Phase Ib and Phase II Studies of anti-PD-1 Antibody Pembrolizumab (MK-3475) in Combination with Bevacizumab for the Treatment of Metastatic Renal Cell Carcinoma: Big Ten Cancer Research Consortium BTCRC-GU14-003

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VERSION DATE: 11OCT2018

I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, or the applicable laws and regulations of the country of the study site for which I am responsible, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable ethical review board(s).

Instructions to the investigator: Please **SIGN** and **DATE** this signature page. **PRINT** your name and title, the name and location of the facility in which the study will be conducted, and the expected IRB approval date. Scan and email the completed form to BTCRC Administrative Headquarters and keep a record for your files.

_____ _____
Signature of Investigator Date

_____
Investigator Name (printed)

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Investigator Title

_____
Name of Facility

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Location of Facility (City and State)

_____ ❑ Not Submitting to IRB
Expected IRB Approval Date

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STUDY SYNOPSIS

TITLE	Phase Ib and Phase II Studies of anti-PD-1 Antibody Pembrolizumab (MK-3475) in Combination with Bevacizumab for the Treatment of Metastatic Renal Cell Carcinoma: Big Ten Cancer Research Consortium BTCRC-GU14-003
PHASE	Phase Ib/II
OBJECTIVES	**Primary Objectives:** **Phase Ib Dose Escalation Cohort**: To establish the maximum tested safe dose of study drug pembrolizumab (MK-3475) and bevacizumab in combination for subjects with metastatic clear cell renal carcinoma after failure of at least one systemic therapy for metastatic disease. **Phase II Study:** To determine the activity of combination of pembrolizumab and bevacizumab in first line therapy for subjects with treatment naïve metastatic clear cell RCC as assessed by response rate (RR) (complete or partial response) based on RECIST 1.1. **Secondary Objective(s):** To evaluate: • progression-free survival (PFS) at 6 months using RECIST 1.1 • PFS • clinical benefit rate (complete, partial response, or stable disease) • toxicity of this combination therapy • 2-year overall survival (OS) **Correlative Objectives:** • Correlate PD-L1 expression in archived diagnostic tumor tissue with clinical response. • Correlate tumor vascular density in archived diagnostic tumor tissue with clinical response during treatment. • Correlate CD4(+) and CD8(+) T-cell tumor infiltration in archived diagnostic tumor tissue with clinical response during treatment. • Correlate change in number of circulating tumor cells during therapy, relative to baseline expression, with clinical response. • Correlate change in soluble PD-L1 level in serum during therapy, relative to baseline level, with clinical response. • Correlate change in plasma VEGFc level during therapy, relative to baseline level, with clinical response. • To explore the association of proteomic and lipidomic tests at baseline with measures of response.
STUDY DESIGN	Single arm study with dose escalation phase Ib cohort followed by a phase II cohort
TOTAL NUMBER OF SUBJECTS	Up to 61
KEY ELIGIBILITY CRITERIA	1. Age ≥ 18 years 2. **Phase Ib dose escalation cohort study**: subjects with histologically assessed metastatic clear cell RCC (defined as more than 50% clear cell component) after failure of at least one systemic therapy (including, but not limited to prior therapy with interleukin 2, interferon, bevacizumab, VEGF TKI, and mTOR) for metastatic disease.

	NOTE: A biopsy to prove metastatic disease is not required. 3. **Phase II study**: subjects with treatment-naïve histologically assessed metastatic clear cell RCC (defined as more than 50% clear cell component) and who are candidates for standard first-line therapy. NOTE: A biopsy to prove metastatic disease is not required. 4. Measurable disease that can be monitored throughout the course of the study participation per RECIST 1.1 5. Karnofsky Performance Status (KPS) ≥ 70% 6. Life expectancy of 6 months or greater 7. Adequate hematologic function, as defined by central laboratory values for all three of the following criteria: a. Absolute neutrophil count (ANC) ≥ 1.5×10^9/L, and b. Platelets ≥ 100×10^9/L, and c. Hemoglobin (Hgb) ≥ 9.0 g/dL 8. Adequate renal function, as defined by either of the following criteria: a. Serum creatinine ≤ 3 mg/dL. b. OR, if serum creatinine > 3 mg/dL, estimated glomerular filtration rate (eGFR) ≥ 20 mL/min 9. Adequate hepatic function, as defined by both of the following: a. Total serum bilirubin ≤ 1.5 × ULN b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × ULN − OR, AST and ALT ≤ 5 × ULN if liver function abnormalities are due to underlying malignancy 10. Adequate coagulation function as defined by either of the following criteria: a. INR < 1.5 × ULN b. For subjects receiving warfarin or LMWH, the subjects must, in the investigator's opinion, be clinically stable with no evidence of active bleeding while receiving anticoagulant therapy. The INR for these subjects may exceed 1.5 × ULN if that is the goal of anticoagulant therapy. 11. Negative pregnancy test for female subjects with reproductive potential, and agreement of all male and female subjects of reproductive potential to use a reliable form of contraception during the study and for 120 days after the last dose of study drug 12. Able to abstain from taking prohibited drugs, either prescription or non-prescription, during the treatment phase of the study 13. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures 14. Signed and dated informed consent document indicating that the subject (or legally acceptable representative) has been informed of all pertinent aspects of the trial prior to enrollment
OUTCOME MEASURES	Response rate
STATISTICAL CONSIDERATIONS	**Phase Ib:** A standard "3+3" design will be used with maximum number of subjects accrued to be 12.

	Phase II: Phase II study endpoint will be response (PR or CR) as assessed by RECIST v1.1 criteria. Clinical studies identified a response rate with pembrolizumab of 27% in kidney cancer. With assumptions of 80% power to detect a 55% improvement to a response rate of 42% in response by RECIST v1.1 in the combination arm over historic data on single agent pembrolizumab activity in RCC, and an alpha error is 0.107, the optimal Simon's two stage design proceeds as follows. After testing the drug on 22 patients in the first stage, the trial will be terminated if 6 or fewer respond. If at least 7 respond, the trial goes on to the second stage. A total of 49 patients will be studied. If the total number responding is less than or equal to 16, the drug is rejected. Otherwise the drug will be accepted for further studies.
ENROLLMENT PERIOD	Estimated 24 months
TOTAL STUDY DURATION	Estimated 36 months

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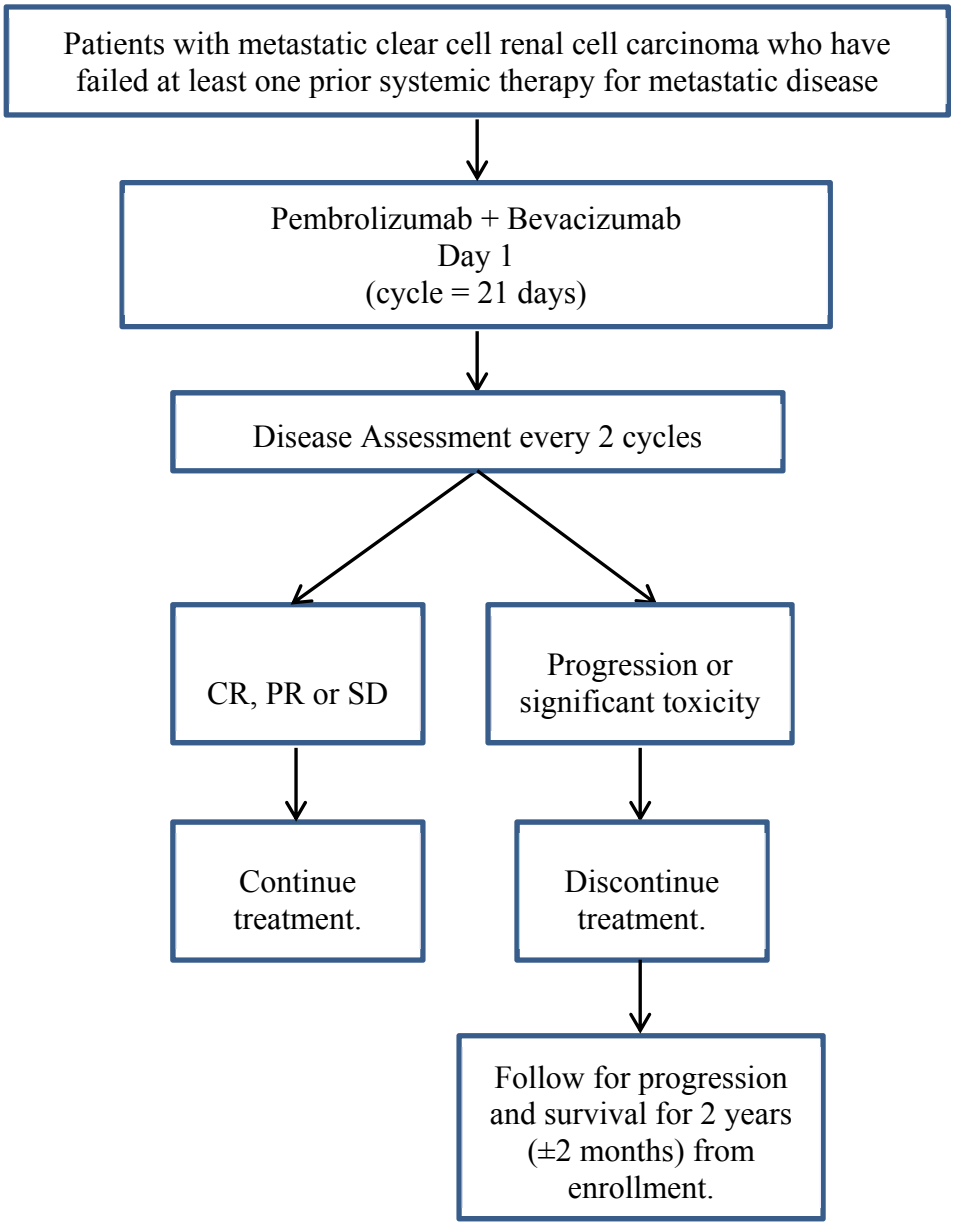
PHASE Ib SCHEMA

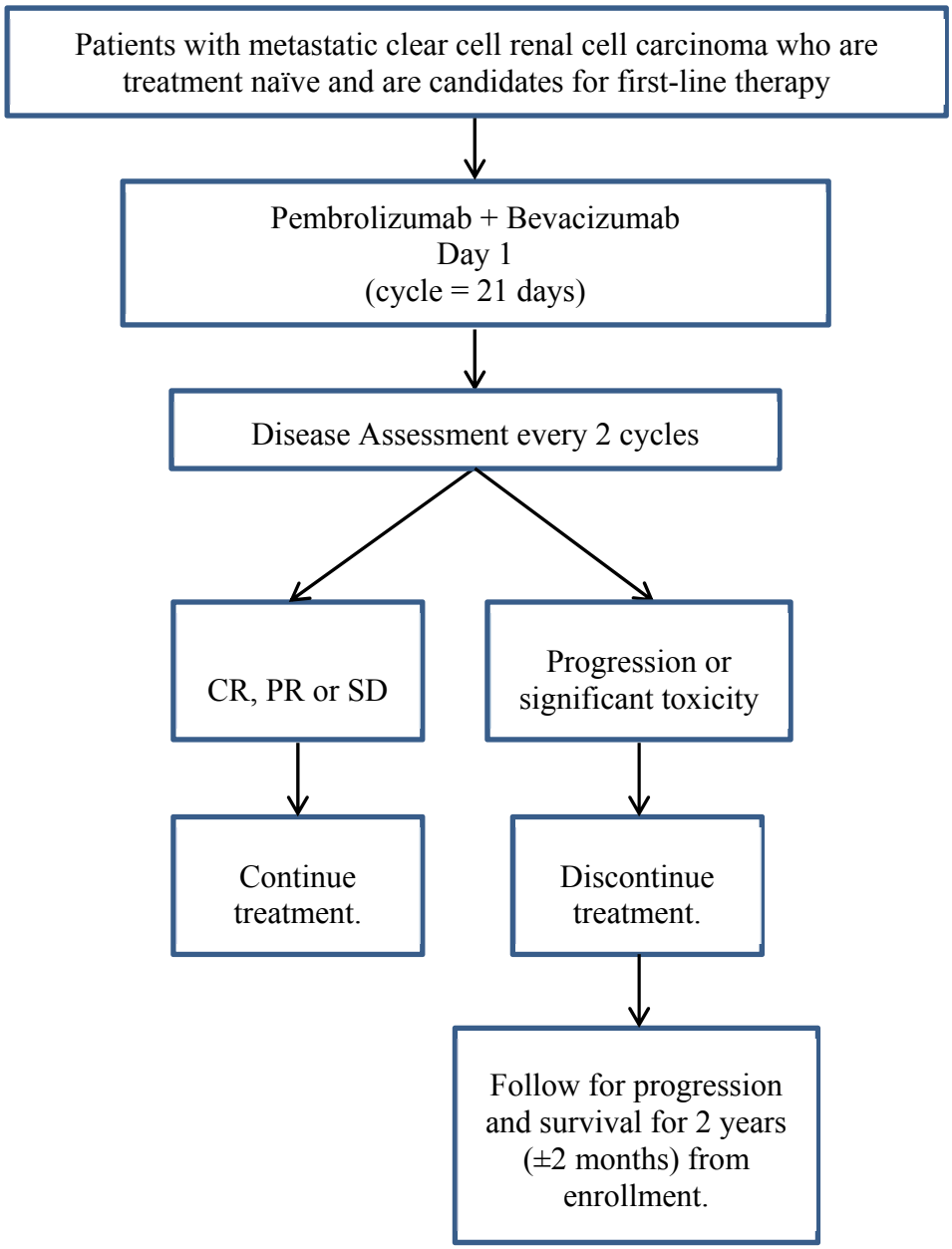
Phase Ib and Phase II Studies of anti-PD-1 Antibody Pembrolizumab (MK-3475) in Combination with Bevacizumab for the Treatment of Metastatic Renal Cell Carcinoma: Big Ten Cancer Research Consortium BTCRC-GU14-003



Dose Cohort	# of Subjects	Pembrolizumab (mg)	Bevacizumab (mg/kg)
1	3-6	200	10
2	3-6	200	15

PHASE II SCHEMA

Phase Ib and Phase II Studies of anti-PD-1 Antibody Pembrolizumab (MK-3475) in Combination with Bevacizumab for the Treatment of Metastatic Renal Cell Carcinoma: Big Ten Cancer Research Consortium BTCRC-GU14-003



Subjects will be treated with pembrolizumab at a 200 mg dose and bevacizumab at 15mg/kg (dose established by Dose Escalation Cohort to be safe).

ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AHQ	Administrative Headquarters
ANC	absolute neutrophil count
Anti-PD-1 antibody	anti-programmed death-ligand 1 antibody
Anti-PD-L1 antibody	anti-programmed death-ligand 1 antibody
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATE	arterial thromboembolic event
BMP	basic metabolic panel
BOR	best overall response
CA	cancer antigen
CBC	complete blood cell count
CIK	cytokine-induced killer
cm	centimeter
CR	complete response
CTC	cytotoxic T cell
CTCAE	(NCI) Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTLA4	cytotoxic T-lymphocyte-associated antigen 4
dL	deciliter
DLT	dose-limiting toxicity
ECI	event of clinical interest
eCRF	electronic case report form
EDC	electronic data capture
eGFR	Estimated Glomerular Filtration Rate
FDA	Food and Drug Administration
Hgb	hemoglobin
HIF-1	hypoxia-inducible factor-1
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
hr	hour
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IND	Investigational New Drug
INR	international normalized ratio
I/O	input/output
IRB	Institutional Review Board
kg	kilogram
KPS	Karnofsky Performance Status
LAK	lymphocyte-activated killer

Abbreviation	Definition
lb	pound
LDH	lactate dehydrogenase
LMWH	low-molecular-weight heparin
mCRC	metastatic colorectal cancer
MDSC	myeloid-derived suppressor cell
mg	milligram
min	minute
mL	milliliter
mm^3	cubic millimeters
NCI	National Cancer Institute
NDC	National Drug Code
OS	overall survival
PD-1	programmed death 1
PD-L1	programmed death ligand 1
PD-L2	programmed death ligand 2
PFS	progression-free survival
PR	partial response
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RPLS	Reversible Posterior Leukoencephalopathy Syndrome
RR	response rate
SAE	serious adverse event
SPM	Study Procedures Manual
SD	stable disease
TAA	tumor-associated antigen
TAM	tumor-associated macrophage
TIL	tumor-infiltrating lymphocyte
ULN	upper limit of normal
UPIRSO	unanticipated problems involving risk to subjects or others
US	United States
USP	United States Pharmacopeia
VEGF	vascular endothelial growth factor
WHO	World Health Organization
WOCP	women of childbearing potential
wt	weight

1. BACKGROUND & RATIONALE

Introduction

Anti-angiogenic treatment may improve efficacy of anticancer immunotherapies.
In recent years, there has been an emergence of anticancer immunotherapies in treating various tumor types.[1] These adoptive cell immunotherapies include tumor-infiltrating lymphocytes (TIL), cytokine-induced killer (CIK) cells, lymphokine-activated killer (LAK) cells, and tumor-associated antigen (TAA)-specific cytotoxic T cell (CTL).[2] Despite the renewed hope for cancer immunotherapy, survival benefits from adoptive cell immunotherapy alone remain modest. One of the critical challenges that adoptive cell immunotherapy faces is the immunosuppressive tumor microenvironment. The tumor microenvironment contains a vasculature that is structurally and functionally abnormal. In certain regions of tumors, the vessels are leaky, twisted, and lack stabilizing pericytes and basement membrane. The structurally abnormal tumor vessels do not provide nutritive blood flow. The immature tumor vessels contribute to an abnormal tumor microenvironment with one of the key characteristics being that of hypoxia.[3] Abnormal tumor vasculature and subsequent tumor hypoxia contribute to immune tolerance of tumor cells by impeding the homing of cytotoxic T cells into tumor parenchyma and inhibiting their antitumor efficacy.[4] These obstacles might explain why the promising approach of adoptive cell immunotherapy does not exert significant antitumor activity.[5] Hypoxia contributes to immune suppression by activating hypoxia-inducible factor (HIF-1) and the vascular endothelial growth factor (VEGF) pathway, which plays a determining role in promoting tumor cell growth and survival.[6] Tumor hypoxia creates an immunosuppressive microenvironment via the accumulation and subsequent polarization of inflammatory cells toward immune suppression phenotypes, such as myeloid-derived suppressor cells (MDSC)[7], tumor-associated macrophages (TAM)[8], and dendritic cells[9]. Adoptive cell immunotherapy alone is not efficient enough to decrease tumor growth as its antitumor effect is inhibited by the immunosuppressive hypoxic tumor microenvironment. **Antiangiogenic therapy could normalize tumor vasculature and decrease hypoxic tumor area and thus may be an effective modality to potentiate immunotherapy**[3].

Recent studies have demonstrated that there is an interaction between immune response and tumor angiogenesis. Huang et al. demonstrated that lower doses of an anti-VEGF receptor 2 (VEGFR2) antibody treatment enhanced the anti-cancer efficacy of a vaccine therapy in a model of immune tolerant breast cancer.[10] Furthermore, it was demonstrated that lower doses of the same anti-angiogenic treatment normalized breast tumor vasculature and improved tissue distribution of functional vasculature within the tumor. As stated earlier, myeloid-derived suppressor cells (MDSC) and tumor-associated macrophages (TAM) promote tumor progression by suppressing innate anti-cancer immunity. Low doses of this treatment decreased the number of MDSCs and increased the number of TAMs. On profile analysis, however, these TAMs were polarized from an immunosuppressive (M2-like) to an immune-stimulatory (M1-like) phenotype. A low dose of the anti-angiogenic treatment was also demonstrated to enhance tumor infiltration by CD4+ and CD8+ T-cells. An improvement in tumor vasculature and polarization of TAMs was shown to reduce immune-regulatory signals, and facilitated recruitment of activated CD8 (+) T cells that could exact an anti-tumor effect.

Similarly, Shi et al. demonstrated that using an anti-angiogenic agent rh-endostatin improved the anti-cancer effect of adoptive cytokine-induced killer (CIK) cells against lung carcinoma[3]. The proposed mechanism was a synergistic therapeutic effect in which endostatin contributed to structural normalization of tumor vasculature. They also demonstrated that the addition of endostatin augmented homing of the CIK cells and subsequently intratumoral CD3(+) T lymphocytes, suggesting that the addition of an anti-angiogenic agent normalized vasculature, reduced hypoxia, and altered the tumor microenvironment to enhance tumor infiltration by transferred CIK cells and T-lymphocytes.

The Programmed Death (PD-1) Receptor, Its Ligand PD-L1, and a Novel Immunotherapy: Anti-PD-1 Antibody

The Programmed death 1 (PD-1) receptor is expressed on activated T- and B-cells.[12] Its major ligand PD-L1 (B7-H1) is typically expressed on a subset of macrophages, but can be induced by inflammatory cytokines in a variety of tissue types.[13-17] When activated T-cells expressing PD-1 encounter PD-L1, T-cell effector functions are diminished. PD-1 also binds PD-L2 (B7-DC), which is expressed selectively on macrophages and dendritic cells.[17-19] These unique expression patterns suggest that PD-L1 promotes self-tolerance in peripheral tissues, while PD-L2 may function in lymphoid organs, although the role of PD-L2 in immunomodulation is not as well understood.[20] Multiple tumor types have been shown to express PD-L1 and PD-L2, effectively co-opting a native tolerance mechanism.[21-24] It has been postulated that antibodies that block the interaction between PD-1 and PD-L1 in tumors may preferentially release the cytotoxic function of tumor-specific T cells with fewer systematic toxic effects than those that are seen with other immune checkpoint inhibitors, such as CTLA-4[1]

Two large, dose-escalation, phase 1 clinical trials evaluating the safety of the anti–PD-1 antibody nivolumab (formerly known as BMS936558) and the anti–PD-L1 antibody BMS936559 showed significant antitumor activity in subjects with advanced melanoma, lung carcinoma, and renal cell carcinoma, among other cancers, thus validating the PD-1–PD-L1 axis as a therapeutic target.[25-27] Most clinical responses were durable beyond 1 year.[26,27] Toxic effects were generally of low grade. Especially relevant to this protocol, cumulative response rate among subjects with renal cell carcinoma was 27% (9/33 subjects).[27]

Pembrolizumab (MK-3475) is a highly selective, humanized monoclonal IgG4–kappa isotype antibody against PD-1 that is designed to block the negative immune regulatory signaling of the PD-1 receptor expressed by T cells.[28] The variable region sequences of a very-high-affinity mouse antihuman PD-1 antibody (dissociation constant, 28 pM) were grafted into a human IgG4 immunoglobulin with a stabilizing S228P Fc alteration. The IgG4 immunoglobulin subtype does not engage Fc receptors or activate complement, thus avoiding cytotoxic effects of the antibody when it binds to the T cells that it is intended to activate. In T-cell activation assays that used human donor blood cells, the 50% effective concentration was in the range of 0.1 to 0.3 nM.[29] The first dose escalation phase 1 study involving subjects with solid tumors showed that MK-3475 was safe at the dose levels tested (1 mg per kilogram of body weight, 3 mg per kilogram, and 10 mg per kilogram, administered every 2 weeks) without reaching a maximum tolerated dose. In addition, clinical responses were observed at all the dose levels.[30] In a recent multicenter study of 135 subjects with advanced melanoma, treatment with MK-3475 was demonstrated to have a high rate of sustained tumor regression with mainly grade 1 or 2 toxicities, and a very low incidence of grade 3 or 4 toxicities.[29]

The dose regimen of 200 mg Q3W of pembrolizumab is planned for all urothelial cancer trials. Available PK results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in PK exposures obtained at a given dose among tumor types. An open-label Phase 1 trial (PN001) in melanoma subjects is being conducted to evaluate the safety and clinical activity of single agent pembrolizumab. 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 pembrolizumab 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 maximum tolerated dose (MTD) has been identified.

In KEYNOTE-001, two randomized cohort evaluations of melanoma subjects receiving pembrolizumab at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed. The clinical efficacy and safety data demonstrate a lack of clinically important differences in efficacy response or safety profile at these doses. For example, in Cohort B2, advanced melanoma subjects who had received prior ipilimumab therapy were randomized to receive pembrolizumab at 2 mg/kg versus 10 mg/kg Q3W. The overall response rate (ORR) was 26% (21/81) in the 2mg/kg group and 26% (25/79) in the 10 mg/kg group (full analysis set (FAS)). The proportion of subjects with drug-related adverse events (AEs), grade 3-5 drug-related AEs, serious drug-related AEs, death or discontinuation due to an AE was comparable between groups or lower in the 10 mg/kg group.

Available pharmacokinetic results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in pharmacokinetic exposures obtained at a given dose among tumor types. Population PK analysis has been performed and has confirmed the expectation that intrinsic factors do not affect exposure to pembrolizumab to a clinically meaningful extent. Taken together, these data support the use of lower doses (with similar exposure to 2 mg/kg Q3W) in all solid tumor indications. 2 mg/kg Q3W is being evaluated in NSCLC in PN001, Cohort F30 and PN010, and 200 mg Q3W is being evaluated in head and neck cancer in PN012, which are expected to provide additional data supporting the dose selection.

Selection of 200 mg as the appropriate dose for a switch to fixed dosing is based on simulation results indicating that 200 mg will provide exposures that are reasonably consistent with those obtained with 2 mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. A population PK model, which characterized the influence of body weight and other patient covariates on exposure, has been developed using available data from 476 subjects from PN001. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose, with some tendency for individual values to range slightly higher with the 200 mg fixed dose. The slight increase in PK variability predicted for the fixed dose relative to weight-based dosing is not expected to be clinically important given that the range of individual exposures is well contained within the range of exposures shown in the melanoma studies of 2 and 10 mg/kg to provide similar efficacy and safety. 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 tumor types and indication settings.

Bevacizumab has gained approval for the treatment of metastatic renal cell carcinoma, when it was combined with Interferon Alfa-2a as reported by the AVOREN study. In the study 649 patients with previously untreated mRCC were randomized to treatment with either IFN+ Bevacizumab or IFN+ Placebo. In that study overall response rate (ORR) was 31% vs 13% respectively ($p<0.001$). This was associated with an improvement in PFS and a trend towards improvement in OS. In a similar trial CALGB 90206, 732 previously untreated patients were also randomized to IFNa + Bevacizumab vs IFNa + placebo. This trial also showed an improvement in ORR of 25.5% vs 13.1% respectively.

Study Rationale

There is recent promising evidence that anti-PD-1 antibodies have efficacy in treating metastatic RCC.[27] However as reviewed in the Introduction, immunotherapies such as anti-PD-1 antibodies must contend with a tumor microenvironment that is immunosuppressant, in part because of angiogenesis that results in hypoxia, diminishing the ability of the antibodies to infiltrate the tumor.[3,10,11] One of the front-line treatments for metastatic RCC is the anti-angiogenic agent, bevacizumab.[31-33] We hypothesize that through the strategy of adding the anti-VEGF agent bevacizumab to the anti-PD-1 agent pembrolizumab, tumor vasculature can be normalized (by reducing the area of the tumor that is hypoxic), thereby allowing tumor infiltration by T-lymphocytes. We will conduct two studies based on this premise. The first study is a Phase Ib dose escalation trial to establish the safe dose of pembrolizumab in combination with bevacizumab for subjects with metastatic clear cell RCC after failure of at least one systemic therapy of the disease. Once that safe dose is determined, we will conduct a Phase II study to assess superiority of disease response by adding bevacizumab to pembrolizumab in subjects with treatment naïve metastatic RCC.

2. OBJECTIVES AND ENDPOINTS

2.1. Phase Ib Objectives

2.1.1. Primary Objective

The primary objective of the Phase Ib dose escalation cohort study is to establish the safe dose of study drug pembrolizumab when used in combination with bevacizumab for subjects with metastatic clear cell renal cell carcinoma (RCC) after failure of at least one systemic therapy for metastatic disease.

2.1.2. Secondary Objectives

- Characterize adverse effects (AE) of pembrolizumab in combination with bevacizumab in subjects with metastatic RCC after failure of at least one systemic therapy.
- Evaluate clinical benefit rate (complete, partial response, or stable disease) measured by RECIST 1.1 of pembrolizumab in combination with bevacizumab in subjects with metastatic RCC after failure of at least one systemic therapy.
- Measure Progression-Free Survival (PFS) at 6 months in subjects with metastatic RCC after failure of at least one systemic therapy treated with pembrolizumab in combination with bevacizumab.

- Measure overall survival (OS) at 2 years in subjects with metastatic RCC after failure of at least one systemic therapy treated with pembrolizumab in combination with bevacizumab.

2.1.3. Correlative Objectives

- Correlate PD-L1 expression in archived diagnostic tumor tissue with clinical response.
- Correlate tumor vascular density in archived diagnostic tumor tissue with clinical response during treatment.
- Correlate CD4(+) and CD8(+) T-cell tumor infiltration in archived diagnostic tumor tissue with clinical response during treatment.
- Correlate change in number of circulating tumor cells during therapy, relative to baseline expression, with clinical response.
- Correlate change in soluble PD-L1 level in serum during therapy, relative to baseline level, with clinical response.
- Correlate change in plasma VEGFc level during therapy, relative to baseline level, with clinical response.
- To explore the association of proteomic and lipidomic tests at baseline with measures of response.

2.2. Phase II Objectives

2.2.1. Primary Objective

The primary objective of the Phase II trial is to determine the activity of the combination of pembrolizumab and bevacizumab as a first line therapy for subjects with treatment naïve metastatic clear cell RCC as assessed by response rate (RR) (complete or partial response) based on RECIST 1.1.

2.2.2. Secondary Objectives

- Characterize adverse effects (AE) of pembrolizumab in combination with bevacizumab in subjects with treatment-naïve metastatic RCC.
- Evaluate clinical benefit rate (complete, partial response, or stable disease) of pembrolizumab in combination with bevacizumab in subjects with treatment-naïve metastatic RCC.
- Measure Progression-Free Survival (PFS) using RECIST 1.1 at 6 months in subjects with treatment-naïve metastatic RCC treated with pembrolizumab in combination with bevacizumab.
- Measure overall survival (OS) at 2 years in subjects with treatment-naïve metastatic RCC treated with pembrolizumab in combination with bevacizumab.

2.2.3. Correlative Objectives

- Correlate PD-L1 expression in archived diagnostic tumor tissue with clinical response.
- Correlate tumor vascular density in archived diagnostic tumor tissue with clinical response during treatment.

- Correlate CD4(+) and CD8(+) T-cell tumor infiltration in archived diagnostic tumor tissue with clinical response during treatment.
- Correlate change in number of circulating tumor cells during therapy, relative to baseline expression, with clinical response.
- Correlate change in soluble PD-L1 level in serum during therapy, relative to baseline level, with clinical response.
- Correlate change in plasma VEGFc level during therapy, relative to baseline level, with clinical response.
- To explore the association of proteomic and lipidomic tests at baseline with measures of response.

3. ELIGIBILITY CRITERIA

Study entry is open to adults regardless of gender or ethnic background. While there will be every effort to seek out and include women and minorities, the subject population is expected to be no different than that of other advanced solid tumor cancer studies at each participating institution.

3.1. Inclusion Criteria

3.1.1 Male or female ≥ 18 years of age at time of consent.

3.1.2 **Phase Ib dose escalation cohort study**: subjects with histologically assessed metastatic clear cell RCC (defined as more than 50% clear cell component) after failure of at least one systemic therapy (including, but not limited to prior therapy with interleukin 2, interferon, bevacizumab, VEGF TKI, and mTOR) for metastatic disease.
NOTE: A biopsy to prove metastatic disease is not required.

3.1.3 **Phase II study**: subjects with treatment-naïve histologically assessed metastatic clear cell RCC (defined as more than 50% clear cell component) and who are candidates for standard first-line therapy.
NOTE: A biopsy to prove metastatic disease is not required.

3.1.4 Measurable disease, defined as at least 1 tumor that fulfills the criteria for a target lesion according to RECIST 1.1 (Section 8), and obtained by imaging within 28 days prior to registration for protocol therapy.

3.1.5 Karnofsky Performance Status ≥ 70% within 28 days prior to registration for protocol therapy.

3.1.6 Life expectancy of 6 months or greater as determined by the treating physician.

3.1.7 Adequate hepatic function within 28 days prior to registration for protocol therapy defined as meeting all of the following criteria:

- total bilirubin ≤ 1.5 × upper limit of normal (ULN) **OR** direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 x ULN

- and aspartate aminotransferase (AST) ≤ 2.5 × ULN or ≤ 5 × ULN for subjects with known hepatic metastases
- and alanine aminotransferase (ALT) ≤ 2.5 × ULN or ≤ 5 × ULN for subjects with known hepatic metastases

3.1.8 Adequate renal function within 28 days prior to registration for protocol therapy defined by either of the following criteria:
- serum creatinine ≤ 3 mg/dL
- **OR** if serum creatinine > 3 mg/dL, estimated glomerular filtration rate (GFR) ≥ 20 mL/min

3.1.9 Adequate hematologic function within 28 days prior to registration for protocol therapy defined as meeting all of the following criteria:
- hemoglobin ≥ 9 g/dL
- and absolute neutrophil count (ANC) ≥ 1.5×10^9/L
- and platelet count ≥ 100×10^9/L

3.1.10 Adequate coagulation functioning within 28 days prior to registration for protocol therapy defined by either of the following criteria:
- INR < 1.5 × ULN
- **OR** for subjects receiving warfarin or LMWH, the subjects must, in the investigator's opinion, be clinically stable with no evidence of active bleeding while receiving anticoagulant therapy. The INR for these subjects may exceed 1.5 × ULN if that is the goal of anticoagulant therapy.

3.1.11 Provided written informed consent and HIPAA authorization for release of personal health information, approved by an Institutional Review Board/Independent Ethics Committee (IRB/IEC).
NOTE: HIPAA authorization may be included in the informed consent or obtained separately.

3.1.12 Women of childbearing potential (WOCP) must not be pregnant or breast-feeding. A negative serum or urine pregnancy test is required within 72 hours of study registration. If the urine test cannot be confirmed as negative, a serum pregnancy test will be required.

3.1.13 Women of childbearing potential (WOCP) must be willing to use two effective methods of birth control such as an oral, implantable, injectable, or transdermal hormonal contraceptive, an intrauterine device (IUD), use of a double barrier method (condoms, sponge, diaphragm, or vaginal ring with spermicidal jellies or cream), or total abstinence for the course of the study until 120 days after the last dose of study drug.
NOTE: Women are considered to be of childbearing potential unless they are postmenopausal for at least 12 consecutive months or surgically sterile (bilateral tubal ligation, bilateral oophorectomy, or hysterectomy).

3.1.14 Men who are not surgically sterile (vasectomy) must agree to use an acceptable method of contraception. Male subjects with female sexual partners who are pregnant, possibly

pregnant, or who could become pregnant during the study must agree to use condoms from the first dose of study drug through at least 120 days after the last dose of study drug. Total abstinence for the same study period is an acceptable alternative.

3.1.15 Availability of tissue if applicable (from the primary tumor or metastases) for correlative studies.

3.1.16 Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures.

3.2. Exclusion Criteria

3.2.1 **Phase Ib**: Received prior monoclonal antibody therapy other than bevacizumab within 4 weeks of study registration or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events of such agents administered more than 4 weeks earlier.

3.2.2 **Phase II**: has had prior therapy for metastatic RCC.

3.2.3 Surgery within 4 weeks prior to study treatment except for minor procedures.
NOTE: Hepatic biliary stent placement is allowed.
NOTE: Subject must have adequately recovered from the toxicity and/or complications of major surgery prior to study registration, as determined by the treating physician.

3.2.4 Known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with neurological symptoms must undergo a head CT scan or brain MRI to exclude brain metastasis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to study registration. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability.

3.2.5 Previously received an organ or allogeneic progenitor/stem cell transplant.

3.2.6 Received a live vaccine within 30 days prior to the first dose of trial treatment.
Examples of live vaccines include, but are not limited to: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines and are not allowed.

3.2.7 History of blood clots, pulmonary embolism, or deep vein thrombosis unless controlled by anticoagulant treatment.

3.2.8 Known history of human immunodeficiency virus [(HIV) HIV 1/2 antibodies].

3.2.9 Known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

3.2.10 Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to study registration.

3.2.11 Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs).
NOTE: Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

3.2.12 Received prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study registration or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events from previously administered agents.
NOTE: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and can still be considered for the study.

3.2.13 Any clinically significant infection defined as any acute viral, bacterial, or fungal infection that requires specific treatment.
NOTE: Anti-infective treatment must be completed ≥ 7 days prior to study registration.

3.2.14 Evidence of interstitial lung disease, history of (non-infectious) pneumonitis that required steroids, or current pneumonitis

3.2.15 Known history of active tuberculosis.

3.2.16 Any other severe, uncontrolled medical condition, including uncontrolled diabetes mellitus or unstable congestive heart failure

3.2.17 Known allergy to pembrolizumab or any of its excipients

3.2.18 Known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies

3.2.19 Any condition that, in the opinion of the treating physician, would exclude the subject from receiving bevacizumab. Examples may include but are not limited to:

- Hemoptysis (defined as ≥ ½ teaspoon of blood)
- Pre-existing bleeding diathesis, coagulopathy or hemorrhage
- Myocardial infarction or cerebrovascular accident within 6 months prior to study registration
- Any drugs or supplements that interfere with blood clotting can raise the risk of bleeding during treatment with bevacizumab. These drugs include vitamin E, non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen (Advil, Motrin), and naproxen (Aleve, Naprosyn), warfarin (Coumadin), ticlopidine (Ticlid), and clopidogrel (Plavix). These agents should be used with caution.

3.2.20 Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product

administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for enrollment in this study.

3.2.21 Presence of any non-healing wound, fracture, or ulcer within 28 days prior to study registration.

3.2.22 Any condition that, in the opinion of the investigator, might jeopardize the safety of the subject or interfere with protocol compliance.

3.2.23 Any mental or medical condition that prevents the subject from giving informed consent or participating in the trial.

3.2.24 No prior malignancy is allowed except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, Gleason ≤ grade 7 prostate cancers, or other cancer for which the subject has been disease-free for at least 5 years.

3.2.25 Received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

3.2.26 Treatment with any investigational agent within 28 days prior to registration for protocol therapy and the subject must have recovered from the acute toxic effects of the regimen.

4. SUBJECT REGISTRATION

All subjects must be registered through BTCRC Administrative Headquarters' electronic data capture (EDC) system. A subject is considered registered when an 'On Study' date is entered into the EDC system.

Subjects must be registered after signing consent but prior to starting protocol therapy. Protocol therapy must begin therapy within 5 business days of registration.

Subjects Who Do Not Begin Study Treatment

If a subject signs consent, is registered to the study, and later is not able to begin the planned study treatment, for whatever reason, the subject will be removed from study and treated at the physician's discretion. The subject will be considered a screen/baseline failure and be replaced. The reason for removal from study will be clearly indicated in EDC system.

If a subject begins treatment, and then is discontinued for whatever reason, the subject must be followed per section 7.5.

5. TREATMENT PLAN

5.1. Overall Design and Study Plan

5.1.1. Phase Ib Dose Escalation Study

This phase Ib dose escalation study will evaluate pembrolizumab in combination with bevacizumab in subjects with metastatic clear cell renal carcinoma after failure of at least one systemic therapy for metastatic disease. Both drugs are given on Day 1 of the 21-day cycle. The drugs are administered 15-30 minutes apart in separate intravenous infusions. Treatment will continue until disease progression, unacceptable toxicity, subject refusal, or subject death either from progression of disease, the therapy itself, or from other causes. Subjects who voluntarily stop the study, have progressive disease, or unacceptable toxicities will be followed for up to 24 months.

The primary objective of the Phase Ib portion is to determine the maximum safe dose of pembrolizumab when given in combination with bevacizumab in subjects with metastatic clear cell renal carcinoma after failure of at least one systemic therapy for metastatic disease.

Dose Cohort	# of Subjects	Pembrolizumab (mg)	Bevacizumab (mg/kg)
1	3-6	200	10.0
2	3-9	200	15.0

The maximum safe dose of pembrolizumab in combination with bevacizumab will be determined using a standard "3+3" design.

- Three subjects will be enrolled at dose level 1. If none of the 3 subjects experience a dose limiting toxicity (DLT) during the first cycle of therapy, an additional 3 subjects will be enrolled at dose level 2. If all three subjects in dose level 2 complete the first cycle of therapy without DLT, 3 more subjects will be enrolled to ensure only 0-1 of 6 subjects have a DLT. There will be no further escalation beyond dose level 2.

- Alternatively, if 1 of the first 3 subjects experiences a dose limiting toxicity (DLT), the cohort will be expanded to 6 subjects. If only 1 of the total 6 subjects in a dose level experience DLT, the study will proceed to dose level 2. If there are 2 DLTs experienced during first cycle of therapy (>33% of subjects experiencing DLT), the cohort will be deemed unsafe. If this occurs at dose level 2, dose level 1 will be expanded to 6 subjects (if applicable). If there are 2 DLTs experienced during the first cycle of therapy at dose level 1, the combination will be considered unsafe for further development.

- The maximum safe dose of pembrolizumab in combination with bevacizumab is the dose of pembrolizumab combined with bevacizumab with dose limiting toxicity of less than 33% in first cycle of therapy. That dose will be recommended for the Phase II study.

- An expansion cohort of 6 patients will be allowed at the maximum safe dose prior to opening Phase II portion of the study. This will ensure ample safety data of the

combination and provide pilot activity data from 12 patients in the second-line RCC setting.

Dose limiting toxicity (DLT) is defined as one of the following events occurring during cycle 1:

- Grade 4 or greater treatment-related hematologic toxicity for > 7 days during the first cycle (21 days) of therapy.
- Febrile neutropenia
- Grade 4 or greater thrombocytopenia of any duration.
- Grade 3 thrombocytopenia with significant hemorrhage of any duration.
- Grade 3 or greater treatment-related clinical non-hematological toxicity
  Excluding:
  - Grade 3-4 nausea, vomiting in the absence of maximal medical therapy that resolves in 72 hours.
  - Grade 3-4 laboratory abnormalities that are not clinically significant and which resolve in 72 hours.
  - Grade 3 fatigue lasting < 5 days.
  - Grade 3 hypertension that can be controlled with medical therapy.
- Delay of cycle 2 treatment start by more than 2 weeks due to incomplete hematologic recovery (ANC > 1.5 x 10^9/L or platelets 100 x 10^9/L) or unresolved treatment related grade 3 or greater non-hematologic toxicity.

DLTs will be counted based on the number of subjects with DLT at a given dose level, not the absolute number of DLTs. No single subject can trigger more than one DLT event.

Additional subject cohorts will not be enrolled at the second dosing level until all subjects at the initial dosing level complete all planned treatment for cycle 1 (defined as 2 doses of pembrolizumab, and two doses of bevacizumab) and are able to start cycle 2 with no more than a 2-week delay.

Intra-subject dose escalation is not permitted.

Once the maximum tested safe dose of pembrolizumab in combination with bevacizumab is determined, enrollment will continue until at least 9 subjects total are accrued at the maximum tested safe dose.

Correlative research analyses includes examining the relationship between clinical response at the end of Cycle 2 (Week 6) with PD-L1 expression, tumor vascular density, and CD4(+) and CD8(+) T-cell tumor infiltration of the archived diagnostic tumor tissue. Research analyses also include examining the relationship between changes in number of circulating tumor cells, soluble PD-L1 levels, and VEGFc levels from baseline to the end of Cycle 2 (Week 6) of the treatment period and clinical response at that time. Correlative samples will continue to be collected every 6 or 9 weeks for exploratory analysis of circulating tumor cells, soluble PD-L1 levels, and VEGFc levels. Correlative sample analysis will also explore the association of proteomic and lipidomic tests at baseline with measures of response.

5.1.2. Phase II Study

The primary objective of the Phase II trial is to determine the activity of the combination of pembrolizumab and bevacizumab in first line therapy for subjects with metastatic clear cell RCC as assessed by response rate (RR) (complete or partial response) based on RECIST 1.1. The maximum safe dose of pembrolizumab in combination bevacizumab will be given on Days 1 of each 21 day cycle. Treatment will continue until disease progression, unacceptable toxicity, subject refusal, or subject death either from progression of disease, the therapy itself, or from other causes. Subjects who voluntarily stop the study, have progressive disease, or unacceptable toxicities will be followed for a total of 24 months.

Correlative research analyses includes examining the relationship between clinical response at the end of Cycle 2 (Week 6) with PD-L1 expression, tumor vascular density, and CD4(+) and CD8(+) T-cell tumor infiltration of the archived diagnostic tumor tissue. Research analyses also include examining the relationship between changes in number of circulating tumor cells, soluble PD-L1 levels, and VEGFc levels from baseline to the end of Cycle 2 (Week 6) of the treatment period and clinical response at that time. Correlative samples will continue to be collected every 6 or 9 weeks for exploratory analysis of circulating tumor cells, soluble PD-L1 levels, and VEGFc levels. Correlative sample analysis will also explore the association of proteomic and lipidomic tests at baseline with measures of response.

5.2. Pre-medication

Pre-medication is not required but may be administered per physician discretion.

5.3. Drug Administration

5.3.1. Pembrolizumab + Bevacizumab Administration

Phase Ib

Dosing will occur in 21-day cycles. Pembrolizumab in the Phase Ib dose escalation study will be dosed at 200 mg IV followed by bevacizumab at either 10 mg/kg or 15 mg/kg IV on day 1 of a 21 day cycle.

Phase II

In Phase II, the pembrolizumab dose will be 200 mg administered via IV followed by bevacizumab at 15mg/kg (dose established in the Phase Ib study) administered via IV. Pembrolizumab will be administered as a 30-minute intravenous infusion. Bevacizumab will be administered as a one-hour intravenous infusion. All treatment will be administered 15-30 minutes apart. Subsequent cycles must meet the criteria found in section 6.1 and may begin 1 day earlier or up to 2 days later to accommodate scheduling issues.

Monitoring

Vital signs including blood pressure, pulse, temperature, respirations, and pulse oximetry, will be measured as follows:

- Pembrolizumab infusion: before and after the infusion and every 30 minutes (±5 min) until the bevacizumab infusion is complete.
- During bevacizumab infusion: every 30 minutes (±5 min) for one hour during infusion.

Subjects will be closely monitored for toxicities. Toxicity will be assessed using CTCAE version 4.

Drug	Administration Sequence	Dose	Length and route of administration	Frequency of administration	Length of cycle
pembrolizumab	1st	200 mg	30-min (-5/+10), IV	Day 1	21 days
bevacizumab	2nd (15-30 min post pembrolizumab)	10 mg/kg	1-hr[a], IV	Day 1	
		15 mg/kg			

a: Length of first infusion and subsequent infusion will be per institutional standards.

NOTE: Infusions may be given -1 day or +2 days for reasons such as observed holidays, inclement weather, scheduling conflicts, etc. It should be clearly documented in subject's chart and case report forms.

The body surface area and bevacizumab dose should be recalculated if the subject's weight changes by ≥ 10% during the course of the study.

5.4. Supportive Care

Optimal patient care is to be given to all subjects.

Subjects should receive full supportive care during the study, including transfusion of blood and blood products, treatment with antibiotics, analgesics, erythropoietin, or bisphosphonates, when appropriate.

Although acetaminophen at doses of ≤2 grams/day is permitted, it should be used with caution in subjects with impaired liver function.

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 the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below).

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

Management of Pembrolizumab Infusion Related Reactions
Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Table 5 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab.

Table 5 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, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: 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.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab 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;	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	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. **In cases of anaphylaxis, epinephrine should be used immediately. **Subject is permanently discontinued from further trial treatment administration.**	
An appropriate resuscitation plan should in place and a physician readily available during the period of drug administration. For Further information, please refer to the Common Terminology Criteria for Adverse Events v4 (CTCAE) at http://ctep.cancer.gov		

5.5. Concomitant Medications

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

Permitted Concomitant Medications and Procedures
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 medications will be recorded on the electronic case report form (eCRF).

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 beyond 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 11.

Myeloid growth factors to treat subjects with neutropenia according to the American Society of Clinical Oncology (ASCO) Guidelines are permitted. Myeloid growth factors should be avoided (if medically appropriate) in Cycle 1 until subjects have developed a DLT or dose-limiting Grade 4 neutropenia.

Antiemetic agents may be administered at the discretion of the investigator but are not commonly required as a prophylactic agent. All other manifestations of the subject's malignancy should be treated at the discretion of the investigator.

Medications with potential CNS effects are not prohibited in this study, but it is recommended that their use be minimized to avoid confusion in the interpretation of CNS effects should they occur during the course of treatment with pembrolizumab and bevacizumab.

In appropriate settings, such as combinations with agents known to produce frequent thrombocytopenia, restricted uses of anticoagulants should be considered.

All other medical conditions should be treated at the discretion of the investigator in accordance with local community standards of medical care.

The Effects of Other Drugs on Bevacizumab

Any drugs or supplements that interfere with blood clotting can raise the risk of bleeding during treatment with bevacizumab. These drugs include vitamin E, non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen (Advil, Motrin), and naproxen (Aleve, Naprosyn), warfarin (Coumadin), ticlopidine (Ticlid), and clopidogrel (Plavix).These agents should be used with caution.

Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Anti-cancer systemic chemotherapy or biological therapy not specified in this protocol
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
  - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with sponsor-investigator. Please contact the BTCRC Project Manager.
- 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, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the sponsor-investigator via the BTCRC Project Manager.

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.

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

5.6. Diet/Activity/Other Considerations

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

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. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study drug.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

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 they must adhere to the contraception requirements described above for the duration of the study and 120 days following the last dose of study drug. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

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 BTCRC Administrative Headquarters (AHQ) and to Merck immediately and within 24 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 BTCRC AHQ. If a male subject impregnates his female partner, he must immediately inform the site study personnel and the pregnancy reported to BTCRC AHQ and to Merck and followed as described above and in Section 11.

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.

6. DOSE DELAYS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4 will be used to grade adverse events.

Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Section 7.

Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring protocol therapy interruption or discontinuation at each study visit for the duration of their participation in the study.

Subjects discontinued from the treatment phase of the study for any reason will be evaluated at least 30 days (+ 7) after the last dose of protocol therapy.

6.1. Start of a New Cycle

A new treatment cycle will only be initiated when all of the following conditions are met:
- ANC $\geq 1{,}500\times 10^9$/L
- platelets $\geq 100\times 10^9$/L
- non-hematologic treatment related toxicities have improved to $\leq$ Grade 1 or to the subject's baseline values (except alopecia)

If blood counts are below this threshold, blood work is to be repeated weekly until counts are at an acceptable level. If treatment is unable to restart within 12 weeks of the planned treatment date, the subject will be permanently discontinued from study therapy.

NOTE: For cycle 1 only, the inability to restart therapy within 2 weeks of the planned date is a DLT (per section 5.1.1); however, the subject is allowed an additional week of recovery and is allowed to remain on study if treatment restarts within 12 weeks.

Any delay to the start of pembrolizumab will result in the same delay to bevacizumab (and vice versa) so that both treatments are given together. Study procedures associated with each cycle of therapy will also be delayed accordingly (including scans for tumor assessment). Blood tests and/or clinical evaluations should occur at the discretion of the treating investigator to monitor these parameters. If one drug is permanently discontinued the other drug can be continued.

6.2. Management of Allergic Reaction/ Hypersensitivity

Description	Action

CTCAE Grade I Allergic Reaction/Hypersensitivity: (Transient flushing or rash, drug fever < 38°C):	Supervise without further treatment for allergic reaction/hypersensitivity.
CTCAE Grade 2 Allergic Reaction/Hypersensitivity: (Rash, flushing, dyspnea, urticaria, drug fever greater than or equal to 38°C) and/or asymptomatic bronchospasm:	Interrupt the infusion. If symptoms abate, attempt re-infusion at a slower rate. If the symptoms recur, discontinue infusion and follow for recurrent allergic reaction/hypersensitivity in the next paragraph.
Recurrent CTCAE Grade 2 or CTCAE Grade 3 or 4 Allergic Reaction/Hypersensitivity:	Stop the infusion. Administer additional doses of H1 and H2 blockers intravenously. Administer IV steroids and consider epinephrine and bronchodilators as clinically indicated.
CTCAE Grade 3 or 4 Allergic Reaction/Hypersensitivity:	Will be permanently discontinued from study treatment.

Prior to re-challenge of Grade 2 allergic reaction/ hypersensitivity reaction and with all subsequent cycles, give both an H1 and H2 blocker intravenously plus dexamethasone 20 mg × 2 doses (orally or intravenously) 12 and 6 hours **before the chemotherapy session**. Dexamethasone could be used at the investigator's discretion in subsequent cycles for recurrent (i.e. occurring despite slowing infusion as discussed above) Grade 2 reactions but would not be mandated.

6.3. Other Adverse Event Guidelines

Description	Treatment Delay
Any other grade 3 non-hematologic toxicity	Up to 4 week delay
Any other grade 4 non-hematologic toxicity	Discontinue treatment
Neutrophils 999-500 cells/mm^3	Up to 4 week delay
Neutrophils <500 cells/mm^3	Discontinue treatment
Febrile Neutropenia	Discontinue treatment
Platelets 50,000 /mm^3 to 75,000/mm^3	Up to 4 week delay
Platelets <50,000/mm^3	Discontinue treatment
Any other grade 4 hematologic toxicity	Discontinue treatment

If treatment delay necessitates a period longer than 12 weeks, treatment is stopped and the subject is discontinued from the study.

6.4. Dose Modifications

There will be no dose modification of bevacizumab in the Phase Ib study. Once the doses are established for the Phase II study, there will be no dose modification of bevacizumab.

Pembrolizumab Dose Modifications
Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than on body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 3 below.

Other allowed dose interruptions for pembrolizumab
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 BTCRC Project Manager. The reason for interruption should be documented in the patient's study record.

Table 3: Dose modification and toxicity management guidelines for immune-related adverse events associated with pembrolizumab.

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently

	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	until liver enzyme value returned to baseline or is stable
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE: For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

7. STUDY CALENDAR & EVALUATIONS [Cycle = 21 days]

Study Day	Screening	Cycle 1	Cycle 2+	Every 6 or 9 weeks	End of treatment visit	Follow Up until 2 yrs from registration
	-28 days	Day 1[5]	Day 1 (±3)		30 days (+7) post last protocol therapy dose	Every 3 months (±14 days)
REQUIRED ASSESSMENTS						
Informed Consent/ HIPAA auth.	X					
Medical history including prior therapies and pathology	X					
Substance use: smoking history (amnt, freq, start/stop)	X					
Physical examination, height, weight	X	X	X		X	
Vital Signs	X	X[12]	X		X	
Karnofsky Performance status	X	X[12]	X		X	
Blood Chemistries[1]	X	X[12]	X			
Thyroid Function (TSH, T3, T4)	X					
PT/INR and aPTT	X	X[12]				
Platelets, ANC & Hgb	X	X[12]	X			
Urinalysis for protein[2]	X	X[12]	X		X	
Pregnancy test for WOCP[10]	X					
AE, ECI and irAE assessment		X[12]	X		X[6]	
Concomitant medications	X	X	X		X	
Survival						X
DISEASE ASSESSMENT						
CT chest, abdomen/pelvis	X[3]			X (± 7 days)[3]		X[13]
CT or MRI Brain, if indicated	[X]					
TREATMENT						
Pembrolizumab		X	X			
Bevacizumab		X	X			
CORRELATIVE STUDIES						
Unstained slides from an archived tumor tissue[4] - Mandatory		X				
Whole blood for circulating tumor cells - Mandatory		X[11]		X[11]		
Serum for soluble PD-L1 analysis - Mandatory		X[11]		X[11]		
Plasma for VEGFc levels - Mandatory		X[11]		X[11]		
BANKING SAMPLES						
Whole Blood[7]		X				
Unstained slides from archived tumor tissue[8]		X				
Serum and plasma[9]		X			X	

Footnotes:

1: Blood Chemistries to include: sodium, potassium, serum creatinine (or GFR; see 3.1.8), calcium, albumin, ALT, AST, bilirubin, alkaline phosphatase, total protein
2: Urinalysis for protein to be performed within one week of study enrollment. If urine dipstick is 2+, then 24-hr urine for protein must demonstrate < 1 g protein in 24 hr to allow participation in the study.
3: Appropriate scans to assess disease status will be obtained within 4 weeks of study enrollment including CT chest, abdomen/pelvis. Disease imaging will be performed every 6 weeks through Cycle 9 (cycle 3, 5, 7, 9). Thereafter, imaging will be performed every 9 weeks (cycle 12, 15, 18, etc.).
4: Mandatory submission of unstained slides from an archived tumor tissue for PD-L1 expression, tumor vascular density and CD4(+) and CD8(+) T-cell infiltration are to be submitted after the patient is registered to the trial. These must be submitted prior to Cycle 2. If archived tumor tissue is not available, the patient does not need to undergo a biopsy to obtain tissue. See SPM for collection, labeling and shipping instructions.
5: For cycle 1 only: labs do not need to be repeated if done within 7 days of day 1.
6: For subjects with unresolved treatment related toxicity, follow as medically appropriate until resolution or stabilization
7: Submission of whole blood for banking is to be collected at Pre-Treatment Cycle 1 Day 1. See SPM for collection, processing, labeling and shipping instructions.
8: Submission of unstained slides for banking from an archived FFPE tumor block is requested. See SPM for collection, labeling, and shipping instructions.
9: Submission of serum and plasma for banking are to be collected at Pre-Treatment Cycle 1 Day 1 and at the End of Treatment visit. See SPM for collection, labeling, processing, and shipping instructions.
10: A negative serum or urine pregnancy test is required within 72 hours of study registration. If the urine test cannot be confirmed as negative, a serum pregnancy test will be required.
11: Mandatory submission of whole blood (circulating tumor cell analysis), plasma (VEGFc analysis) and serum (soluble PD-L1 analysis) will be collected **pre-dose** Cycle 1 Day 1 and every 6 or 9 weeks thereafter (i.e. **pre-dose** Cycle 3 Day 1, **pre-dose** Cycle 5 Day 1, etc.). Correlative samples will be collected every 6 weeks through Cycle 9 (cycle 3, 5, 7, 9). Thereafter, samples will be collected every 9 weeks (cycle 12, 15, 18, etc.). See SPM for collection, processing, labeling and shipping instructions.
12: **Phase Ib only**: To be performed weekly during Cycle 1 (DLT evaluation period).
13: Disease assessment will be performed during the 6-month follow up visit for subjects who did not progress during treatment.

7.1. Screening

7.1.1. Within 28 days prior to registration for protocol therapy:

- Informed consent, HIPAA authorization
- Medical history including prior therapies and pathology
- Substance use: smoking history. To include: amount, frequency, start and stop dates of cigarette, cigar and pipe usage.
- Physical exam, height, weight
- Vital signs (blood pressure, heart rate, temperature)
- Karnofsky performance status
- Blood chemistries (sodium, potassium, serum creatinine [or GFR; see 3.1.8], calcium, albumin, ALT, AST, bilirubin, alkaline phosphatase, total protein)
- PT/INR and aPTT
- Thyroid function (TSH, T3 and T4)
- Platelets, ANC and hemoglobin
- Urinalysis (urine protein, white blood cells, red blood cells). Urinalysis for protein to be performed within one week of study enrollment. If urine dipstick is 2+, then 24-hr urine for protein must demonstrate < 1 g protein in 24 hr to allow participation in the study.
- Concomitant medications
- CT chest, abdomen, pelvis
- CT or MRI of brain, if indicated

7.1.2. Within 72 hours prior to registration for protocol therapy:

- Pregnancy test for women of childbearing potential (WOCP). A negative serum or urine pregnancy test is required within 72 hours of study registration. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

7.2. On Treatment

7.2.1. Day 1 of Cycle 1:

Note: Cycle 1 Day 1 lab testing need not be repeated if completed within 7 days of starting protocol therapy.

- Physical exam, weight
- Vital signs
- Karnofsky performance status
- Blood chemistries (sodium, potassium, serum creatinine [or GFR; see 3.1.8], calcium, albumin, ALT, AST, bilirubin, alkaline phosphatase, total protein)
- Platelets, ANC and hemoglobin
- Urinalysis for protein. If urine dipstick is 2+, then 24-hr urine for protein must demonstrate < 1 g protein in 24 hr.
- Assess adverse events (AE), events of clinical interest (ECI) and immune-related adverse events (irAE)
- Concomitant medications
- Pembrolizumab

- Bevacizumab
- Correlative and Banking samples. See Study Procedures Manual for specific instructions.

7.2.1.1. Weekly during Cycle 1 of Phase Ib only:

The following will be performed weekly during Cycle 1 (DLT evaluation period):

- Vital signs (blood pressure, heart rate, temperature)
- Karnofsky performance status
- Blood chemistries (sodium, potassium, serum creatinine [or GFR; see 3.1.8], calcium, albumin, ALT, AST, bilirubin, alkaline phosphatase, total protein)
- PT/INR and aPTT
- Platelets, ANC and hemoglobin
- Urinalysis (urine protein, white blood cells, red blood cells). If urine dipstick is 2+, then 24-hr urine for protein must be collected. If protein is < 2 g, bevacizumab may resume but continue to monitor until 24-hr protein demonstrates < 1 g of protein.
- Assess adverse events (AE), events of clinical interest (ECI) and immune-related adverse events (irAE)

7.2.2. Day 1 of Cycle 2+ (±3 days):

- Physical exam, weight
- Vital signs
- Karnofsky performance status
- Blood chemistries (sodium, potassium, serum creatinine [or GFR; see 3.1.8], calcium, albumin, ALT, AST, bilirubin, alkaline phosphatase, total protein)
- Platelets, ANC and hemoglobin
- Urinalysis. If urine dipstick is 2+, then 24-hr urine for protein must be collected. If protein is < 2 g, bevacizumab may resume but continue to monitor until 24-hr protein demonstrates < 1 g of protein.
- Assess adverse events, events of clinical interest and immune-related adverse events
- Concomitant medications
- Pembrolizumab
- Bevacizumab

7.2.3. Every 6 or 9 weeks:

Disease imaging and correlative sample collection will be performed every 6 weeks through Cycle 9 (cycle 3, 5, 7, 9). Thereafter, they will be performed every 9 weeks (cycle 12, 15, 18, etc.).

- CT chest, abdomen, pelvis (±7 days)
- Correlative samples (**pre-dose** Cycle 3 Day 1, **pre-dose** Cycle 5 Day 1, etc.). See Study Procedures Manual for specific instructions.

7.3. Off Treatment

7.3.1. Protocol therapy discontinuation:

A subject will be discontinued from the protocol therapy under the following circumstances:

- If there is evidence of disease progression
- If the treating physician thinks a change of therapy would be in the best interest of the subject
- If the subject requests to discontinue protocol therapy
- If the protocol therapy exhibits unacceptable toxicity
- If a female subject becomes pregnant
- If there is a ≥ 12-week delay between cycles due to a treatment related adverse event.

Subjects can stop study participation at any time. However, if they decide to stop, subjects will continue to be followed for survival for 24 months after discontinuation.

7.4. End of Treatment 30 days (+7 days) after final protocol therapy dose

- Physical exam, weight
- Vital signs
- Karnofsky performance status
- Urinalysis. If urine dipstick is 2+, then 24-hr urine for protein must be collected. Continue to monitor until 24-hr protein demonstrates < 1 g of protein.
- Assess adverse events, events of clinical interest and immune-related adverse events
- Concomitant medications
- Banking samples. See Study Procedures Manual for specific instructions.

7.5. Follow-up (±14 days)

Administration of study medication may continue until disease progression, unacceptable toxicity, or subject withdrawal. A final study visit will occur at least 30 days (+ 7 days) after the last dose of study drugs.

Subjects will continue to be followed for survival every 3 months for 24 months after registration.

Disease assessment will be performed during the 6-month follow up visit for subjects who did not progress during treatment.

8. CRITERIA FOR DISEASE EVALUATION

Response assessments will be made both using the Immune Related Response Criteria (irRC), and using RECIST v1.1, allowing additional comparisons among these criteria for disease response assessment. The same measurable and non-measurable lesions will be followed by both RECIST v1.1 & irRC. Disease progression will be determined using RECIST 1.1 criteria.

8.1. Definitions Associated with Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1

8.1.1. Measurable disease: The presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

8.1.1.1. ***Measurable lesions:*** Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

8.1.1.2. ***Non-measurable lesions:*** All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

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

8.1.1.4. ***Baseline documentation of "Target" and "Non-Target" lesions:***

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to

further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

8.2. Response Criteria for Target Lesions

8.2.1. Evaluation of target lesions

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

8.2.2. Evaluation of non-target lesions

Response Criteria	Evaluation of non-target lesions
* Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level
* Incomplete Response/ Stable Disease (SD)	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
* Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions*

* Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the Sponsor-Investigator.

8.3. Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/ Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD/ or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Non-evaluable
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD
*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.			

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

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

8.4. Definitions for Response Evaluation –RECIST version 1.1

8.4.1. First Documentation of Response:

The time between initiation of therapy and first documentation of PR or CR.

8.4.2. Confirmation of Response:

To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met.

8.4.3. Duration of Response:

Duration of overall response—the period measured from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until

the date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since treatment started).

8.4.4. Duration of Overall Complete Response:
The period measured from the time that measurement criteria are met for complete response until the first date that progressive disease is objectively documented.

8.4.5. Response Rate:
The response rate is the proportion of all subjects with confirmed PR or CR according to RECIST v1.1.

8.4.6. Clinical Benefit Rate
The proportion of patients with a confirmed complete response, a partial response or stable disease based on RECIST 1.1.

8.4.7. Progression-Free Survival:
A measurement from the start of the treatment until the criteria for disease progression is met as defined by RECIST 1.1 or death occurs. Patients who have not progressed or died will be right-censored at the date of the last disease evaluation.

8.4.8. Overall Survival
A measurement from the start of the treatment until death from any cause. Patients alive at last time of contact will be right-censored.

8.5. Methods of Measurement

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 28 days before the beginning of the treatment.

Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam. The same imaging modality must be used throughout the study to measure disease.

8.5.1. CT and MRI:
CT and MRI are the best currently available and most reproducible methods for measuring target lesions. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the

type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

8.5.2. Chest X-Ray:

Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by an aerated lung (CT is preferable).

8.5.3. Clinical Examination:

Clinically detected lesions will only be considered measurable when they are superficial (e.g. skin nodules and palpable lymph nodes). For skin lesions, documentation by color photography, including a ruler to estimate size of the lesion, is recommended. Photographs should be retained at the institution.

8.5.4. Cytology and Histology:

Cytologic and histologic techniques can be used to differentiate between complete and partial responses in rare cases (e.g. after treatment to differentiate residual benign lesions and residual malignant lesions in germ cell tumors). Cytologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met response or stable disease criteria.

8.6. Immune Related Response Criteria:

This study will evaluate concordance of the Immune Related Response Criteria (irRC) with RECIST 1.1 and OS. These response criteria were developed to overcome the variable and unusual patterns of response to immunotherapeutic agents, in particular, ipilimumab [34]. The development of the guidelines were prompted by observations, mostly in subjects with metastatic melanoma, of initial disease progression followed by later response, late responses, and mixed responses with an overall decrease in tumor burden.

8.6.1. Antitumor response based on total measurable tumor burden

For the irRC, only index and measurable new lesions are taken into account (in contrast to conventional WHO criteria, which do not require the measurement of new lesions, nor do they include new lesion measurements in the characterization of evolving tumor burden). At the baseline tumor assessment, the sum of the products of the two largest perpendicular

diameters (SPD) of all index lesions (5 lesions per organ, up to 10 visceral lesions) is calculated. At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (up to 5 new lesions per organ; 10 visceral lesions) are added together to provide the total tumor burden:

Tumor Burden = $SPD_{\text{index lesions}} + SPD_{\text{new, measurable lesions}}$

Table 8: Comparison of WHO and irRC criteria

	WHO	irRC
New, measurable lesions	Always represent PD	Incorporated into tumor burden
New, non-measurable lesions	Always represent PD	Do not define progression (but preclude irCR)
Non-index lesions	Changes contribute to defining BOR of CR, PR, SD, and PD	Contribute to defining irCR (complete disappearance required)
CR	Disappearance of all lesions in two consecutive observations not less than 4 wk apart	Disappearance of all lesions in two consecutive observations not less than 4 wk apart
PR	≥50% decrease in SPD of all index lesions compared with baseline in two observations at least 4 wk apart, in absence of new lesions or unequivocal progression of non-index lesions	≥50% decrease in tumor burden compared with baseline in two observations at least 4 wk apart
SD	50% decrease in SPD compared with baseline cannot be established nor 25% increase compared with nadir, in absence of new lesions or unequivocal progression of non-index lesions	50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir
PD	At least 25% increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point)	At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 wk apart

8.6.2. Time-point response assessment using irRC

Percentage changes in tumor burden per assessment time point describe the size and growth kinetics of both conventional and new, measurable lesions as they appear. At each tumor assessment, the response in index and new, measurable lesions is defined based on the change in tumor burden (after ruling out irPD). Decreases in tumor burden must be assessed relative to baseline measurements (i.e., the SPD of all index lesions at screening). The irRC were derived from WHO criteria and, therefore, the thresholds of response remain the same. However, the irRC response categories have been modified from those of WHO criteria as detailed in Tables 8 and 9.

8.6.3. Overall response using the irRC

The sum of the products of diameters at tumor assessment using the immune-related response criteria (irRC) for progressive disease incorporates the contribution of new measurable lesions. Each net Percentage Change in Tumor Burden per assessment using

irRC criteria accounts for the size and growth kinetics of both old and new lesions as they appear.

Definition of Index Lesions Response Using irRC

- **irComplete Response (irCR):** Complete disappearance of all *index* lesions. This category encompasses exactly the same subjects as "CR" by the mWHO criteria.
- **irPartial Response (irPR):** Decrease, relative to baseline, of 50% or greater in the sum of the products of the 2 largest perpendicular diameters of all *index* and all new measurable lesions (ie, Percentage Change in Tumor Burden). **Note:** the appearance of new measurable lesions is factored into the overall tumor burden, but does not automatically qualify as progressive disease until the SPD increases by ≥ 25% when compared to SPD at nadir.
- **irStable Disease (irSD):** Does not meet criteria for irCR or irPR, in the absence of progressive disease.
- **irProgressive Disease (irPD):** At least 25% increase Percentage Change in Tumor Burden (i.e., taking sum of the products of all *index* lesions and any new lesions) when compared to SPD at nadir.

Definition of Non-Index Lesions Response Using irRC

- **irComplete Response (irCR):** Complete disappearance of all *non-index* lesions. This category encompasses exactly the same subjects as "CR" by the mWHO criteria.
- **irPartial Response (irPR) or irStable Disease (irSD):** *non-index* lesion(s) are not considered in the definition of PR, these terms do not apply.
- **irProgressive Disease (irPD):** Increases in number or size of *non-index* lesion(s) does not constitute progressive disease unless/until the Percentage Change in Tumor Burden increases by 25% (i.e., the SPD at nadir of the index lesions increases by the required amount).

Impact of New Lesions on irRC

New lesions in and by themselves do not qualify as progressive disease. However, their contribution to total tumor burden is included in the SPD, which in turn feeds into the irRC criteria for tumor response. Therefore, new non-measurable lesions will not discontinue any subject from the study.

Definition of Overall Response Using irRC

Overall response using irRC will be based on these criteria (see Table 9):

- **Immune-Related Complete Response (irCR):** Complete disappearance of *all* tumor lesions (index and non-index together with no new measurable/unmeasurable lesions) for at least 4 weeks from the date of documentation of complete response.
- **Immune-Related Partial Response (irPR):** The sum of the products of the two largest perpendicular diameters of all index lesions is measured and captured as the SPD baseline. At each subsequent tumor assessment, the sum of the products of the two largest perpendicular diameters of all index lesions and of new measurable lesions are added together to provide the Immune Response Sum of Product Diameters (irSPD). A decrease, relative to baseline of the irSPD compared to the previous SPD baseline, of 50% or greater is considered an immune Partial Response (irPR).

- **Immune-Related Stable Disease (irSD):** irSD is defined as the failure to meet criteria for immune complete response or immune partial response, in the absence of progressive disease.
- **Immune-Related Progressive Disease (irPD):** It is recommended in difficult cases to confirm PD by serial imaging. Any of the following will constitute progressive disease:
  - At least 25% increase in the sum of the products of all index lesions over nadir SPD calculated for the index lesions.
  - At least a 25% increase in the sum of the products of all index lesions and new measurable lesions (irSPD) over the baseline SPD calculated for the index lesions.

Immune-Related Best Overall Response Using irRC (irBOR)

irBOR is the best confirmed irRC overall response over the study as a whole, recorded between the date of first dose until the last tumor assessment before subsequent therapy (except for local palliative radiotherapy for painful bone lesions) for the individual subject in the study. For the assessment of irBOR, all available assessments per subject are considered.

irCR or irPR determinations included in the irBOR assessment must be confirmed by a second (confirmatory) evaluation meeting the criteria for response and performed no less than 4 weeks after the criteria for response are first met.

Table 9: Derivation of irRC overall responses

Measurable response	Nonmeasurable response		Overall response
Index and new, measurable lesions (tumor burden),*%	Non-index lesions	New, nonmeasurable lesions	Using irRC
↓100	Absent	Absent	irCR†
↓100	Stable	Any	irPR†
↓100	Unequivocal progression	Any	irPR†
↓≥50	Absent/Stable	Any	irPR†
↓≥50	Unequivocal progression	Any	irPR†
↓<50 to <25↑	Absent/Stable	Any	irSD
↓<50 to <25↑	Unequivocal progression	Any	irSD
≥25	Any	Any	irPD†

*Decreases assessed relative to baseline (scan prior to start of any protocol therapy), including measurable lesions only

†Assuming response (irCR) and progression (irPD) are confirmed by a second, consecutive assessment at least 4 wk apart.

9. BIOLOGICAL CORRELATIVES

9.1. Evaluate PD-L1 expression of archived tumor tissue and correlate to clinical response.

Expression of PD-L1 in archived diagnostic tumor tissue will be determined by IHC by referring laboratory used by Merck, and will be correlated with clinical response assessed by imaging. Unstained slides are to be submitted; a tumor block is not acceptable.

A fine needle aspirate, frozen sample, plastic embedded sample, cell block, clot, bone, bone marrow or cytologic specimen are not be acceptable for PD-L1 analysis.

Refer to the Study Procedures Manual (SPM) for collection, labeling and shipping instructions.

9.2. Assess tumor vascular density of archived tumor tissue and correlate to clinical response.

Tumor vascular density of archived diagnostic tumor tissue will be determined by IHC in the Department of Pathology at UI-Health and will be correlated with clinical response assessed by imaging. Unstained slides are to be submitted; a tumor block is not acceptable.

Refer to the Study Procedures Manual (SPM) for collection, labeling and shipping instructions.

9.3. Assess CD4(+) and CD8(+) T-cell infiltration of archived tumor tissue and correlate to clinical response.

Using archived diagnostic tumor tissue, CD4(+) and CD8(+) T-cell infiltration of the tissue will be determined by IHC in the Department of Pathology at UI-Health and will be correlated with clinical response assessed by imaging. Unstained slides are to be submitted; a tumor block is not acceptable.

Refer to the Study Procedures Manual (SPM) for collection, labeling and shipping instructions.

9.4. Assess number of circulating tumor cells at baseline and during treatment and correlate to clinical response.

Whole blood will be collected at pre-dose Cycle 1 Day 1 and every 6 or 9 weeks thereafter (i.e. pre-dose Cycle 3 Day 1, pre-dose Cycle 5 Day 1, etc.) for subsequent analysis of circulating tumor cells. Samples will be collected every 6 weeks through Cycle 9 (cycle 3, 5, 7, 9). Thereafter, samples will be collected every 9 weeks (cycle 12, 15, 18, etc.). Change in number as a result of treatment will be examined in relation to the best clinical response assessed by imaging. This analysis will be conducted at the University of Illinois Cancer Center.

Refer to the Study Procedures Manual (SPM) for collection, processing, labeling and shipping instructions.

9.5. Measure soluble PD-L1 level at baseline and during treatment and correlate to clinical response.

Whole blood for serum submission will be collected at pre-dose Cycle 1 Day 1 and every 6 or 9 weeks thereafter (i.e. pre-dose Cycle 3 Day 1, pre-dose Cycle 5 Day 1, etc.) for subsequent analysis of soluble PD-L1 levels. Samples will be collected every 6 weeks through Cycle 9 (cycle 3, 5, 7, 9). Thereafter, samples will be collected every 9 weeks (cycle 12, 15, 18, etc.). Change in soluble PD-L1 levels as a result of treatment will be examined in relation to the best clinical response assessed by imaging. This analysis determined by ELISA assay will be conducted at the University of Illinois Cancer Center.

Refer to the Study Procedures Manual (SPM) for collection, processing, labeling and shipping instructions.

9.6. Measure VEGFc at baseline and during treatment and correlate to clinical response.

Whole blood for plasma submission will be collected at pre-dose Cycle 1 Day 1 and every 6 or 9 weeks thereafter (i.e. pre-dose Cycle 3 Day 1, pre-dose Cycle 5 Day 1, etc.) for subsequent analysis of VEGFc levels. Samples will be collected every 6 weeks through Cycle 9 (cycle 3, 5, 7, 9). Thereafter, samples will be collected every 9 weeks (cycle 12, 15, 18, etc.). Change in VEGFc levels as a result of treatment will be examined in relation to the best clinical response assessed by imaging. This analysis will be conducted at the University of Illinois Cancer Center.

Refer to the Study Procedures Manual (SPM) for collection, processing, labeling and shipping instructions.

9.7. Correlate baseline proteomic and lipidomic immune classifiers to clinical response.

Subjects who consent to allow future analysis of left over correlative samples will have baseline serum analyzed for immune classifiers. Predictive tests to aid in therapeutic decision making are critical for optimizing patient outcomes while minimizing toxicity and associated treatment costs. These samples will provide data for proteomics and biomarker development via mass spectroscopy. This can be accomplished with a process of proteomic profiling, followed by targeted assay development, and then measuring the identified target proteins. These samples may also provide data for metabolomics guided by functional groups. This approach, known as multiple reaction monitoring (MRM)-profiling, uses specific metabolite fragmentations related to functional groups and classes to interrogate the metabolome. Immunotherapy mechanisms are dependent upon the interactions between the tumor, tumor microenvironment, and the host immune system. As such, a successful predictive test will reflect the complex interplay between tumor and host. Pre-treatment serum and/or plasma samples will be used to explore the association of proteomic and lipidomic tests at baseline with measures of response.

9.8. Samples for future studies

Subject consent will be obtained for additional samples collected for future Big Ten Cancer Research Consortium studies. Hoosier Cancer Research Network, as Administrative Headquarters for the BTCRC, will manage the banked samples. Samples will be banked indefinitely in the Hoosier Cancer Research Network Biorepository.

This includes:

- Whole blood:
  - Whole blood will be collected prior to treatment on Cycle 1 Day 1.
- Pre- and Post-treatment plasma:
  - Whole blood for plasma will be collected prior to treatment on Cycle 1 Day 1 and at End of Treatment.
- Pre- and Post-treatment serum:
  - Whole blood for serum will be collected prior to treatment on Cycle 1 Day 1 and at End of Treatment.
- Unstained slides:
  - Unstained slides will be obtained from the subject's archived formalin fixed paraffin embedded tumor sample.

Please refer to the Study Procedures Manual for all sample collection, processing, labeling, and shipping instructions.

10. DRUG INFORMATION

10.1. Drug Name

Bevacizumab (Avastin®)

Classification

Recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor.

Mechanism of Action

Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in in vitro models of angiogenesis. Administration of bevacizumab to xenotransplant models of colon cancer in nude (athymic) mice caused reduction of microvascular growth and inhibition of metastatic disease progression.

How Supplied

Bevacizumab is supplied in sterile single-use vials individually packaged in a carton (one vial to a carton) containing either 100 mg per 4 mL vial (NDC: 50242-060) or 400 mg per 16 mL vial (NDC: 50242-061)

Availability

Commercial supplies of bevacizumab will be used in this study and billed to third party payers or the subject.

Storage, Handling, and Accountability
Unopened vials of bevacizumab are stable until the expiration date indicated on the package when stored at 2° to 8ºC (36° to 46ºF). Bevacizumab vials should be protected from light. **Do not freeze or shake.** Diluted bevacizumab solutions may be stored at 2° to 8ºC (36° to 46ºF) for up to 8 hours. Store in the original carton until time of use. No incompatibilities between bevacizumab and polyvinylchloride or polyolefin bags have been observed.

Description
Bevacizumab is supplied in a sterile form for intravenous use only. Bevacizumab is a clear to slightly opalescent, colorless to pale brown, sterile, pH 6.2 solution for intravenous infusion. Bevacizumab is supplied in 100 mg and 400 mg preservative-free, single-use vials to deliver 4 mL or 16 mL of bevacizumab (25 mg/mL). The 100 mg product is formulated in 240 mg α,α-trehalose dihydrate, 23.2 mg sodium phosphate (monobasic, monohydrate), 4.8 mg sodium phosphate (dibasic, anhydrous), 1.6 mg polysorbate 20, and Water for Injection, USP. The 400 mg product is formulated in 960 mg α,α-trehalose dihydrate, 92.8 mg sodium phosphate (monobasic, monohydrate), 19.2 mg sodium phosphate (dibasic, anhydrous), 6.4 mg polysorbate 20, and Water for Injection, USP.

Administration
Use appropriate aseptic technique. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Withdraw necessary amount of bevacizumab and dilute in a total volume of 100 mL of 0.9% Sodium Chloride Injection, USP. Discard any unused portion left in a vial, as the product contains no preservatives.

- Do not administer as an intravenous push or bolus. Administer only as an intravenous (IV) infusion.
- Do not initiate bevacizumab until at least 28 days following major surgery.
- Administer bevacizumab after the surgical incision has fully healed.
- First infusion and subsequent infusions duration as per institutional standards.

Risks

Please refer to the package insert for a complete list of adverse events.

Delayed toxicities which occur within hours to days include bleeding gums, blood in urine or stools, burning, crawling, itching, numbness, prickling, "pins and needles", or tingling feelings, chest pain, cloudy urine, coughing up blood, cough or hoarseness, diarrhea, difficult or labored breathing, difficulty in moving, difficulty in swallowing, dizziness, fever or chills, general feeling of discomfort or illness, headache, increased menstrual flow or vaginal bleeding, joint pain, lack or loss of strength, loss of appetite, lower back or side pain, muscle aching or cramping, muscle pains or stiffness, nausea, nosebleeds, painful or difficult urination, pale skin, paralysis, pinpoint red spots on skin, prolonged bleeding from cuts, red or black, tarry stools, red or dark brown urine, runny nose, shivering, shortness of breath, sores, ulcers, or white spots on lips or in mouth, sore throat, sweating, swelling of hands, ankles, feet, or lower legs, swollen glands, swollen joints, tightness in chest, troubled breathing with exertion, trouble sleeping, unusual bleeding or bruising, unusual tiredness or weakness, vomiting, weight loss, and wheezing.

Less common toxicities include blurred vision, chest discomfort, fainting, fast, slow, or irregular heartbeat, headache (sudden and severe), inability to speak, nervousness, noisy breathing, pain or discomfort in arms, jaw, back or neck, pounding in the ears, seizures, slurred speech, temporary blindness, weakness in arm and/or leg on one side of the body (sudden and severe), and wheezing.

Rare toxicities include allergic reactions, confusion, lightheadedness, and rapid, shallow breathing.

Warnings and Precautions

Please refer to the package insert for a complete list of adverse events.

Gastrointestinal Perforations
Serious and sometimes fatal gastrointestinal perforation occurs at a higher incidence in bevacizumab treated patients compared to controls. The incidence of gastrointestinal perforation ranged from 0.3 to 2.4% across clinical studies.

The typical presentation may include abdominal pain, nausea, emesis, constipation, and fever. Perforation can be complicated by intra-abdominal abscess and fistula formation. The majority of cases occurred within the first 50 days of initiation of bevacizumab.

Discontinue bevacizumab in subjects with gastrointestinal perforation.

Surgery and Wound Healing Complications
Bevacizumab impairs wound healing in animal models. In clinical trials, administration of bevacizumab was not allowed until at least 28 days after surgery. In a controlled clinical trial, the incidence of wound healing complications, including serious and fatal complications, in patients with mCRC who underwent surgery during the course of bevacizumab treatment was 15% and in patients who did not receive bevacizumab, was 4%.

Bevacizumab should not be initiated for at least 28 days following surgery and until the surgical wound is fully healed. Discontinue bevacizumab in subjects with wound healing complications requiring medical intervention.

The appropriate interval between the last dose of bevacizumab and elective surgery is unknown; however, the half-life of bevacizumab is estimated to be 20 days. Suspend bevacizumab for at least 28 days prior to elective surgery. Do not administer bevacizumab until the wound is fully healed.

Necrotizing fasciitis, including fatal cases, has been reported in patients treated with bevacizumab, usually secondary to wound healing complications, gastrointestinal perforation, or fistula formation. Discontinue bevacizumab therapy in subjects who develop necrotizing fasciitis.

Hemorrhage
Bevacizumab can result in two distinct patterns of bleeding: minor hemorrhage, most commonly Grade 1 epistaxis; and serious, and in some cases fatal, hemorrhagic events. Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleeding occurred up to five-fold more frequently in patients receiving bevacizumab compared to patients receiving only chemotherapy. Across indications, the incidence of Grade ≥ 3 hemorrhagic events among patients receiving bevacizumab ranged from 1.2 to 4.6%.

Serious or fatal pulmonary hemorrhage occurred in four of 13 (31%) patients with squamous cell histology and two of 53 (4%) patients with non-squamous non-small cell lung cancer receiving bevacizumab and chemotherapy compared to none of the 32 (0%) patients receiving chemotherapy alone.

In clinical studies in non–small cell lung cancer where patients with CNS metastases who completed radiation and surgery more than 4 weeks prior to the start of bevacizumab were evaluated with serial CNS imaging, symptomatic Grade 2 CNS hemorrhage was documented in one of 83 bevacizumab -treated patients (rate 1.2%, 95% CI 0.06%–5.93%).

Intracranial hemorrhage occurred in 8 of 163 patients with previously treated glioblastoma; two patients had Grade 3–4 hemorrhage.

Do not administer bevacizumab to subjects with recent history of hemoptysis of ≥ 1/2 teaspoon of red blood. Discontinue bevacizumab in subjects with hemorrhage.

Non-Gastrointestinal Fistula Formation
Serious and sometimes fatal non-gastrointestinal fistula formation involving tracheoesophageal, bronchopleural, biliary, vaginal, renal, and bladder sites occurs at a higher incidence in bevacizumab -treated patients compared to controls. The incidence of non-gastrointestinal perforation was ≤ 0.3% in clinical studies. Most events occurred within the first 6 months of bevacizumab therapy.

Discontinue bevacizumab in subjects with fistula formation involving an internal organ.

Arterial Thromboembolic Events
Serious, sometimes fatal, arterial thromboembolic events (ATE) including cerebral infarction, transient ischemic attacks, myocardial infarction, angina, and a variety of other ATE occurred at a higher incidence in patients receiving bevacizumab compared to those in the control arm. Across indications, the incidence of Grade ≥ 3 ATE in the bevacizumab containing arms was 2.6% compared to 0.8% in the control arms. Among patients receiving bevacizumab in combination with chemotherapy, the risk of developing ATE during therapy was increased in patients with a history of arterial thromboembolism, diabetes, or age greater than 65 years.

The safety of resumption of bevacizumab therapy after resolution of an ATE has not been studied. Discontinue bevacizumab in subjects who experience a severe ATE.

Hypertension
The incidence of severe hypertension is increased in patients receiving bevacizumab as compared to controls. Across clinical studies, the incidence of Grade 3 or 4 hypertension ranged from 5-18%.

Monitor blood pressure every two to three weeks during treatment with bevacizumab. Treat with appropriate anti-hypertensive therapy and monitor blood pressure regularly. Continue to monitor blood pressure at regular intervals in subjects with bevacizumab -induced or -exacerbated hypertension after discontinuation of bevacizumab.

Temporarily suspend bevacizumab in subjects with severe hypertension that is not controlled with medical management. Discontinue bevacizumab in subjects with hypertensive crisis or hypertensive encephalopathy.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
RPLS has been reported with an incidence of < 0.1% in clinical studies. The onset of symptoms occurred from 16 hours to 1 year after initiation of bevacizumab. RPLS is a neurological disorder, which can present with headache, seizure, lethargy, confusion, blindness, and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging (MRI) is necessary to confirm the diagnosis of RPLS.

Discontinue bevacizumab in subjects developing RPLS. Symptoms usually resolve or improve within days, although some patients have experienced ongoing neurologic sequelae. The safety of reinitiating bevacizumab therapy in patients previously experiencing RPLS is not known.

Proteinuria
The incidence and severity of proteinuria is increased in patients receiving bevacizumab as compared to controls. Nephrotic syndrome occurred in < 1% of patients receiving bevacizumab in clinical trials, in some instances with fatal outcome. In a published case series, kidney biopsy of six patients with proteinuria showed findings consistent with thrombotic microangiopathy.

Monitor proteinuria by dipstick urine analysis for the development or worsening of proteinuria with serial urinalyses during bevacizumab therapy. Subjects with a 2 + or greater urine dipstick reading should undergo further assessment with a 24-hour urine collection.

Suspend bevacizumab administration for ≥ 2 grams of proteinuria/24 hours and resume when proteinuria is < 2 gm/24 hours. Continue to monitor until 24-hr protein demonstrates < 1 g of protein. Discontinue bevacizumab in subjects with nephrotic syndrome. Data from a post-marketing safety study showed poor correlation between UPCR (Urine Protein/Creatinine Ratio) and 24 hour urine protein (Pearson Correlation 0.39 (95% CI 0.17, 0.57).

Infusion Reactions
Infusion reactions reported in the clinical trials and post-marketing experience include hypertension, hypertensive crises associated with neurologic signs and symptoms, wheezing,

oxygen desaturation, Grade 3 hypersensitivity, chest pain, headaches, rigors, and diaphoresis. In clinical studies, infusion reactions with the first dose of bevacizumab were uncommon (< 3%) and severe reactions occurred in 0.2% of subjects.

Stop infusion if a severe infusion reaction occurs and administer appropriate medical therapy.

Ovarian Failure
The incidence of ovarian failure was higher (34% vs. 2%) in premenopausal women receiving bevacizumab in combination with mFOLFOX chemotherapy as compared to those receiving mFOLFOX chemotherapy alone for adjuvant treatment for colorectal cancer, a use for which bevacizumab is not approved. Inform females of reproductive potential of the risk of ovarian failure prior to starting treatment with bevacizumab.

Nursing Considerations
Advise subjects:

- To undergo routine blood pressure monitoring and to contact their health care provider if blood pressure is elevated.
- To immediately contact their health care provider for unusual bleeding, high fever, rigors, sudden onset of worsening neurological function, or persistent or severe abdominal pain, severe constipation, or vomiting.
- Of increased risk of wound healing complications during and following bevacizumab.
- Of increased risk of an arterial thromboembolic event.
- Of the potential risk to the fetus during and following bevacizumab and the need to continue adequate contraception for at least 6 months following last dose of bevacizumab.
- Of the increased risk for ovarian failure following bevacizumab treatment.

10.2. Drug Name

Keytruda® (Pembrolizumab; MK-3475 [Anti-PD-1 Antibody MK-3475])

Chemical name and properties
Humanized X PD-1_mAb (H409A11) IgG4

Availability
Merck will supply pembrolizumab at no charge to subjects participating in this clinical trial. 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.

Storage
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.

Dosage and Administration

Please refer to the Pharmacy Manual for a comprehensive description of pembrolizumab preparation.

Merck & Co. Inc. will supply pembrolizumab directly to sites at no cost to patients in this clinical trial. Pembrolizumab is provided as a white to off-white lyophilized powder (50 mg/vial) or as a liquid solution (100 mg/vial) in Type I glass vials intended for single use only. Pembrolizumab Powder for Solution for Infusion, 50 mg/vial, is reconstituted with sterile water for injection prior to use. Pembrolizumab is formulated with L-histidine as buffering agent, polysorbate 80 as surfactant, sucrose as stabilizer/tonicity modifier, and hydrochloric acid (HCl) and/or sodium hydroxide (NaOH) for pH adjustment (if necessary). The drug product is stored as a stable lyophilized powder or liquid solution under refrigerated conditions (2°C - 8°C).

The product after reconstitution with sterile water for injection and the liquid drug product is a clear to opalescent solution, which may contain extraneous and proteinaceous particulates. The reconstituted product and liquid product is intended for IV administration. The reconstituted drug product solution and liquid drug product can be further diluted with normal saline in IV containers made of polyvinyl chloride (PVC) or non-PVC material. Reconstituted vials should be immediately used to prepare the infusion solution in the IV bag and the infusion solution should be immediately administered. If not used immediately, vials and/or IV bags may be stored at 2-8 °C for up to a cumulative time of 20 hours. If refrigerated, the vials and/or IV bags should be allowed to equilibrate to room temperature prior to subsequent use. Pembrolizumab solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes room temperature storage of reconstituted drug product solution and liquid drug product in vials, room temperature storage of infusion solution in the IV bag and the duration of infusion.

Side Effects

Please refer to the current version of the Investigator's Brochure for a complete list of adverse events.

Pembrolizumab is generally well tolerated and demonstrates a favorable safety profile in comparison to chemotherapy. Pembrolizumab is an immunomodulatory agent, and based on this mechanism of action, immune mediated adverse events are of primary concern. Important identified risks for pembrolizumab are of an immune mediate nature, including: pneumonitis, colitis, hepatitis, nephritis, endocrinopathies that include hypophysitis (including hypopituitarism and secondary adrenal insufficiency), thyroid disorder (hypothyroidism, hyperthyroidism and thyroiditis), Type I diabetes mellitis, uveitis, myositis, Guillain-Barré syndrome, pancreatitis, myocarditis, myasthenic syndrome, encephalitis, sarcoidosis, severe skin reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome; and "solid organ transplant rejection following pembrolizumab treatment in donor organ recipients" (risk applicable to post-marketing setting only, as such patients are currently excluded from Merck clinical trials with pembrolizumab).

The majority of immune-mediated adverse events were mild to moderate in severity, were manageable with appropriate care, and rarely required discontinuation of therapy.

Since the last IB (v15) update, the safety profile for pembrolizumab also includes 2 important potential risks – i.e. increased risk of severe complications (such as early severe graft versus host disease and veno-occlusive disease) of allogeneic transplant in patients with hematologic malignancies who have previously been treated with PD-1 inhibitors; and GVHD after pembrolizumab administration in patients with a history of allogeneic HSCT.

No new identified or potential risks have been added to the safety profile for pembrolizumab since IBv15.

However, based upon additional information received from the clinical study and post-marketing environments after release of IBv15, the following changes have been made to the safety information for pembrolizumab:

1. further information was added to product labeling to note that immune-mediated adverse drug reactions may be fatal and may occur after discontinuation of pembrolizumab therapy; and
2. a new ADR of "arthritis" was identified based primarily on post-marketing experience.

Further details around frequency, reporting, and management of immune-related adverse events (irAEs) can be found in the current version of the Investigator's Brochure.

In addition to the previously noted identified risks, infusion-related reactions are a risk but are not considered immune mediated; these are also further described in the current IB.

11. ADVERSE EVENTS

11.1. Definitions of Adverse Events

11.1.1. Adverse Event (AE):

Any untoward medical occurrence in a patient or clinical trial subject administered an investigational product and which does not necessarily have a causal relationship with the treatment. An adverse event (AE) can, therefore, be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

11.1.2. Serious Adverse Event (SAE):

A serious adverse event is any untoward medical occurrence resulting in one or more of the following:

- Results in death
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.
- Pembrolizumab overdose. For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for pembrolizumab by 20% over the prescribed dose.

11.1.3. Unexpected Adverse Event:

An adverse event not mentioned in the Investigator's Brochure or package insert or the specificity or severity of which is not consistent with the Investigator's Brochure or package insert.

11.2. Adverse Event (AE) Reporting

Adverse events (AEs) will be recorded from the time of consent and for at least 30 days after treatment discontinuation, regardless of whether or not the event(s) are considered related to trial medications. All AEs considered related to trial medication will be followed until resolution, return to baseline, or deemed clinically insignificant, even if this occurs post-trial. All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

11.3. Definition and Reporting of an Overdose

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for pembrolizumab by 20% over the prescribed dose. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, 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."

All reports of overdose with and without an adverse event must be reported within 1 working day to BTCRC Administrative Headquarters (AHQ). BTCRC AHQ will report

the event within 1 working day to Merck Global Safety (Attn: Worldwide Product Safety; FAX 215-993-1220).

11.4. Reporting of Pregnancy and Lactation

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), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and female partners of male subjects who become pregnant 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.

Such events must be reported within 1 working day to BTCRC AHQ. BTCRC AHQ will report the event within 1 working day to Merck Global Safety (Attn: Worldwide Product Safety; FAX 215-993-1220).

11.5. Definition and Reporting of Events of Clinical Interest (ECI)

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported to BTCRC AHQ within 1 working day of the event.

Events of clinical interest for this trial include:

1. An overdose of Merck product, as defined above, 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.

Subjects should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

ECIs that occur in any subject from the date of first dose through 90 days following cessation of treatment, or the initiation of a new anticancer therapy, whichever is earlier, whether or not related to the Merck's product, must be reported within 1 working day to

BTCRC AHQ. BTCRC AHQ will report the event within 1 working day to Merck Global Safety (Attn: Worldwide Product Safety; FAX 215-993-1220).

11.6. Serious Adverse Event (SAE) Reporting

11.6.1. Study Center (Site) Requirements for Reporting SAEs:

Progression of the cancer under study is not considered an adverse event unless it results in hospitalization or death.

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, must be reported within 1 working day to BTCRC AHQ.

Non-serious Events of Clinical Interest will be reported to BTCRC AHQ and will be handled in the same manner as SAEs.

Additionally, any serious adverse event, considered by an investigator to be related to the Merck product, which is brought to the attention of the investigator at any time outside of the 90-day time period specified in the previous paragraph, also must be reported immediately to BTCRC AHQ.

The completed SAE Report Form (see SPM) must be sent to Big Ten Cancer Research Consortium (BTCRC) Administrative Headquarters (AHQ) within 1 working day of discovery of the event. The form will be sent electronically to Big Ten CRC AHQ at safety@hoosiercancer.org.The investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

The original copy of the SAE Report and the email correspondence must be kept within the Trial Master File at the study site.

Follow-up information will be sent electronically to BTCRC AHQ, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable), and whether the subject continued or withdrew from study participation. All subjects with serious adverse events must be followed up for outcome. Sites will electronically submit follow up SAE Submission Forms within a reasonable timeframe to Big Ten CRC AHQ at safety@hoosiercancer.org.

11.6.2. Death and Immediately Life-Threatening Events:

Any death and immediately life-threatening event from any cause while a subject is receiving trial treatment on this protocol or up to 30 days after the last dose of trial treatment, or any death and immediately life-threatening event occurring more than 30

days after trial treatment has ended but which is felt to be treatment related must be reported **within one business day of discovery of the event**. All deaths must be reported primarily for the purposes of SAE reporting; however, deaths due unequivocally to progression are not SAEs.

Participating sites are responsible for informing their IRB and/or the Regulatory Authority of the SAE as per local requirements. The completed SAE Reporting Form should be emailed to BTCRC AHQ (safety@hoosiercancer.org) **within one working day of discovery of the event**.

11.6.3. BTCRC AHQ Requirements for Reporting SAEs:

BTCRC AHQ will submit all immediately reportable events (e.g. SAEs, ECIs, overdose, pregnancy, etc.) received from sites to Merck **within one working day** of receipt of the SAE Reporting Form and to regulatory authorities (FDA) per federal guidelines.

BTCRC AHQ will fax a MedWatch for all SAE reports and any other relevant safety information to Merck Global Safety (Attn: Worldwide Product Safety) at:
Facsimile number: +1-215-993-1220

BTCRC AHQ will provide follow-up information to Merck as reasonably requested.

BTCRC AHQ will submit a copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices Agency (PMDA) or other local regulators to Merck. The sponsor-investigator will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally, BTCRC AHQ will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215-993-1220) at the time of submission to FDA.

11.7. IND Safety Reports Unrelated to This Trial

IND safety reports not occurring on this trial but involving the study intervention (outside SAEs) received from outside sources will be forwarded to participating sites for submission to their Institutional Review Boards per their guidelines.

12. STATISTICAL CONSIDERATIONS

12.1. Study Design

Phase Ib:
The primary objective of the Phase Ib dose escalation cohort study is to establish the safe dose of study drug pembrolizumab when used in combination with bevacizumab for subjects with metastatic clear cell renal cell carcinoma (RCC) after failure of at least one systemic therapy for metastatic disease. A standard “3+3” design will be used to establish the safe dose. An expansion cohort of 6 patients will be carried out during the Phase Ib study at the maximum safe dose, prior to opening the Phase II portion. This will ensure

ample safety data of the combination and provide pilot activity data from 12 patients in the second-line RCC setting.

Phase II:
The primary objective of the Phase II trial is to determine the activity of the combination of pembrolizumab and bevacizumab in first line therapy for subjects with metastatic clear cell RCC as assessed by response rate (RR) (complete or partial response) based on RECIST 1.1. The maximum safe dose of pembrolizumab in combination bevacizumab will be given on day 1 of each 21 day cycle. Treatment continues until disease progression, unacceptable toxicity, subject refusal, or subject death either from progression of disease, the therapy itself, or from other causes. Subjects who voluntarily stop the study, have progressive disease, or unacceptable toxicities will be followed for a total of 24 months. An optimal two-stage design is used to determine whether the new treatment has sufficient biological activity against the disease under study to warrant future development.

Correlative research analyses includes examining the relationship between clinical response at the end of Cycle 2 (Week 6) of the treatment period with PD-L1 expression, tumor vascular density, and CD4(+) and CD8(+) T-cell tumor infiltration of the archived diagnostic tumor tissue. Research analyses also include examining the relationship between changes in number of circulating tumor cells, soluble PD-L1 levels, and VEGFc levels from baseline to the end of Cycle 2 (Week 6) of the treatment period and clinical response at that time.

12.2. Criteria for Stopping Study

The Phase Ib portion of the study will be stopped if 2 or more DLTs occur at dose level 1.

The Phase II portion of the study will be stopped if ≥ 2 subjects in first 20, or ≥ 3 in first 30 subjects, or ≥ 4 in first 40 subjects develop grade 5 toxicity during first 4 cycles of therapy.

12.3. Analysis Datasets

Methods of Statistical Analysis
The definitions of the study populations are listed below. The appropriate study population for each analysis should be chosen and defined in the protocol.

Population	Definition
Enrolled	This will comprise all subjects who meet the eligibility criteria and are registered onto the study.
Evaluable	This will comprise all subjects who receive at least one dose of trial drug and either undergo at least one post-baseline assessment or die before any evaluation.
Safety	This will comprise all subjects who received at least one dose of study drug.

Intention-To-Treat Principle - The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a subject (i.e. the planned treatment regimen) rather than the actual treatment given. It has the consequence that subjects allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.

12.4. Sample Size

Phase Ib:
A standard "3+3" design will be used with maximum number of subjects accrued to be 12. An expansion cohort of 6 patients will be carried out during the Phase Ib study at the maximum safe dose, prior to opening the Phase II portion.

Phase II:
Study endpoint will be response (PR or CR) as assessed by the RECIST v1.1 criteria. Clinical studies identified a response rate with pembrolizumab of 27% in kidney cancer. With assumptions of 80% power to detect a 55% improvement to a response rate of 42% in response by RECIST v1.1 in the combination arm over historic data on single agent pembrolizumab activity in RCC, and an alpha error is 0.107, the optimal Simon's two stage design proceeds as follows. After testing the drug on 22 patients in the first stage, the trial will be terminated if 6 or fewer respond. If at least 7 respond, the trial goes on to the second stage. A total of 49 patients will be studied. If the total number responding is less than or equal to 16, the drug is rejected. Otherwise the drug will be accepted for further studies. The sample size analyses are conducted using the software PASS 13 (NCSS, Kaysville, Utah, USA.)

12.5. Analysis of Primary Objectives/Aims

Phase Ib Analysis of Primary Endpoint
The primary endpoint is determination of the maximum safe dose. The maximum safe dose will be defined as that dose of pembrolizumab combined with bevacizumab with the highest clinical benefit rate, i.e., complete response + partial response + stable disease (CR+PR+SD) (RECIST v1.1, Section 8) after 2 cycles of therapy, and best safety profile in the first 6-week treatment period.

Phase II Analysis of Primary Endpoint
The primary endpoint is determination of the activity of the combination of pembrolizumab and bevacizumab in first line therapy for metastatic disease as assessed by response rate (RR) (complete or partial response) based on RECIST 1.1. The response rate and 95% confidence interval for the response rate will be computed using PROC FREQ in SAS (Cary, NC).

12.6. Analysis of Secondary Endpoints

Phase Ib Analysis of Secondary Endpoints

Characterize adverse effects (AE) of pembrolizumab in combination with bevacizumab in subjects with metastatic RCC after failure of at least one systemic therapy.

- Proportion of subjects with each grade of adverse events as defined by CTCAE v4 will be computed along with 95% confidence intervals, and reported in a tabular and descriptive manner.

Evaluate clinical benefit rate (complete, partial response, or stable disease) of pembrolizumab in combination with bevacizumab in subjects with metastatic RCC after failure of at least one systemic therapy.

- Clinical benefit rate (complete, partial response, or stable disease) will be assessed every 6 or 9 weeks +/- 1 week while on study treatment using the Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1- Section 8). Response will be recorded as clinical benefit rate, or stable disease plus partial response plus complete response, and reported via waterfall plot. The response rate and 95% confidence interval for the response rate will be computed using PROC FREQ in SAS (Cary, NC).

Measure Progression-Free Survival (PFS) at 6 months in subjects with metastatic RCC after failure of at least one systemic therapy treated with pembrolizumab in combination with bevacizumab.

- Median PFS times will be computed, and PFS rate at 6 months +/- 1 month will be calculated with associated 95% confidence intervals. Kaplan-Meier curves will be plotted. Data will be analyzed using the PROC FREQ and PROC LIFETEST in SAS.

Measure overall survival (OS) at 2 years from registration in subjects with metastatic RCC after failure of at least one systemic therapy treated with pembrolizumab in combination with bevacizumab.

- Median OS times will be computed, and OS rate at 2 years +/- 3 months will be calculated with associated 95% confidence intervals. Kaplan-Meier curves will be plotted. Data will be analyzed using the PROC FREQ and PROC LIFETEST in SAS.

Phase II Analysis of Secondary Endpoints

Characterize adverse effects (AE) of pembrolizumab in combination with bevacizumab in subjects with treatment-naïve metastatic RCC.

- Proportion of subjects with each grade of adverse events as defined by CTCAE v4 will be computed along with 95% confidence intervals and reported in a tabular and descriptive manner.

Evaluate clinical benefit rate (complete, partial response, or stable disease) of pembrolizumab in combination with bevacizumab in subjects with treatment-naïve metastatic RCC.

- Clinical benefit rate (complete, partial response, or stable disease) will be assessed every 6 or 9 weeks +/- 1 week while on study treatment using the Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1- Section 8). Response will be recorded as clinical benefit rate, or stable disease plus partial response plus complete response, and reported via waterfall plot.

Measure Progression-Free Survival (PFS) at 6 months in subjects with treatment-naïve metastatic RCC treated with pembrolizumab in combination with bevacizumab.

- Median PFS times will be computed, and PFS rate at 6 months +/- 1 month will be calculated with associated 95% confidence intervals. Kaplan-Meier curves will be plotted. Data will be analyzed using the PROC FREQ and PROC LIFETEST in SAS.

Measure overall survival (OS) at 2 years after registration in subjects with treatment-naïve metastatic RCC treated with pembrolizumab in combination with bevacizumab.

- Median OS times will be computed, and OS rate at 2 years +/- 2 months will be calculated with associated 95% confidence intervals. Kaplan-Meier curves will be plotted. Data will be analyzed using the PROC FREQ and PROC LIFETEST in SAS.

12.7. Analysis of Phase II Correlative Endpoints

- PD-L1 expression by IHC of archived diagnostic tumor tissue will be correlated with the best clinical response (RECIST v1.1). Spearman correlation will be computed using PROC CORR in SAS (Cary, NC).
- Tumor vascular density of archived diagnostic tumor tissue will be correlated with the best clinical response (RECIST v1.1). Spearman correlation will be computed using PROC CORR in SAS (Cary, NC).
- CD4(+) and CD8(+) T-cell tumor infiltration of archived diagnostic tumor tissue will be correlated with the best clinical response (RECIST v1.1). Spearman correlation will be computed using PROC CORR in SAS (Cary, NC).
- Change in PD-L1 expression on circulating tumor cells during therapy relative to baseline will be examined in relation to the best clinical response (RECIST v1.1). Spearman correlation will be computed using PROC CORR in SAS (Cary, NC).
- Change in soluble PD-L1 level during therapy relative to baseline will be examined in relation to the best clinical response (RECIST v1.1). Spearman correlation will be computed using PROC CORR in SAS (Cary, NC).
- Change in VEGFc level during therapy relative to baseline will be examined in relation to the best clinical response (RECIST v1.1). Spearman correlation will be computed using PROC CORR in SAS (Cary, NC).
- Proteomic and lipidomic test results from pre-treatment blood samples will be correlated with measures of response (RECIST v1.1). Spearman correlation will be computed using PROC CORR in SAS (Cary, NC).

13. TRIAL MANAGEMENT

13.1. Quality Controls and Quality Assurance

13.1.1. Study Monitoring:

Study monitoring will include a risk-based monitoring strategy as defined in the Data Management Plan associated with this protocol. Monitoring visits to the trial sites will be made periodically during the trial, to ensure all aspects of the protocol are followed. Source documents will be reviewed for verification of agreement with data as submitted

via the data collection system. The investigator/institution guarantee access to source documents by BTCRC AHQ or its designee and appropriate regulatory agencies.

The trial site may also be subject to quality assurance audit by Merck or its designee as well as inspection by appropriate regulatory agencies.

It is important for the investigator and their relevant personnel to be available during the monitoring visits and possible audits and for sufficient time to be devoted to the process.

13.1.2. Data and Safety Monitoring Plan:

The study will be conducted in accordance with the University of Illinois Cancer Center's Data and Safety Monitoring Plan. The University of Illinois Cancer Center Data Safety and Monitoring Committee will review and make recommendations on this trial. BTCRC AHQ will provide the University of Illinois Cancer Center DSMC with periodic data reports to comply with the UICC DSMC review requirements.

In addition, BTCRC AHQ data and safety monitoring activities include:

- Conduct review of clinical trial for progress and safety
- Review of all adverse events requiring expedited reporting as defined in the protocol
- Provide the Sponsor Investigator with trial progress and safety data as required
- Notification of participating sites of adverse events requiring expedited reporting and subsequent committee recommendations for study modifications

Data and Safety Monitoring and Reporting Guidelines:

BTCRC AHQ will compile data summary reports for this trial and submit these reports monthly to the Sponsor Investigator. BTCRC AHQ will submit data summary reports at minimum twice per year for review by the University of Illinois Cancer Center Data Safety Monitoring Committee (DSMC).

13.2. Data Handling and Record Keeping

13.2.1. Case Report Forms:

An electronic case report form (eCRF) is required and must be completed for each included subject. The completed dataset is housed at BTCRC AHQ and is the sole property of the sponsor-investigator's institution. It should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from the sponsor-investigator and BTCRC AHQ. After the initial publication, the complete data set will be available to all BTCRC institutions.

13.2.2. Record Retention:

To enable evaluations and/or audits from Health Authorities/BTCRC AHQ, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records; e.g., hospital records), all original signed

informed consent forms, copies of all source documents, and detailed records of drug disposition. To comply with international regulations, the records should be retained by the investigator in compliance with regulations.

During data entry, range and missing data checks will be performed on-line. The checks to be performed will be documented in the Data Monitoring Plan for the study. A summary report (QC Report) of these checks together with any queries resulting from manual review of the eCRFs will be generated for each site and transmitted to the site and the site monitor. Corrections will be made by the study site personnel. This will be done on an ongoing basis.

13.3. Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Information collected will be maintained on secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study team. Samples that are collected will be identified by a subject study number assigned at the time of registration to the trial. Any material issued to collaborating researchers will be anonymized and only identified by the subject study number.

Subjects will be informed in writing that some organizations including the sponsor-investigator and his/her research associates, BTCRC AHQ, Merck, IRB, or government agencies, like the FDA, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

13.4. Changes to the Protocol

Study procedures will not be changed without the mutual agreement of the Sponsor Investigator, BTCRC AHQ, and Merck.

If it is necessary for the study protocol to be amended, the amendment or a new version of the study protocol (amended protocol) will be generated by BTCRC AHQ and must be approved by each IRB, Merck, and if applicable, also the local regulatory authority. Local requirements must be followed.

If a protocol amendment requires a change to the Written Informed Consent Form, then the IRB must be notified. Approval of the revised Written Informed Consent Form by the IRB is required before the revised form is used.

The principal investigator is responsible for the distribution of these documents to his or her IRB, and to the staff at his or her center. The distribution of these documents to the regulatory authority will be handled according to local practice.

Merck's willingness to supply study drug is predicated upon the review of the protocol. BTCRC AHQ agrees to provide written notice to Merck of any modifications to the protocol or informed consent.

13.5. Ethics

13.5.1. Ethics Review

The final study protocol, including the final version of the Written Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB. The investigator must submit written approval to the BTCRC AHQ office before he or she can enroll any subject into the study.

The principal investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB annually, as local regulations require.

Progress reports and notifications of serious unexpected adverse drug reactions will be provided to the IRB according to local regulations and guidelines.

The investigator is also responsible for providing the IRB with reports of any serious adverse drug reactions from any other study conducted with the investigational product. Merck will provide this information to the Sponsor Investigator. These reports will be reviewed by the Sponsor-Investigator and will be forwarded to participating sites every 2 weeks for submission to their Institutional Review Boards per their guidelines.

13.5.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki, which are consistent with ICH Good Clinical Practice, and applicable regulatory requirements.

13.5.3. Written Informed Consent

The investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The investigator must store the original, signed Written Informed Consent Form. A copy of the signed Written Informed Consent Form must be given to the subject.

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