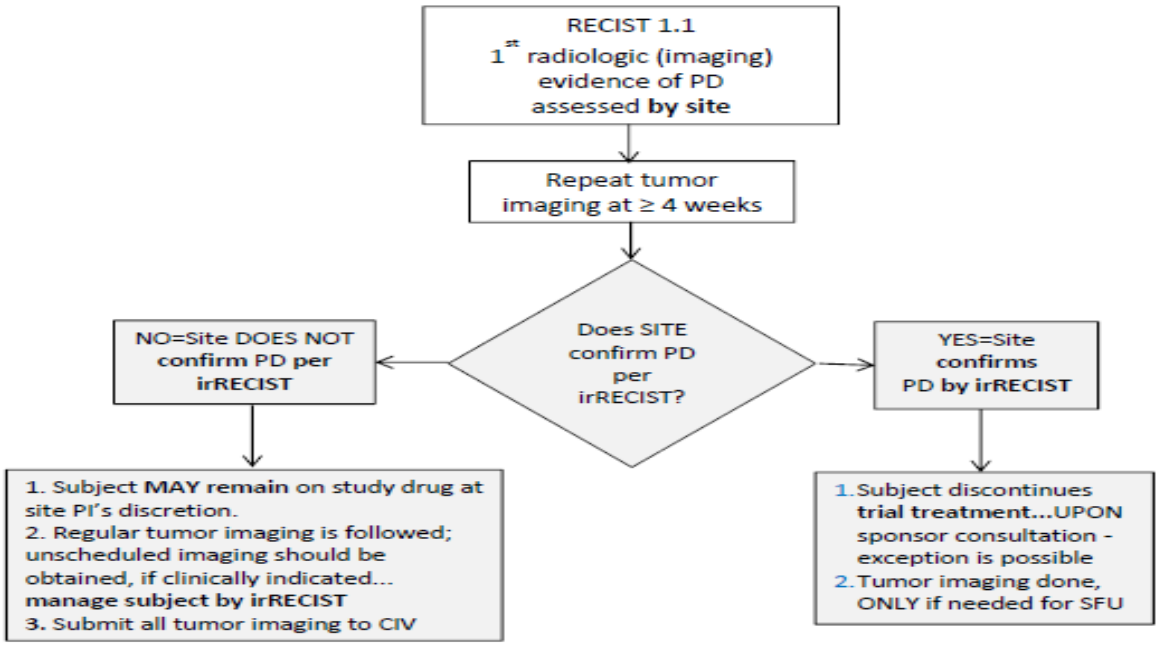
Table 8. Imaging and Treatment after First Radiologic Evidence of PD:

	Clinically Stable	**Clinically Unstable**

	Imaging	Treatment	Imaging	Treatment
1st radiologic evidence of PD by RECIST 1.1	Repeat imaging at ≥4 weeks at site to confirm PD	May continue study treatment at the Investigator's discretion while awaiting confirmatory tumor imaging by site by irRECIST.	Repeat imaging at ≥4 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat tumor imaging confirms PD by irRECIST	No additional imaging required	Discontinue treatment (exception is possible upon consultation with Merck)	No additional imaging required	N/A
Repeat tumor imaging shows SD, PR or CR by irRECIST	Continue regularly scheduled imaging assessments	Continue study treatment at the Investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion. Next tumor image should occur according to the regular imaging schedule outlined in the protocol

CR = complete response; irRECIST = immune-related Response Evaluation Criteria in Solid Tumors; N/A = not applicable; PD = progressive disease; PR= partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

Figure 2. Imaging and Treatment for Clinically Stable Subjects after First Radiologic Evidence of Progressive DiseaseImaging and Treatment for Clinically Stable Subjects after First Radiologic Evidence of Progressive Disease.



CIV = central imaging vendor; irRECIST = immune-related Response Evaluation Criteria In Solid Tumors; PD = progressive disease; PI = principal investigator; Q9W = every 9 weeks; RECIST = Response Evaluation Criteria In Solid Tumors; SFU = survival follow-up.

7.1.5 Other Procedures

7.1.5.1 Withdrawal/Discontinuation

Subjects who discontinue/withdraw from treatment prior to completion of the treatment regimen should be encouraged to continue to be followed for all remaining study visits.

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the end of study visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

7.1.5.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical specimens from the trial are still available, the investigator will contact Merck using the designated mailbox (clinical.specimen.management@merck.com), and a form will be provided by Merck to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from Merck to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by Merck will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject’s personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

7.1.6 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.6.1 Screening

7.1.6.1.1 Screening Period

Approximately 28 days prior to treatment initiation, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Screening procedures may be repeated.

Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments performed during the initial screening period are acceptable in lieu of repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria is met. Subjects who are rescreened will retain their original screening number. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame.

Screening procedures are to be completed within 28 days prior to the first dose of trial treatment except for the following:

- The informed consent form must be signed prior to completing any protocol-specified procedure.

- To meet the requirement for the submission of tumor tissue from a newly obtained specimen, the tissue sample must have been collected since the completion of the most recent cancer therapy.

- The investigator or qualified designee will perform a full physical exam within 28 days prior to Cycle 1 Day 1.

- Laboratory tests and evaluation of ECOG status are to be performed within 28 days prior to the first dose of trial treatment.

- For women of reproductive potential, a urine pregnancy test will be performed within 3 days prior to the first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the MDA laboratory).

Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments performed during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria is met.

7.1.6.2 Treatment Period

Visit requirements are outlined in the Trial Flow Chart (Section 6.0). Specific procedure-related details are provided above in the Trial Procedures (Section 7.1 Trial Procedures).

Patients are eligible for up to 17 cycles (approximately 1 year) of treatment on Pembrolizumab.

Treatment will follow the paradigm outlined in section 2.2. Cycle 1 will consist of single agent BL-8040. Cycle 2 will consist of BL-8040 plus pembrolizumab, given on day 1. The third week of each cycle will be without therapy.

7.1.6.3 Post-Treatment Visits

7.1.6.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 30 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

7.1.6.3.2 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 9 weeks (± 3 weeks) by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, or end of the study. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

7.1.6.3.3 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.2 Investigator Communication with Merck and BiolineRx for Overdose, Pregnancy, Lactation, Serious Adverse Events, Events of Clinical Interest (ECI), and non-serious Events of Clinical Interest.

All events described within this section (7.2.X) must be reported to Merck and BiolineRx within two working days. All Such events must be reported within 2 working days to **Merck Global Safety**. (Attn: Worldwide Product Safety; FAX 215 993-1220) and **BioLineRx** (BioLineRx Safety: safety8040@biolinerx.com, Fax: +972 8 6429137)

All life-threatening or fatal events, that are unexpected, and related to the study drug, must also have a written report submitted **within 24 hours** (next working day) of knowledge of the event to the **Safety Project Manager in the IND Office**.

All such events will be recorded using the PDMS/CORe and DMI systems.

7.2.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Merck's and/or BioLineRx products, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Progression of the cancer under study is not considered an adverse event.

All adverse events that occur after the consent form is signed but before treatment begins must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

From the start of treatment through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

7.2.2 Definition of an Overdose

Pembrolizumab

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose

of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Merck's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

BL-8040

For this trial, an overdose will be defined as ≥3.75 mg/kg (3 times the dose) of BL-8040. In case of overdose the subject should be observed closely for any signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated. In case of abnormal low blood counts due to BL-8040 overdose, subjects should be followed until blood counts recover.

7.2.3 Reporting of Pregnancy and Lactation to Merck and BioLineRx

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before the start of treatment must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

Pregnancies and lactations that occur from the start of treatment through 120 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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 to Merck. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to Merck and BiolineRx and followed as described above.

7.2.4 Serious Adverse Events and Events of Clinical Interest

7.2.4.1 Serious Adverse Events

Refer to Table 9 for additional details regarding each of the above criteria.

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to

the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:
• Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

7.2.4.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 2 working days to Merck Global Safety and the MDA IND office.

For the time period beginning when the consent form is signed until the start of treatment, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 2 working days to Merck Global Safety and BioLineRx 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, or a procedure.

For the time period beginning at the start of treatment through 30 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck and/or BioLineRx product, must be reported within 2 working days to Merck Global Safety and BioLineRx safety.

Additional Events of clinical interest for this trial include:

1. An overdose of Merck and/or BioLineRx product, as defined in Section 7.2.2, that is not associated with clinical symptoms or abnormal laboratory results.

2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

> *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

3. In addition to overdose, Hepatic Events of Clinical Interest (ECIs) will include any of the following events. All of these events will require holding pembrolizumab, notification of Merck and BiolineRx within 24 hours (as an adverse event), and, if appropriate, hepatology consultation. All cases of permanent discontinuation must also be reported within 7 days. For dose interval modification and treatment guidelines for these events, refer to Section 5.8.

4. Summary of Hepatic Events of Clinical Interest

a. ALT*:

i. Among subjects with Day 1 ALT <2x ULN, ALT ≥5x ULN
ii. Among subjects with Day 1 ALT ≥2x ULN, ALT >3x the Day 1 level
iii. ALT >500 U/mL regardless of baseline level

(Subjects with ALT >5x ULN at Day 1 are not eligible for enrollment)

b. AST:

i. Among subjects with Day 1 AST <2x ULN, AST ≥5x ULN
ii. Among subjects with Day 1 AST ≥2x ULN, AST >3x the Day 1 level
iii. AST >500 U/mL regardless of baseline level

(Subjects with ALT >5x ULN at Day 1 are not eligible for enrollment)

c. Total Bilirubin:

i. Among subjects with Day 1 levels <1.5 mg/dL, a value of >2.0 mg/dL
ii. Among subjects with Day 1 levels that are ≥1.5 mg/dL, a value ≥2x the D1 level
iii. Total bilirubin >3.0 mg/dL regardless of baseline level

(Subjects with Total Bilirubin >2.0 mg/dL at Day 1 are not eligible for enrollment)

d. Regardless of laboratory values, hepatic decompensation diagnosed <u>clinically</u>, including:

i. New onset ascites
ii. GI bleeding suggestive of portal hypertension (eg esophageal or gastric varices)
iii. Encephalopathy

(Subjects with clinically apparent ascites or encephalopathy, or untreated varices are not eligible for enrollment)

7.2.4.3 Required Reporting Procedures

1. Immediate assessment

<u>All subjects</u>

- All subjects should be evaluated according to directions below within 72 hours of alert for non-overdose ECI
- Procedures:
  - Obtain consult with hepatologist if appropriate
  - Obtain workup for hepatitis if no underlying hepatitis, including Hepatitis A, B,C, D, E, EBV, CMV
  - Assess for ingestion of drugs/supplements with hepatotoxic potential (see List of Prohibited medicine, section 5.5.2 of the protocol, for a list)
  - Assess for alcohol ingestion
  - Assess for potential bacterial infection, biliary obstruction, or occult GI bleeding

- Repeat ALT, AST, T. bili, D. bili, alk phos, GGT, INR, CBC with differential
- Other laboratories or imaging studies as clinically indicated
- Consider liver biopsy if indicated by hepatologist

2. Permanent Discontinuation Criteria for Subjects With Non-overdose Hepatic ECI

Therapy should also be <u>permanently discontinued</u> for:

- ALT >20x ULN
- CP score of ≥9 points;
- GI bleeding suggestive of portal hypertension (e.g., esophageal or gastric varices);
- New onset ascites;
- Encephalopathy; or
- Recurrence of a severe or life-threatening event, or of any of the laboratory abnormalities listed in #1 that are presumed immune-related.

3. Diagnosis and Management of Non-Overdose Hepatic ECIs

a. <u>Other Hepatic Events of Clinical Interest</u>

- Infection needs to be ruled out with cultures of blood, urine, and ascites (if possible), as well as CXR and abdominal imaging if relevant. If infection is found, antibiotics should be started.
- If T. bili is elevated above baseline, MRCP or ultrasound with doppler should be obtained to rule out vascular compromise, biliary obstruction and/or tumor progression. If biliary obstruction is present, consultation with gastroenterology and/or interventional radiology should be obtained to see if obstruction may be relieved.
- A careful review of drugs, including herbal and alternative medications, should be obtained, and alcohol use should be ruled out. Please see section 5.5.2 or drugs which may interfere with hepatic function.
- For all of these cases, subjects may resume pembrolizumab if they are clinically stable after appropriate therapy, or discontinuation of offending agent, as long as laboratory values have returned to grade 1 or baseline (if normal or grade 1 at start), or baseline grade within 3 weeks.
- Subjects must be permanently discontinued if they are off pembrolizumab therapy for infection, obstruction, or drug/alcohol related toxicity more than 3 weeks, or if they have an esophageal bleed.

7.2.4.4 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to Merck.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The investigator will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the subjects in the trial. An efficacy/safety summary to the IND Office Medical Monitor will be submitted after the first five patients have completed study therapy, or administration is discontinued, whichever comes first, and every five evaluable patients thereafter, until 15 patients have completed study therapy.

Any suspected SAE which upon review is not progression of the cancer under study will be forwarded to Merck Global Safety and BioLineRx safety as a SAE within 2 working days of determination that the event is not progression of the cancer under study

Hospitalization related to convenience (e.g.transportation issues etc.) will not be considered a SAE.

7.2.5 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.03. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets. We will use the DMI database. The PI or designee will be responsible for assigning attributions of adverse events to the study agent.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Table 9. Evaluating Adverse Events:

An investigator who is a qualified physician, will evaluate all adverse events as to:

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.);	

	or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck or BioLineRx product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to Merck and BioLineRx within 2 working days to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported to Merck within 2 working days.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause Merck or BioLineRx product to be discontinued?	
Relationship to Merck Product	Did Merck or BioLineRx product cause the adverse event? The determination of the likelihood that Merck or BioLineRx product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between Merck and BioLineRx product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Merck Product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was Merck and/or BioLineRx product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the product; or (3) the trial is a single-dose drug trial); or (4) Merck or Bioline's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to Merck and/or BioLineRx product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY MERCK PRODUCT, OR IF REEXPOSURE TO MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY MERCK AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of Merck product relationship).**	
Yes, there is a reasonable possibility of Merck and/or BiolineRx product relationship.	There is evidence of exposure to Merck and/or BioLineRx product. The temporal sequence of the AE onset relative to the administration of Merck product is reasonable. The AE is more likely explained by Merck or BioLineRx product than by another cause.	
No, there is not a reasonable possibility of Merck or BioLineRx product relationship	Subject did not receive the Merck or BioLineRx product OR temporal sequence of the AE onset relative to administration of Merck or BioLineRx product is not reasonable OR the AE is more likely explained by another cause than the Merck or BioLineRx product. (Also entered for a subject with overdose without an associated AE.)	

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

Simon's 2-stage design will be used. The null hypothesis that the true response rate is 10% will be tested against a one-sided alternative. In this treatment arm, 15 patients will be accrued. If there is </= 1 response in these 15 patients, research into this combination will be halted. If we see >/= 2 responses,

we will plan to study (in a subsequent protocol) an additional 26 patients, for a total of 41. The null hypothesis will be rejected if 8 or more responses are observed in 41 patients. This design yields a type I error rate of 5% and power of 80% when the true response rate is 25%.

The 15 patients needed for this analysis will be enrolled as one cohort. Patients who do not receive study drug, and patients who receive BL only (cycle 1) and who withdraw from the study for reasons unrelated to safety or efficacy may be replaced in the cohort at the discretion of the investigator.

Key elements of the statistical analysis plan are summarized below. The comprehensive plan is provided in Sections 8.1 to 8.12.

Table 10. Key Elements of the Statistical Analysis Plan:

Study Design Overview	A Phase IIb Pilot study to assess the efficacy, safety and pharmacodynamics effects of Pembrolizumab and BL-8040 in Patients with Metastatic Pancreatic Cancer.
Treatment Assignment	This is a single arm open-label study.
Analysis Populations	Efficacy: All Subjects as Treated (ASaT) Safety: All Subjects as Treated (ASaT)
Primary Endpoints	Overall Response rate.
Statistical Methods for Key Efficacy Analyses	Objective Response Rate (ORR) based on RECIST 1.1 assessed by the MDACC imaging staff. The estimate of the ORR, along with its 95% confidence interval (CI) based on the Clopper-Pearson method [32], will be provided.
Statistical Methods for Key Safety Analyses	Counts and percentages of subjects with AEs will be provided.
Interim Analysis	No planned interim analysis for this pilot study.
Multiplicity	No multiplicity adjustment is planned in this Phase II study.
Sample Size and Power	The planned sample size is 15 subjects.

8.2 Responsibility for Analyses

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Merck.

This trial is being conducted as a non-randomized, open-label study, i.e., subjects, investigators, BiolineRx and Merck personnel will be aware of subject treatment assignments after each subject is enrolled.

8.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.

8.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated are listed below.

8.4.1 Efficacy Endpoints

8.4.1.1 Primary Efficacy Endpoint

Overall Response Rate

8.4.1.2 Secondary Efficacy Endpoints

To estimate the safety and tolerability of the combination treatment.

To determine the impact of the two study agents on T cell infiltration into tumor

To determine the impact of BL-8040 on circulating immune cells.

8.4.1.3 Exploratory Efficacy Endpoints

To evaluate Overall response rate (ORR) per irRECIST and duration of response (DOR), disease control rate (DCR), time to progression (TTP), progression free survivial (PFS), and Overall survivial (OS) per RECIST and irRECIST assessed by MD Anderson investigators.

To explore the association between PD-L1 expression by immunohistochemistry, shed PD-L1 level, somatic gene expression profiling and antitumor efficacy of pembrolizumab based on RECIST 1.1 imaging criteria as well as overall survival.

To explore the relationship between genomic variation and response to the treatment administered. Variation across the human genome may be analyzed for association with clinical data collected in this study.

Tissue and blood immune monitoring will be conducted through our immune platform group as detailed per the biomarker section based on 3 biopsies done at the following time points: 1) pre-treatment, 2) during the third week of cycle 1, and 3) during the third week of cycle 3.

8.4.2 Safety Endpoints

To determine the rate of adverse events associated with study treatment.

8.5 Analysis Populations

Eligible subjects enter the study when the patient number is assigned.

8.5.1 Efficacy Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of ORR, DCR, PFS, and OS. The ASaT population consists of all allocated subjects who received at least one dose of study treatment.

The analysis population for DOR consists of responders (PR and CR).

Details on the approach to handling missing data are provided in Table 13.

8.5.2 Safety Analysis Populations

The ASaT population will be used for the analysis of safety data in this study. The ASaT population consists of all allocated subjects who received at least one dose of study treatment.

At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

8.6 Statistical Methods

8.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives.

This is an open-label pilot study. Fifteen patients will be treated. Descriptive statistics including with 90% confidence interval will be computed. Observed response profile and PFS along with relevant confidence interval will be used to guide future development decisions.

Table 11. Analysis Strategy for Efficacy Variables:

Total evaluable patients	Number of responders	Response rate	Lower 90% CI*	Upper 90% CI*
15	1	7%	<1%	27%
15	2	13%	2%	36%

15	3	20%	6%	44%
15	4	27%	10%	51%
15	5	33%	14%	58%
15	6	40%	19%	64%
15	7	47%	24%	70%
15	8	53%	30%	76%
15	9	60%	36%	81%
15	10	67%	43%	86%

* Exact confidence interval computed by the method of Clopper and Pearson (Biometrika 26:404-413, 1934)

Table 12. Statistical Methods Per Endpoint Anaylsis:

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoint			
ORR – RECIST 1.1 by MD Anderson radiology	exact method based on binomial distribution (Clopper-Pearson method)	ASaT	Subjects with missing data are considered non-responders
Key Secondary Endpoints			

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
DOR – RECIST 1.1 by MD Anderson radiology	Summary statistics using Kaplan-Meier method, if sample size permits	All responders	Non-responders are excluded from analysis. Responders are censored according to the censoring rules listed in Table 13.
DCR – RECIST 1.1 by MD Anderson radiology	Exact method based on binomial distribution (Clopper-Pearson method)	ASaT	Subjects with missing data are considered as subjects with disease not under control
TTP – RECIST 1.1 by MD Anderson radiology	Summary statistics using Kaplan-Meier method	ASaT	Censored at last assessment
PFS – RECIST 1.1 by MD Anderson radiology	Summary statistics using Kaplan-Meier method	ASaT	Censored at last assessment
OS	Summary statistics using Kaplan-Meier method	ASaT	Censored at last known alive date

Table 13. Censoring Rules for DOR:

Situation	Date of Progression or Censoring	Outcome
No progression nor death, no new anti-cancer therapy initiated	Last adequate disease assessment	Censor (non-event)
No progression nor death, new anti-cancer therapy initiated	Last adequate disease assessment before new anti-cancer therapy initiated	Censor (non-event)

Situation	Date of Progression or Censoring	Outcome
Death or progression after ≥2 consecutive missed adequate disease assessments	Last adequate disease assessment prior to the after ≥2 consecutive missed adequate disease assessments	Censor (non-event)
Death or progression after ≤1 missed adequate disease assessments	PD or death	End of response (Event)
Subjects are considered to have an ongoing response if censored, alive, have not progressed, have not started a new anti-cancer therapy and have not been determined to be lost to follow-up.		

8.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests, and vital signs.

Counts and percentages of subjects with AEs will be provided.

8.6.3 Demographic and Baseline Characteristics

The number and percentage of subjects screened, allocated, the primary reasons for screening failure, and the primary reasons for discontinuation will be displayed. Demographic variables (e.g., age, gender), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized either by descriptive statistics or categorical tables for all enrolled subjects.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by Merck and BioLineRx as summarized in Table 14.

Table 14. Product Descriptions:

Product Name & Potency	Dosage Form
Pembrolizumab 50 mg	Lyophilized Powder for Injection

Product Name & Potency	Dosage Form
Pembrolizumab 100 mg/ 4mL	Solution for Injection
BL-8040 73mg per vial	Lyophilized Powder for Injection

BL-8040, a white to off-white powder synthetic polypeptide, is freely soluble in water and in 0.45% Sodium Chloride (half normal saline). It is manufactured in accordance with current good manufacturing practice (cGMP) by MSD/N.V. (Organon, Kloosterstraat 6, 5349 AB, Oss, Netherlands).

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

All supplies will be provided open label. Pembrolizumab will be provided as non-kitted single vials.

BL-8040 will be provided in kit of 8 or 12 vials

9.3 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.4 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck and BioLineRx or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is Merck's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by Merck in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Merck to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by Merck or through a secure password-protected electronic portal provided by Merck. The investigator/subinvestigator(s) also consent to the transmission of this information to Merck in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.2 Confidentiality of Subject Records

Merck, BiolineRx, IRB/ERC, or regulatory authority representatives may consult and/ or copy trial documents in order to verify source documents/ case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying source documents/ case report form information, the subject will be identified by unique code only; protected health information, such as full names and medical records number, will be masked prior to transmission to Merck or BiolineRx.

All subject data used and disclosed in connection with this trial must be treated in accordance with all applicable privacy laws, rules and regulations.

10.1.3 Confidentiality of Investigator Information

Certain personal identifying information with respect to the investigator, and all sub-investigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;

2. hospital or clinic address and telephone number;

3. curriculum vitae or other summary of qualifications and credentials; and

4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to Merck, BiolineRx, and subsidiaries and affiliates, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

10.1.4 Confidentiality of IRB/IEC Information

The investigator is required to record the name and address of each IRB/IEC member that reviews and approves this trial. The investigator is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

11.0 APPENDICES

11.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine subject preferences, etc.

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate subjects, adequacy of facilities and staff, previous performance in Merck trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Subject Protection

A. IRB/ERC review

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect subject safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck will approve the subject informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding subject confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck does not pay incentives to enroll subjects in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/ERC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

11.2 Common Terminology Criteria for Adverse Events

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html).

11.3 List of Abbreviations

Table 15. List of Abbreviations:

Abbreviation/Term	Definition
2L	Second Line
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AP	Alkaline Phosphatase
APaT	All Patients as Treated
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
CI	Confidence Interval
CNS	Central Nervous System
CR	Complete Response
CrCl	Calculated Creatinine Clearance
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DCR	Disease Control Rate
DNA	Deoxyribonucleic acid
DOR	Duration of Response
DR	Drug Related
ECI	Events of Clinical Interest
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EGJ	Esophagogastric Junction
eDMC	external Data Monitoring Committee
EOC	Executive Oversight Committee

Abbreviation/Term	Definition
EORTC	European Organisation for Research and Treatment of Cancer
ERC	Ethics Review Committee
ESMO	European Society for Medical Oncology
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FNA	Fine Needle Aspirate
GCP	Good Clinical Practice
GEP	Gene Expression Profile
GI	Gastrointestinal
GFR	Glomerular Filtration Rate
HBsAg	Hepatitis B surface Antigen
HCV	Hepatitis C Virus
HEA	Health Economic Assessment
HIV	Human Immunodeficiency Virus
HNSCC	Head and Neck Squamous Cell Carcinoma
HR	Hazard Ratio
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IHC	Immunohistochemistry
INR	International Normalized Ratio
irRECIST	Immune related RECIST (Modification of RECIST 1.1)
IRB	Institutional Review Board
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Integrated Web Response System
LDH	Lactate Dehydrogenase
mAb	Monoclonal Antibody
MRI	Magnetic Resonance Imaging
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
MSI-H	Microsatellite Instability High
NA or N/A	Not Applicable
NCI	National Cancer Institute
NSAID	Non-Steroidal Anti-inflammatory Drug
ORR	Objective Response Rate
OS	Overall Survival
OTC	Over-the-counter
PD	Progressive Disease
PFS	Progression Free Survival

Abbreviation/Term	Definition
PIN	Personal Identification Number
PK	Pharmacokinetic
PK/PD	Pharmacokinetic/Pharmacodynamic
PO	Oral Administration
PR	Partial Response
PT	Prothrombin Time
PS	Performance Status
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
RR	Response Rate
Q3W	Every 3 Weeks
Q9W	Every 9 Weeks
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SD	Stable Disease
SFU	Survival Follow-Up
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SIM	Site Imaging Manual
SOP	Standard Operating Procedures
TIL	Tumor Infiltrating Lymphocytes
TSH	Thyroid Stimulating Hormone
TTP	Time to Progression
ULN	Upper Limit of Normal
WBC	White Blood Cell

11.4 ECOG Performance Status

Table 16. ECOG Performance:

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-

	care. 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 Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

11.5 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

RECIST version 1.1[33] will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study. In addition, volumetric analysis will be explored by central review for response assessment.

11.6 Tip sheet for Resist 1.1 and irRESIST

irRECIST is RECIST 1.1 adapted as described below to account for the unique tumor response seen with immunotherapeutic drugs. irRECIST will be used by site investigator/local radiology review to assess tumor response and progression, and make treatment decisions. This data will be collected in the clinical database. Treatment efficacy based on irRECIST as assessed by the central imaging vendor review will be evaluated retrospectively.

When feasible, subjects should not be discontinued until progression is confirmed by the local site investigator/radiology assessment. This allowance to continue treatment despite initial radiologic progressive disease (PD) takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. Subjects that are deemed clinically unstable are not required to have repeat tumor imaging for confirmation of PD. Tumor flare includes any of the following scenarios:

- Worsening of existing target lesion(s)
- Worsening of existing non-target lesion(s)
- Development of new lesion(s)

In subjects who have initial evidence of radiological PD by RECIST 1.1 as determined by the site, it is at the discretion of the PI whether to continue a subject on trial treatment until repeat imaging is obtained (using irRECIST for subject management, see Table 6 and Figure 2). This clinical judgment decision by the site investigator should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive trial treatment and tumor assessment should be repeated ≥4 weeks later to confirm PD by irRECIST per site assessment. Clinical stability is defined as the following:

1) Absence of symptoms and signs indicating clinically significant progression of disease, including worsening of laboratory values,

2) No decline in ECOG performance status,

3) Absence of rapid progression of disease, and

4) Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

Any subject deemed clinically unstable should be discontinued from trial treatment at site-assessed first radiologic evidence of PD and is not required to have repeat imaging for PD confirmation.

In determining whether or not the tumor burden has increased or decreased per irRECIST, the local site investigator should consider all target and non-target lesions as well as any incremental new lesion(s).

Scenarios where PD is not confirmed at repeat imaging if ALL of the following occur by irRECIST:

· Target lesion sum of diameters is <20% or <5 mm absolute increase compared to nadir,

· Non-target disease resulting in initial PD is qualitatively stable or improved,

· New lesion resulting in initial PD is qualitatively stable or improved,

· No incremental new lesion(s) since last evaluation, and

· No incremental new non-target lesion progression since last evaluation.

If repeat imaging does not confirm PD by irRECIST as assessed by the local site investigator and the subject continues to be clinically stable, treatment may continue and follow the regular imaging schedule.

Scenarios where PD is confirmed at repeat imaging if ANY of the following occur by irRECIST:

· Target lesion sum of diameters remains ≥20% and at least 5 mm absolute increase compared to nadir,

· Non-target disease resulting in initial PD is qualitatively worse,

· New lesion resulting in initial PD is qualitatively worse,

· Additional new lesion(s) since last evaluation, or

Additional new non-target lesion progression since last evaluation. If repeat imaging confirms PD due to any of the scenarios listed above, subjects will be discontinued from study therapy.

.

NOTE: If a subject has confirmed radiographic progression (i.e., 2 scans at least 4 weeks apart demonstrating progressive disease) per irRECIST, but the subject is achieving a clinically meaningful benefit and there is no further increase in the tumor burden at the confirmatory tumor imaging, an

exception to continue treatment may be considered following consultation with the Sponsor. In this case, if treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 6.0 Trial Flow Chart and be submitted to the central imaging vendor.

12.0 REFERENCES

1. Nishino M, Giobbie-Hurder A, Gargano M, Suda M, Ramaiya NH, Hodi FS. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. Clinical cancer research : an official journal of the American Association for Cancer Research 2013;19:3936-43.
2. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. The New England journal of medicine 2012;366:2455-65.
3. Le DT, Lutz E, Uram JN, et al. Evaluation of ipilimumab in combination with allogeneic pancreatic tumor cells transfected with a GM-CSF gene in previously treated pancreatic cancer. Journal of immunotherapy 2013;36:382-9.
4. Naderi E, Mostafaei M, Pourshams A, Mohamadkhani A. Network of microRNAs-mRNAs interactions in pancreatic cancer. BioMed research international 2014;2014:534821.
5. Feig C, Jones JO, Kraman M, et al. Targeting CXCL12 from FAP-expressing carcinoma-associated fibroblasts synergizes with anti-PD-L1 immunotherapy in pancreatic cancer. Proceedings of the National Academy of Sciences of the United States of America 2013;110:20212-7.
6. Righi E, Kashiwagi S, Yuan J, et al. CXCL12/CXCR4 blockade induces multimodal antitumor effects that prolong survival in an immunocompetent mouse model of ovarian cancer. Cancer research 2011;71:5522-34.
7. Vermi W, Bonecchi R, Facchetti F, et al. Recruitment of immature plasmacytoid dendritic cells (plasmacytoid monocytes) and myeloid dendritic cells in primary cutaneous melanomas. The Journal of pathology 2003;200:255-68.
8. Dhodapkar MV, Steinman RM, Krasovsky J, Munz C, Bhardwaj N. Antigen-specific inhibition of effector T cell function in humans after injection of immature dendritic cells. The Journal of experimental medicine 2001;193:233-8.
9. Fong L, Engleman EG. Dendritic cells in cancer immunotherapy. Annual review of immunology 2000;18:245-73.
10. Furumoto K, Soares L, Engleman EG, Merad M. Induction of potent antitumor immunity by in situ targeting of intratumoral DCs. The Journal of clinical investigation 2004;113:774-83.
11. Dudley ME, Wunderlich JR, Yang JC, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol 2005;23:2346-57.
12. Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annual review of immunology 2005;23:515-48.
13. Hunder NN, Wallen H, Cao J, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. The New England journal of medicine 2008;358:2698-703.
14. Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. Proceedings of the National Academy of Sciences of the United States of America 2001;98:13866-71.

15. Polcher M, Braun M, Friedrichs N, et al. Foxp3(+) cell infiltration and granzyme B(+)/Foxp3(+) cell ratio are associated with outcome in neoadjuvant chemotherapy-treated ovarian carcinoma. Cancer Immunol Immunother 2010;59:909-19.
16. Ropponen KM, Eskelinen MJ, Lipponen PK, Alhava E, Kosma VM. Prognostic value of tumour-infiltrating lymphocytes (TILs) in colorectal cancer. The Journal of pathology 1997;182:318-24.
17. Naito Y, Saito K, Shiiba K, et al. CD8+ T cells infiltrated within cancer cell nests as a prognostic factor in human colorectal cancer. Cancer research 1998;58:3491-4.
18. Galon J, Costes A, Sanchez-Cabo F, et al. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. Science 2006;313:1960-4.
19. Zhang L, Conejo-Garcia JR, Katsaros D, et al. Intratumoral T cells, recurrence, and survival in epithelial ovarian cancer. The New England journal of medicine 2003;348:203-13.
20. Sato E, Olson SH, Ahn J, et al. Intraepithelial CD8+ tumor-infiltrating lymphocytes and a high CD8+/regulatory T cell ratio are associated with favorable prognosis in ovarian cancer. Proceedings of the National Academy of Sciences of the United States of America 2005;102:18538-43.
21. Joyce JA, Fearon DT. T cell exclusion, immune privilege, and the tumor microenvironment. Science 2015;348:74-80.
22. Beider K, Begin M, Abraham M, et al. CXCR4 antagonist 4F-benzoyl-TN14003 inhibits leukemia and multiple myeloma tumor growth. Exp Hematol 2011;39:282-92.
23. Beider K, Ribakovsky E, Abraham M, et al. Targeting the CD20 and CXCR4 pathways in non-hodgkin lymphoma with rituximab and high-affinity CXCR4 antagonist BKT140. Clinical cancer research : an official journal of the American Association for Cancer Research 2013;19:3495-507.
24. Zhang Y, Patel S, Abdelouahab H, et al. CXCR4 inhibitors selectively eliminate CXCR4-expressing human acute myeloid leukemia cells in NOG mouse model. Cell death & disease 2012;3:e396.
25. Fahham D, Weiss ID, Abraham M, et al. In vitro and in vivo therapeutic efficacy of CXCR4 antagonist BKT140 against human non-small cell lung cancer. The Journal of thoracic and cardiovascular surgery 2012;144:1167-75 e1.
26. Tamamura H, Hori A, Kanzaki N, et al. T140 analogs as CXCR4 antagonists identified as anti-metastatic agents in the treatment of breast cancer. FEBS letters 2003;550:79-83.
27. Johnson DB, Rioth MJ, Horn L. Immune checkpoint inhibitors in NSCLC. Current treatment options in oncology 2014;15:658-69.
28. Ribas A, Robert C, Hodi FS, et al. Association of response to programmed death receptor 1 (PD-1) blockade with pembrolizumab (MK-3475) with an interferon-inflammatory immune gene signature. J Clin Oncol 2015;33.
29. Seiwert TY, Burtness B, Weiss J, et al. Inflamed-phenotype gene expression signatures to predict benefit from the anti-PD-1 antibody pembrolizumab in PD-L1+ head and neck cancer patients. J Clin Oncol 2015;33.
30. Shankaran V, Muro K, Bang Y, et al. Correlation of gene expression signatures and clinical outcomes in patients with advanced gastric cancer treated with pembrolizumab (MK-3475). J Clin Oncol 2015;33.
31. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clinical cancer research : an official journal of the American Association for Cancer Research 2009;15:7412-20.
32. Clopper CJ, Pearson ESCFpdD. The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. Biometrika 1934;26:404-13.

33. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European journal of cancer 2009;45:228-47.