Phase I/II Study of Pembrolizumab and Cabozantinib in Patients with Metastatic Renal Cell Carcinoma

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PROTOCOL TITLE:	Phase I/II Study of Pembrolizumab and Cabozantinib in Patients with Metastatic Renal Cell Carcinoma
VERSION DATE:	Version 16, 6/17/2021
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IND NUMBER:	135065
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STATEMENT OF COMPLIANCE

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

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

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

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

Sponsor-Principal Investigator: **Elaine Lam, MD**
Print/Type Name

Date: _____ _____
Signature

Site Principal Investigator: **Steven R. Schuster, MD**
Print/Type Name

Date: _____ _____
Signature

Site Principal Investigator: **Geetika Srivastava, MD**
Print/Type Name

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Signature

1.0 PROTOCOL/TRIAL SUMMARY

Protocol Title	Phase I/II Study of Pembrolizumab and Cabozantinib for Metastatic Renal Cell Carcinoma
Protocol Number	16-2300
Trial Phase	I/II
Objectives	***Primary Objective:*** • To determine the efficacy based on objective response rate [ORR = complete response (CR) + partial response (PR)] of pembrolizumab and cabozantinib when administered in combination in subjects with locally advanced or metastatic renal cell carcinoma. ***Secondary Objectives:*** • To characterize dose-limiting toxicities (DLTs), maximum tolerated dose (MTD), and recommended phase 2 dose (RP2D) for the combination. • To assess other measures of anti-tumor activity of the combination of pembrolizumab and cabozantinib in subjects with locally advanced or metastatic renal cell carcinoma. o irRECIST (Immune-related response criteria) response o Progression-free survival o Overall survival o Time to progression of overall disease o Time to progression of bone metastasis or skeletal-related event o Clinical benefit rate [complete response (CR) + partial response (PR) + stable disease (SD)] o Duration of response or disease stability o Duration on treatment in subjects treated beyond progression ***Exploratory Objectives, may include:*** • Bone turnover markers, such as β C-terminal telopeptide (β-CTX), bone specific alkaline

	phosphatase, and procollagen type 1 amino-terminal propeptide (P1NP). • Bone scan responses • PD-L1 IHC testing on archival samples. • PD-L1 IHC testing on fresh tumor baseline and/or post-treatment samples. • Evaluation of immuno-oncology markers
Endpoints	***Primary Endpoint:*** To determine the efficacy (defined as objective response rate, ORR) of the combination of pembrolizumab and cabozantinib. ***Secondary Endpoints:*** To characterize dose limiting toxicities (DLTs), maximum tolerated dose (MTD), and recommended phase 2 dose (RP2D) for the combination of pembrolizumab and cabozantinib, as well as, other measures of efficacy including response by immune-mediated response criteria (irRECIST), progression-free survival, overall survival, time to progression of overall disease, time to progression of bone metastasis or skeletal-related events, clinical benefit rate [complete response (CR) + partial response (PR) + stable disease (SD)], duration of response or disease stability, and duration on treatment in subjects treated beyond progression. ***Exploratory Endpoint:*** We will include mandatory archival tumor collection and optional pre- and post-treatment tumor biopsies for PD-L1 (QualTek Molecular Laboratories) and other immune-oncology testing which may include evaluation of other immune checkpoint markers, immune cell markers, and
Subject Population	Clinical Indication: Renal Cell Carcinoma (RCC) Gender: Male and Female Age Range: 18-100 years
Trial Type	Interventional

Type of control	Non-randomized
Description of Study Agents	1. Pembrolizumab (Keytruda®) will be administered intravenously (IV). The manufacturer (Merck) is providing this product. 2. Cabozantinib (CABOMETYX™) will be administered orally. This is standard therapy for RCC.
Trial Blinding	Open-label
Treatment Groups	Single arm combination study
Number of trial subjects	25-55
Estimated enrollment period	3 years
Estimated duration of trial	5 years
Duration of Participation	5 years
Estimated average length of treatment per subject	8 months

2.0 TRIAL DESIGN

2.1 Description of Study

This is a Phase I/II open-label study designed to evaluate the combination of pembrolizumab and cabozantinib in subjects with locally advanced, recurrent, or metastatic renal cell carcinoma.

Sequential dose escalation of cabozantinib with standard dose pembrolizumab will occur in the phase I dose escalation part of the study to determine the recommended phase 2 dose (RP2D). Subsequently, subjects will receive cabozantinib at the RP2D in combination with pembrolizumab in the phase II dose expansion part of the study. A standard 3+3 design will be used in Phase I to determine RP2D and a Simon two-stage design will be used in Phase II to determine efficacy of the combination. The planned enrollment for this study is approximately 25-55 total subjects, to account for screen failures, in order to achieve 6-9 evaluable subjects in Phase I dose escalation and 20-38 evaluable subjects in Phase II dose expansion.

Pembrolizumab will be administered by IV infusion on Day 1 of 21-day cycles. Cabozantinib will be taken orally once daily on a continuous basis. Subjects may continue treatment in the absence of unacceptable toxicity or clinically compelling disease progression. Treatment beyond progression per standard RECIST v1.1 criteria may be allowed if certain criteria are met and with the approval of the Principal Investigator.

2.1.1 Phase I Dose Escalation

Approximately 6-9 subjects will be enrolled using a standard 3+3 design. Three to six subjects will be enrolled in each dose cohort and receive cabozantinib and pembrolizumab in accordance with the dose escalation rules described below to determine the maximum tolerated dose (MTD) and RP2D (Section 2.1.3). The dose limiting toxicity (DLT) assessment window will be 21 days (Days 1−21 of Cycle 1). If a delayed DLT is observed, the DLT assessment window may be extended after the first administration of pembrolizumab and cabozantinib for all subjects in that cohort and any subsequent dose-escalation cohorts.

Any dose-escalation stage subject who does not complete the DLT assessment window for a reason other than a DLT will be considered non-evaluable for dose escalation decisions, as well as, the MTD assessment and may be replaced by an additional subject at that same dose level.

A subject who has any component of study treatment held during the DLT assessment window for a reason other than a DLT such that administration of the next planned pembrolizumab dose is delayed by more than 7 days and/or ≥25% of the planned cabozantinib doses are missed, will be considered non-evaluable for dose-escalation decisions and the MTD assessment and may be replaced by an additional subject at that same dose level.

Cohort	Pembrolizumab Dose	Cabozantinib Dose
-1	200 mg IV every 3 weeks	20 mg PO daily
1*	200 mg IV every 3 weeks	40 mg PO daily
2	200 mg IV every 3 weeks	60 mg PO daily

* Starting dose level.

2.1.2 Definition of Dose Limiting Toxicity

Any one of the following events will be considered a DLT if it occurs during the DLT assessment window **and** is assessed by the investigator to be **likely related** to study treatment (pembrolizumab and/or cabozantinib).

- Grade ≥ 3 non-hematologic, non-hepatic adverse event, with the following **exceptions:**
  - Grade 3 hypertension that resolves to Grade ≤ 2 with addition or adjustment of anti-hypertensive therapy in ≤ 7 days
  - Grade 3 fatigue that resolves to Grade ≤ 2 in ≤ 5 days
  - Grade 3 laboratory abnormalities that are asymptomatic, considered by the investigator not to be clinically significant, and that resolve to Grade ≤ 2 in ≤ 48 hours
  - Grade 3 rash that resolves to Grade ≤ 2 in ≤ 5 days with or without therapy equivalent to prednisone 10 mg/day or less
  - Grade 3 hand-foot syndrome that resolves to baseline within 3 weeks
  - Grade 3 arthralgia and/or myalgia that resolves to baseline within 3 weeks
  - Grade 3 autoimmune thyroiditis or other endocrine abnormality that resolves to Grade ≤ 2 within 3 weeks

- Grade 3 nausea, vomiting, or diarrhea lasting >72 hours despite maximal medical therapy.
- Grade ≥ 4 neutropenia (ANC < 500 cells/ μ L) lasting > 7 days
- Grade ≥ 3 febrile neutropenia
- Grade ≥ 4 anemia
- Grade ≥ 4 thrombocytopenia, or Grade 3 thrombocytopenia associated with clinically significant bleeding
- Grade ≥ 3 elevation of serum hepatic transaminase (ALT or AST).
- Grade ≥ 3 elevation of serum total bilirubin.
- ALT or AST > 3 × upper limit of normal (ULN) **AND** total bilirubin >2 × ULN will require permanent treatment discontinuation.

2.1.3 Dose Escalation Rules

Pembrolizumab will be administered at a fixed dose of 200 mg IV every 21 days on Day 1 of each cycle.

The starting dose of cabozantinib for subjects in the first cohort will be 40 mg PO once daily for 21 consecutive days of each cycle (Days 1−21). For the second cohort, the dose of cabozantinib will be 60 mg PO once daily. If the starting dose of 40mg is not tolerated (2 or more out of 6 subjects experiencing DLT), then a lower dose of 20 mg will be evaluated.

Once the DLT assessment period has passed, pembrolizumab and/or cabozantinib may be held or dose modified independent of the other agent for adverse events attributed to one but not both drugs. The Principal Investigator should be notified when this occurs.

In addition to any DLTs, other available relevant demographic, adverse event, laboratory, and dose administration data will be reviewed prior to all dose-escalation decisions.

Dose escalation will occur in accordance with the rules:

- A minimum of 3 subjects will be enrolled in each cohort.
- If none of the first 3 DLT-evaluable subjects experiences a DLT, enrollment of the next cohort may proceed.
- If 1 of the first 3 DLT-evaluable subjects experiences a DLT, the cohort will be expanded to a minimum of 6 subjects. If there are no further DLTs in the first 6 DLT-evaluable subjects, enrollment of the next cohort may proceed.
- If 2 or more of the first 6 DLT-evaluable subjects in a cohort experience a DLT, the MTD will have been exceeded and dose escalation will stop. The preceding cohort will also be expanded to a minimum of 6 subjects, unless 6 subjects have already been evaluated at that dose level.
- If the MTD is exceeded at any dose level, the highest dose at which fewer than 2 of 6 DLT-evaluable subjects experience a DLT will be declared the MTD.
- If the MTD is not exceeded at any dose level, the highest dose administered in this study will be declared the maximum administered dose.
- Any dose level may be expanded in the absence of a DLT if warranted based on investigator evaluation of non-DLT adverse events, including events occurring after Cycle 1 and events observed in the expansion cohorts.
- To be considered evaluable for dose escalation, subjects must have received at least 1 dose of pembrolizumab and ≥75% of planned dosing of cabozantinib prior to completing the DLT assessment window of 21 days.

2.1.4 Definition of Maximum Tolerated Dose (MTD)

The Maximum Tolerated Dose (MTD) is defined as the highest dose level with no more than 1 DLT reported in 6 DLT-evaluable subjects.

2.1.5 Definition of Recommended Phase 2 Dose (RP2D)

The Recommended Phase 2 Dose (RP2D) of cabozantinib will be selected based on the clinical data and will not exceed the MTD. If < 2/6 subjects experience a DLT at 60 mg daily during dose escalation, then 60 mg daily will be considered the RP2D. If ≥ 2/6 subjects experience DLTs at 60 mg daily, and ≤ 1/6 subjects experience a DLT at 40 mg daily, then 40 mg daily will be considered the RP2D. The Principal Investigator, in consultation with other investigators, will continue to evaluate the safety data accumulated during the phase II dose expansion part of the study and may amend the RP2D with further experience.

2.1.6 Intra-Subject Dose Escalation

There will be no dose reduction or escalation of pembrolizumab, which is to be administered at a fixed dose of 200 mg IV every 21 days.

Intra-subject dose escalation of cabozantinib to a higher dose level will be allowed if all of the following conditions are met:

- One or fewer of the first 3 DLT-evaluable subjects, or fewer than 2 of the first 6 DLT-evaluable subjects experience a DLT at the higher dose level cohort.
- The subject has completed at least 3 cycles at their originally assigned dose level.
- The subject has not experienced a DLT or an adverse event occurring outside the DLT window that would otherwise meet the definition of a DLT.
- The subject is clinically stable with no decrement in performance status.
- The Principal Investigator has approved the dose escalation.
- The overall benefit/risk balance favors continued treatment, in the opinion of the investigator.

2.1.7 Phase II Dose Expansion

A Simon two-stage design will be used. Based on the primary endpoint of objective response rate, twenty evaluable subjects will be enrolled in Stage I portion of Phase II. If there are at least 2 responses among the 20 evaluable subjects, an additional 18 evaluable subjects will be entered. If there are fewer than 2 responses among the first twenty evaluable subjects, then this trial will be stopped early for futility. If at least 12 are observed among the 38 evaluable subjects, then the treatment will be considered effective.

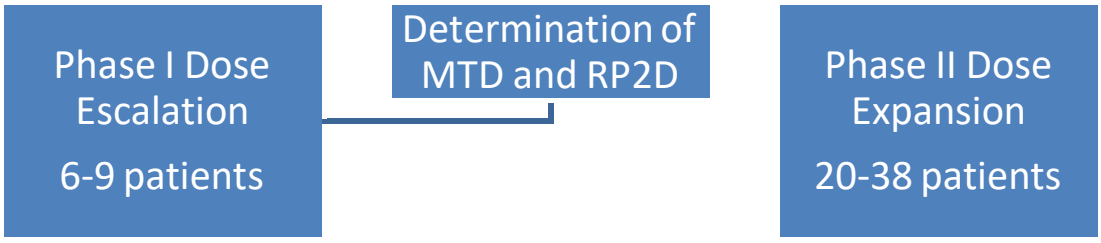
Subjects from the Phase I part of the study who are treated at the RP2D may be included in the efficacy assessments in Stage I of the Phase II part of the study.

2.1.8 Archival Tumor and Optional Fresh Tissue Biopsies

Archival tumor tissue is mandatory for enrollment in both the Phase I dose escalation and Phase II dose expansion parts of the study.

In addition, subjects may consent for optional fresh tissue biopsies at baseline (during screening period) and/or post-treatment at approximately 3-6 weeks (during cycle 2) after initiation of study treatment.

2.2 Trial Diagram



3.0 OBJECTIVES

3.1 Primary Objectives

The primary objective for this study is to determine the efficacy based on objective response rate [ORR = complete response (CR) + partial response (PR)] of pembrolizumab and cabozantinib when administered in combination in subjects with locally advanced or metastatic renal cell carcinoma.

3.2 Secondary Objectives

The secondary objectives for this study are:

- To characterize dose-limiting toxicities (DLTs), maximum tolerated dose (MTD), and recommended phase 2 dose (RP2D) for the combination.
- To assess other measures of anti-tumor activity of the combination of pembrolizumab and cabozantinib in subjects with locally advanced or metastatic renal cell carcinoma.
    - irRECIST (Immune-related response criteria) response
    - Progression-free survival
    - Overall survival
    - Time to progression of overall disease
    - Time to progression of bone metastasis or skeletal-related event
    - Clinical benefit rate [complete response (CR) + partial response (PR) + stable disease (SD)]
    - Duration of response or disease stability
    - Duration on treatment in subjects treated beyond progression

3.3 Exploratory Objectives

The exploratory objectives for this study may include:

- Bone turnover markers, such as β C-terminal telopeptide (β-CTX), bone specific alkaline phosphatase, and procollagen type 1 amino-terminal propeptide (P1NP).

- Bone scan responses
- PD-L1 IHC testing on archival samples.
- PD-L1 IHC testing on fresh tumor baseline and/or post-treatment samples.
- Evaluation of immuno-oncology markers

4.0 BACKGROUND & RATIONALE

4.1 Background

Over the past decade, multiple vascular endothelial growth factor (VEGF) and molecular target of rapamycin (mTOR) pathway targeted therapies have been approved and have significantly improved the morbidity and mortality among subjects with advanced or metastatic renal cell carcinoma (mRCC). Nevertheless, mRCC remains a largely incurable disease. Tyrosine kinase inhibitors (TKI) and VEGF-directed antibodies are widely used as standard first- and second-line treatments for metastatic RCC. Despite the improvements seen with the currently available VEGF-directed therapies, treatment resistance and disease progression occur in the majority of subjects with continued treatment and these agents do not produce durable responses.[1] Acquired resistance to vascular endothelial growth factor (VEGF) pathway inhibitors is frequently mediated through the activation of alternative signaling pathways that restore tumor perfusion, including upregulation of the expression of angiopoietins, c-MET, activin receptor-like kinase-1 (ALK-1) receptor and interleukin 8 (IL-8), and loss of p53 function.[2] In addition, VEGF also acts as an immunosuppressive molecule and can inhibit maturation of dendritic cells, promote immune suppressive cell infiltration and enhance immune checkpoint molecules expression.[3]

Renal cell carcinoma is an immunogenic tumor with a dysfunction immune cell infiltrate that allows malignant progression through evasion of immune surveillance. Novel immune-modulating agents that target cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed death receptor-1 (PD-1) significantly enhances antitumor immunity.[4] The benefit of anti-PD-1 antibodies in the treatment of mRCC was confirmed in the CheckMate 025 study, which was a phase III study of nivolumab (an anti-PD-1 antibody) vs. everolimus in the second-line treatment of mRCC. Compared to everolimus, nivolumab showed significant improvements in overall survival (25.0 vs. 19.6 months; HR 0.73; P=0.002) and objective response rate (25% vs. 5%).[5]

Recent major discoveries in tumor immunology and agents that can trigger immune responses, along with better understanding of the mechanisms of VEGF inhibitor therapy provide rationale for combination therapies in the treatment of mRCC. There are multiple proposed mechanisms of synergy between inhibiting both VEGF- and PD-1. In addition to angiogenic

activity, VEGF may promote immunosuppression by inhibiting dendritic cell maturation and VEGF inhibitors reverse this immunosuppression by reducing numbers of circulating regulatory T cells and myeloid-derived suppressor cells and allowing for better maturation of dendritic cells.[1, 6, 7] VEGF inhibitors such as sunitinib may also enhance CD4+ T and CD8+ T cell intratumoral infiltration.[8] In mouse models, VEGF-A has been shown to modulate the expression of inhibitory checkpoints such as PD-1 on CD8+ T cell in tumors.[9] These data provide rationale for clinical investigations of combined angiogenesis inhibition and immunotherapy/immune checkpoint inhibition.

4.1.1 Pharmaceutical and Therapeutic Background

4.1.1.1 PD-1/PD-L1 Blockade

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

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

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

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) is currently approved in the United States for the treatment of melanoma, non-small cell lung cancer, small cell lung cancer, , head and neck squamous cell carcinoma, classical Hodgkin Lymphoma, primary mediastinal large B-cell lymphoma, ulcerative colitis, microsatellite instability-high tumors, gastric or gastroesophageal junction adenocarcinoma, esophageal cancer, cervical cancer, hepatocellular carcinoma, Merkel cell carcinoma, RCC, endometrial carcinoma, tumor mutational burden – high cancer, cutaneous Squamous Cell Carcinoma, Microsatellite instability-high cancer or mismatch repair deficient Colorectal Cancer.

4.1.1.2 MET and VEGFR2 in Renal Cell Carcinoma

Hepatocyte growth factor receptor protein (MET) and the VEGF receptor 2 (VEGFR2) are receptor tyrosine kinases that play a role in the promotion of tumor cell growth, invasiveness, metastasis, and/or angiogenesis in multiple tumor types including RCC.[10] Clear cell renal carcinomas commonly arise due to mutations in the tumor suppressor von Hippel-Lindau (VHL) gene which trigger an accumulation of hypoxia inducing factor (HIF) protein, which leads to an increase in expression of VEGF and of the receptor tyrosine kinase MET, resulting in angiogenesis, tumor cell proliferation, and invasive growth.[11] High MET expression has been observed in bone and brain metastases in subjects with mRCC and is associated with poor pathologic features and poor prognosis in RCC.[12-14]

Cabozantinib is an oral, small molecule tyrosine kinase inhibitor that targets MET, VEGFR2/KDR, RET, KIT, FLT3, and AXL. In a phase III clinical trial comparing cabozantinib vs. everolimus in subjects with mRCC who have progressed after a VEGFR-targeted therapy, cabozantinib demonstrated improved median progression-free survival (7.4 vs. 3.8 months), objective response rate (21% vs. 5%), and overall survival (HR 0.67, P<0.005).[15] In the phase II CABOSUN study comparing cabozantinib versus sunitinib in the

first-line setting for patients with intermediate- and poor-risk mRCC, cabozantinib was associated with statistically increased median progression-free survival (8.2 months vs 5.6 months), lower rate of progression or death (HR 0.66), and improved overall response rate (46% vs 18%) compared to sunitinib. [16] Based on these two studies, cabozantinib is currently approved for first-line, as well as, second-/subsequent-line treatment for metastatic renal cell carcinoma.

4.1.2 Preclinical and Clinical Trial Data

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

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

PD-1-targeted and VEGF-targeted therapies have separately shown survival benefit in subjects with advanced or metastatic renal cell carcinoma (mRCC). Mechanisms of synergy between VEGF and PD-1 inhibition have been proposed in the current literature. In this study, we will evaluate the efficacy of combining the PD-1 (pembrolizumab) and VEGF-targeted (cabozantinib) therapies in subjects with locally advanced, recurrent, or metastatic renal cell carcinoma.

The phase I dose escalation part will determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of the combination of pembrolizumab and cabozantinib.

The phase II dose expansion part will evaluate efficacy (as defined by objective response rate) of the combination given at the RP2D in mRCC subjects who are immunotherapy-naïve and also those who have previously received immunotherapy.

With the approval of nivolumab, we anticipate that many subjects will have received immunotherapy prior to study entry. Given the preclinical data for synergy with the combination of PD-1 and VEGF inhibition, we hypothesize that there will be subjects who did not previously respond to either PD-1 or VEGF-directed therapies alone, but who may respond to the combination.

The treatment of bone metastases and prevention of skeletal related events for mRCC is particularly challenging, and represents an unmet need for this cancer. There is preclinical evidence of a direct link between loss of von Hippel-Lindau and up-regulation of c-Met, as well as, evidence for high MET expression in bone metastases specimens.[17] High MET expression has been demonstrated both in RCC bone metastases and brain metastases.[13, 14] In addition to anti-angiogenic effects, cabozantinib has activity against MET. In this study, we will also explore the preliminary efficacy of targeting PD-1, VEGFR, and MET simultaneously with the combination of pembrolizumab and cabozantinib, in terms of time to

progression of bone metastasis or skeletal-related events.

4.2.2 Rationale for Dose Selection/Regimen/Modification

4.2.2.1 Rationale for Dose Selection of Pembrolizumab

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent MK-3475 (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 MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD was identified. 10.0 mg/kg Q2W, the highest dose tested in PN001, was the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

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

A population pharmacokinetic analysis has been performed using serum concentration time data from 2,993 subjects. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either

2 mg/kg or 10 mg/kg Q3W in melanoma subjects, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

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

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

The currently approved dose of pembrolizumab across multiple cancers is 200 mg IV every 3 weeks and this is the fixed dose used for this study.

4.2.2.2 Rationale for Dose Selection of Cabozantinib

Cabozantinib at a dose of 140 mg/day has been studied in 25 subjects with advanced RCC enrolled in a Phase 1 study (XL184-008).[18] Adverse events were the primary reason for treatment discontinuation in 24% of subjects and dose reduction was required in 80% (20/25) subjects. The median average daily dose was approximately 75.5 mg/day. Despite the dose reductions, 7 subjects (28%) had partial response and 13 subjects (52%) had stable disease, with a disease control rate of 80%. The median PFS was 12.9 months with a median follow-up of 14.7 months. In some subjects, there was evidence of clinical activity against bone metastatic lesions. Based on the long-term tolerability and clinical activity associated with doses of cabozantinib <140 mg in this and other trials, 60 mg daily was selected as the recommended starting dose in the phase III METEOR study of cabozantinib versus everolimus in advanced renal cell carcinoma.[15] This study showed a significant PFS benefit of cabozantinib over everolimus (median PFS 7.4 months vs. 3.8 months). Dose reductions occurred in 60% (197 of 331) subjects treated with cabozantinib and the median average daily dose was 44mg of cabozantinib. The rate of treatment discontinuation due to adverse events was 9%.

In addition, results from a National Cancer Institute phase 1 trial of cabozantinib in combination with nivolumab in subjects with previously treated genitourinary tumors were presented during a poster discussion session (Abstract #774PD) at the European Society for

Medical Oncology (ESMO) 2016 Congress. Between July 2015 and September 2016, 24 subjects were accrued with metastatic urothelial carcinoma (n=7), urachal adenocarcinoma (n=4), squamous cell carcinoma of the bladder or urethra (n=3), germ cell tumor (n=4), castration-resistant prostate cancer (n=4), renal cell carcinoma (n=1), or trophoblastic tumor (n=1) and were treated in Part I of the study, which evaluated the combination of cabozantinib and nivolumab at four dose levels. The median number of prior systemic therapies was 3, and 10 subjects had received 4 or more prior therapies. The objective response rate was 43 percent among the 23 subjects who were evaluable for response, with one complete response and nine partial responses. Four of six subjects (67 percent) with urothelial cancer achieved a response. **The recommended doses for the ongoing expansion cohorts were determined to be cabozantinib at 40 mg daily and nivolumab at 3 mg/kg once every 2 weeks.**

Given the phase I and phase III cabozantinib dosing and toxicity data, and the recent results of the phase I cabozantinib plus nivolumab study identifying a RP2D of 40 mg/day for cabozantinib, we have chosen a starting dose of cabozantinib 40mg/day for this combination study of cabozantinib and pembrolizumab with standard 3+3 design. If none of the first 3, or if 1 or fewer of the first 6, DLT-evaluable subjects experiences a DLT, subjects will enroll in the next cohort with cabozantinib 60 mg/day. If 2 or more of the first 6 DLT-evaluable subjects in the 40 mg/day cohort experience a DLT, then subjects will enroll at one dose reduction with cabozantinib 20 mg/day.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

The primary endpoint of this study is to determine the efficacy (defined as objective response rate, ORR) of the combination of pembrolizumab and cabozantinib.

The secondary endpoints of this study are to characterize dose limiting toxicities (DLTs), maximum tolerated dose (MTD), and recommended phase 2 dose (RP2D) for the combination of pembrolizumab and cabozantinib, as well as, other measures of efficacy including response by immune-mediated response criteria (irRECIST), progression-free survival, overall survival, time to progression of overall disease, time to progression of bone metastasis or skeletal-related events, clinical benefit rate [complete response (CR) + partial response (PR) + stable disease (SD), duration of response or disease stability, and duration on treatment in subjects treated beyond progression.

4.2.3.2 Biomarker Research

It is unclear whether PD-L1 expression is a predictive biomarker for response and survival with anti-PD-1 and PD-L1 agents in metastatic renal cell carcinoma. In the phase III nivolumab versus everolimus clinical trial in mRCC subjects (CheckMate 025) which

demonstrated overall survival advantage with nivolumab, PD-L1 expression did not correlate with probability of overall survival.[5] Therefore, evaluation of other potential immune biomarkers is necessary.

In this study, we will include mandatory archival tumor collection and optional pre- and post-treatment tumor biopsies for PD-L1 (QualTek Molecular Laboratories) and other immune-oncology testing which may include evaluation of other immune checkpoint markers, immune cell markers, and immune function markers. Biospecimens collected under this study will only be used for this research and will be destroyed upon completion of this study.

5.0 METHODOLOGY

5.1 Trial Participation Criteria

5.1.1 Subject Inclusion Criteria

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

1. Subjects must have histological or cytological documentation of renal cell carcinoma.

2. Subjects must have locally advanced, recurrent, or metastatic disease.

3. Be willing and able to provide written informed consent/assent for the trial.

4. Stated willingness to comply with all study procedures and be available for the duration of the trial.

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

6. Have measurable or evaluable disease based on RECIST 1.1.

7. Recovery to baseline or ≤ Grade 1 CTCAE v.4.0 from toxicities related to any prior treatments, unless AE(s) are clinically non-significant and/or stable on supportive therapy.

8. Confirmed availability of representative archival tumor specimens in paraffin blocks (preferred) or ≥ 10 unstained slides, with an associated pathology report.

   Acceptable samples include core needle biopsies for deep tumor tissue or excisional, incisional, or punch biopsies for cutaneous, subcutaneous, or mucosal lesions.

   Tumor tissue from bone metastases is not evaluable for PD-L1 expression and

is therefore not acceptable.

A subject with insufficient or unavailable archival tissue may be eligible, upon discussion with the Principal Investigator, if the subject is willing to consent to undergo a pretreatment core, punch, or excisional/incisional biopsy sample collection of the tumor.

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

10. Demonstrate adequate organ function as defined in Table 1.

Table 1: Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤ 1.5 X upper limit of normal (ULN) **OR** ≥ 60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Urine protein	≤ 1+ or ≤ 30 mg/dL **OR** urine protein/creatinine ratio ≤ 1
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN. For subjects with Gilbert's disease ≤ 3 mg/dL.
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	≥2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

11. Female participants of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication and should not be breastfeeding. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

12. Female subjects of childbearing potential must be willing to use an adequate method of contraception as outlined in Section 5.5.2 – Contraception, for the course of the study through 120 days after the last dose of study medication.

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

13. Male participants of childbearing potential must agree to use an adequate method of contraception as outlined in Section 5.5.2 – Contraception, starting with the first dose of study therapy through 120 days after the last dose of study therapy and refrain from donating sperm during this period.

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

5.1.2 Subject Exclusion Criteria

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

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.

2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy equivalent to ≥ 10 mg/day of prednisone, or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

3. Has a known history of active TB (Bacillus Tuberculosis).

4. Has had prior treatment with pembrolizumab.

5. Has had prior treatment with cabozantinib.

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

    - Note: Subjects with stable, treated hypothyroidism or adrenal insufficiency may qualify for the study.

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

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

- Note: Subjects with hypertension managed with medication are an exception to this criterion and may qualify for the study.

- Note: Subjects with ≤ Grade 2 endocrinopathy (e.g. hypothyroidism or adrenal insufficiency managed with medication) are an exception to this criterion and may qualify for the study.

8. Has had major surgery within 4 weeks or minor surgery within 2 weeks prior to study Day 1. Subjects must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

9. Prior treatment with immune checkpoint inhibitors is allowed, provided that no treatment-related Grade ≥ 3 adverse events (other than Grade 3 endocrinopathy managed with replacement therapy) were observed and at least a minimum of 28 days have elapsed between the last dose of prior treatment and the proposed Cycle 1 Day 1.

10. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer, carcinoma in situ or superficial bladder cancer, low-grade prostate cancer, intraductal papillary mucinous neoplasm (IPMN), and other low-grade cancers that is suitable for active surveillance in the opinion of the investigator.

11. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Active CNS metastases will be defined as brain lesions that 1) require intervention with surgery, stereotactic radiosurgery (SRS), or whole brain radiotherapy (WBRT) or 2) require anti-epileptic therapy, systemic steroid treatment, or intrathecal therapy. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks after completion of focal therapy for brain metastases 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 trial treatment. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability.

12. 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). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is allowed.

13. Has history of solid organ transplantation.

14. Has history of osteonecrosis of the jaw.

15. Has history of reversible posterior leukoencephalopathy syndrome.

16. Has history of wound dehiscence or complications requiring medical intervention within 6 months of study entry.

17. Has history of (non-infectious) pneumonitis that required steroids or active, non-infectious pneumonitis.

18. Has an active infection requiring systemic therapy with IV antibiotics.

19. Has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:

    a. Cardiovascular disorders:

        i. Symptomatic congestive heart failure, unstable angina pectoris, serious cardiac arrhythmias.

        ii. Uncontrolled hypertension defined as sustained BP > 150 mm Hg systolic or > 100 mm Hg diastolic despite optimal antihypertensive treatment.

        iii. Stroke (including TIA), myocardial infarction, or other ischemic event, or thromboembolic event (e.g., deep venous thrombosis, pulmonary embolism) within 3 months before randomization.

    b. Gastrointestinal (GI) disorders including those associated with a high risk of perforation or fistula formation:

        i. Tumors invading the GI-tract, active peptic ulcer disease, inflammatory bowel disease, diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic or biliary duct, or gastric outlet obstruction.

        ii. Abdominal fistula, gastrointestinal perforation, bowel obstruction, or intra-abdominal abscess within 6 months before randomization. Complete healing of an intra-abdominal abscess must be confirmed before study initiation.

    c. Has clinically significant hematuria, hematemesis, or hemoptysis of > 0.5 teaspoon within 3 months before randomization.

d. Known endobronchial disease manifestation. Patients with suspected endobronchial disease on imaging who have no evidence of endobronchial disease on bronchoscopy are allowed. Patients with treated endobronchial disease are also allowed provided they are stable.

e. Lesions invading major pulmonary blood vessels.

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

21. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

22. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.

23. Has an inability to swallow tablets or capsules.

24. Has a previously identified allergy or hypersensitivity to components of the study treatment formulations.

25. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

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

27. Has received a live vaccine or live-attenuated vaccine within 30 days of planned start of study therapy. Administration of killed vaccines is allowed.

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

5.2 Trial Treatments—Study Agents

The treatment to be used in this trial is outlined below in **Tables 2**a-c

Table 2a: Trial Treatment Overview

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3-week cycle	Experimental
Cabozantinib	20-60 mg	Daily	Oral	Continuous	Experimental

Table 2b: Phase I Dose Escalation

Cohort	Pembrolizumab Dose	Cabozantinib Dose
-1	200 mg IV every 3 weeks	20 mg PO daily
1*	200 mg IV every 3 weeks	40 mg PO daily
2	200 mg IV every 3 weeks	60 mg PO daily

* Starting dose level.

Table 2c: Phase II Dose Expansion

Cohort	Pembrolizumab Dose	Cabozantinib Dose
Expansion	200 mg IV every 3 weeks	RP2D PO daily

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 4.2.2 –Rationale for Dose Selection/Regimen/Modification.

Details on preparation and administration of pembrolizumab (MK-3475) are provided in the Pharmacy Manual.

Cabozantinib (Cabometyx®) will be obtained commercially. CABOMETYX (cabozantinib) tablets are supplied as film-coated tablets containing 20 mg, 40 mg, or 60 mg of cabozantinib, which is equivalent to 25 mg, 51 mg, or 76 mg of cabozantinib (S)-malate, respectively. CABOMETYX also contains the following inactive ingredients: microcrystalline cellulose, lactose anhydrous, hydroxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate. The film coating contains hypromellose, titanium dioxide, triacetin, and iron oxide yellow.

5.2.1.2 Dose Modification (Escalation/Titration/Other)

Subjects will be monitored for AEs from the time of signing informed consent through 30 days after the date of the decision to permanently discontinue pembrolizumab and/or cabozantinib treatment.

Once the DLT assessment period has passed, pembrolizumab and/or cabozantinib may be held or dose modified independent of the other agent for adverse events attributed to one but not both drugs. The Principal Investigator should be notified when this occurs.

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, subject vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Principal Investigator. The reason for interruption should be documented in the subject's study record.

Interruption of pembrolizumab and/or cabozantinib treatment for AEs may occur at any time per investigator discretion, if the investigator feels it is in the interest of the subject's safety and/or will optimize drug tolerability. If treatment is interrupted due to AEs for more than 6 weeks, discussion and approval from the Principal Investigator is required prior to resuming therapy.

5.2.1.3 Pembrolizumab

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment.

There will be no dose modification of pembrolizumab, which is to be administered at a fixed dose of 200 mg IV every 21 days. A window of +/- 3 days is allowed for administrative/ scheduling reasons.

Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below. See Section 5.4 for supportive care guidelines, including use of corticosteroids.

Table 3: Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Study intervention must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last study intervention treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If study intervention has been withheld, study intervention may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

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 • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	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
	Grade 4 or recurrent Grade 3	Permanently discontinue		

				clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
AST / ALT elevation or Increased bilirubin	Grade 2[a]	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 until liver enzyme value returned to baseline or is stable)
	Grade 3[b] or 4[c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold[d]	• Initiate insulin 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 to treat adrenal insufficiency and other 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[d]		
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[d]		
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: grading according to increased creatinine or acute kidney injury	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		
Neurological Toxicities	Grade 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		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2-4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), or Drug Rash with Eosinophilia and Systemic Symptom (DRESS)	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		

All other immune-related AEs	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[e]		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include, but are not limited to: Guillain-Barre Syndrome, pancreatitis, encephalitis, sarcoidosis,myasthenic syndrome-myasthenia gravis (including exacerbation), myelitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

5.2.1.3.2 Pembrolizumab Second Course

The participant's initial course of treatment with pembrolizumab will be the First Course, and in the absence of disease progression may be administered for up to 35 cycles. After the First Course, all participants who stop pembrolizumab after 35 cycles with SD or better may be eligible for up to an additional 17 cycles (approximately 1 year) of pembrolizumab treatment if they progress after stopping pembrolizumab from the initial treatment phase.

This retreatment is termed the Second Course phase and is only available if the participant continues on cabozantinib monotherapy and remains on study after completing the First Course of pembrolizumab and meets the following conditions:

Either

- Stopped initial study intervention after attaining an investigator-determined confirmed CR based on RECIST 1.1, and
  - Was treated with at least 8 cycles of pembrolizumab before discontinuing treatment, and
  - Received at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared

OR

- Had SD, PR, or CR and stopped pembrolizumab after completion of 35 administrations (approximately 2 years) of study intervention for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined radiographic disease progression by RECIST 1.1 after stopping initial treatment, and
  - The participant meets all of the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria, and
  - The patient remained on study while still continuing to dose with cabozantinib monotherapy after stopping initial pembrolizumab treatment (First Course).

Additionally, the treating physician must determine at the time of progression after stopping initial treatment that continuing cabozantinib and resuming pembrolizumab is the best treatment course for the patient.

An objective response or disease progression that occurs during the Second Course Phase for a participant will not be counted as an event for the primary analysis of either endpoint in this study.

Participants who have experienced an initial disease progression by RECIST 1.1 and have an iSD, iPR,or iCR per iRECIST after completion of 35 administrations of study intervention for reasons other than disease progression or intolerability may be considered for the Second Course Phase after consultation with the Sponsor-Investigator.

For patients who have already treated beyond 35 cycles of pembrolizumab at the time of the protocol version 20-OCT-2020, and have SD or better, the patient should discontinue pembrolizumab after their next scheduled cycle. If the patient progresses after discontinuing pembrolizumab, they may be eligible for up to 17 additional cycles of pembrolizumab.

For patients who have already signed consent to treat beyond progression at the time of the protocol version 20-OCT-2020, the patients should discontinue pembrolizumab at cycle 35 or after the next scheduled treatment cycle (if they have already completed 35 cycles or more). If the patient subsequently progresses, they may be eligible for up to 17 additional cycles of pembrolizumab.

5.2.1.4 Cabozantinib

See Sections 2.1.1 to 2.1.6 for dosing of cabozantinib during the DLT assessment window in Phase I dose escalation.

Dose modification criteria for cabozantinib outside the DLT assessment window and in the dose expansion stage are shown in Table 4. Dose reductions and/or interruptions should be implemented for unacceptable toxicity. Dose modifications or interruptions may also occur in the setting of lower grade toxicity than defined in Table 4, if the investigator feels it is in the interest of the subject's safety and will optimize drug tolerability.

Table 4: Dose Modification Guidelines for Cabozantinib Drug-Related Adverse Events

CTCAE v4.0 Grade	**Recommended Guidelines for Management**
Grade 1 AEs	Add supportive care as indicated. Continue cabozantinib treatment at current dose level if AE is manageable and tolerable.
Grade 2 AEs which are tolerable and are easily managed	Continue cabozantinib treatment at current dose level with supportive care.
Grade 2 AEs which are intolerable and cannot be adequately managed	At the discretion of the investigator, cabozantinib should be dose reduced or interrupted until symptoms become more tolerable or are better managed.
Grade 3 AEs (except clinically non-relevant laboratory abnormalities)	Hold cabozantinib treatment and optimize supportive care. Once AE improves to ≤ Grade 2 and is tolerable and manageable, resume cabozantinib: • At same dose if first occurrence of Grade 3 AE despite optimal supportive care. • At one dose reduction (decrease by 20mg/day) if second occurrence of Grade 3 AE despite optimal supportive care. Permanently discontinue cabozantinib if third occurrence of Grade 3 AE despite optimal supportive care.
Grade 4 AEs (except clinically non-relevant laboratory abnormalities)	Hold cabozantinib treatment immediately. Discontinue cabozantinib permanently UNLESS the following criteria are met: • Subject is deriving clear clinical benefit as determined by the investigator and agreed by the Principal Investigator. • Toxicity can be managed with a dose reduction following recovery to Grade 1 (or baseline) and optimal medical care.

Cabozantinib should be permanently discontinued for any of the following:

- Development of visceral perforation or fistula formation
- Severe hemorrhage
- Serious arterial thromboembolic event (e.g., myocardial infarction, cerebral infarction)
- Nephrotic syndrome (e.g. proteinuria > 2 grams/day on 24 hour urine or urine protein creatinine ratio >3.5 AND serum albumin < 2 mg/dL AND edema)
- Malignant hypertension, hypertensive crisis, persistent uncontrolled hypertension despite optimal medical management.
- Osteonecrosis of the jaw
- Reversible posterior leukoencephalopathy syndrome

5.2.1.4.2 Pembrolizumab AND Cabozantinib

In situations where the attribution of toxicities in unclear, of if the toxicity is deemed to be related to both pembrolizumab and cabozantinib, follow dose modification guidelines presented in Table 5.

Table 5: Dose Modification Guidelines for Toxicities of Unclear Attribution or Deemed to be Related to Both Pembrolizumab and Cabozantinib

Toxicity	Grade	Modification
Diarrhea/Colitis	2-3	Hold both pembrolizumab and cabozantinib. Institute maximal anti-diarrheal therapy. Consider corticosteroids if no improvement on anti-diarrheal therapy within 24-48 hours.

		Consider colonoscopy.
	4	Permanently discontinue
Hypothyroidism	2-3	Therapy with pembrolizumab and cabozantinib can be continued while thyroid replacement therapy is instituted.
	4	Hold pembrolizumab and cabozantinib until Grade ≤ 2.
AST, ALT or Increased Bilirubin	2	Hold pembrolizumab and cabozantinib until Grade ≤ 1. Dose reduce cabozantinib by 1 dose level for Grade ≤ 2 ALT, AST, or bilirubin lasting longer than 1 week.
	3-4	Permanently discontinue
AST, ALT **AND** Increased Bilirubin	2-4	ALT/AST elevations > 3 × ULN in combination with a bilirubin elevation > 2 × ULN require permanent treatment discontinuation.
All Other Drug-Related Toxicity	3 or Severe	Hold pembrolizumab and cabozantinib until Grade ≤ 1. Permanently discontinue if G3 or severe toxicity recurs.
	4	Permanently discontinue

These treatment guidelines are intended to be applied when the investigator determines the events to be related to both pembrolizumab and cabozantinib, or if the attribution is unclear. If the investigator determines the events to be related to both study drugs, these dose modifications are required. Any questions about interpretation of the dose modifications or special circumstances should be discussed with the PI.

Note: if after instituting these guidelines and after further evaluation, the event is determined to be more likely related to pembrolizumab or cabozantinib, and not both, then dose modification guidelines for either pembrolizumab (Table 3) or cabozantinib (Table 4) should be followed.

5.2.2 *Timing of Dose Administration*

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

All trial treatments will be administered on an outpatient basis.

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

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

Cabozantinib will be obtained commercially. Subjects will be given oral and/or written instructions on dose to be taken by the investigator or by properly trained staff designee. Subjects will receive a medication diary with written dosing instructions and be asked to record the time and date they take each dose. Subjects will be instructed to bring their medication diary to each study visit for assessment of compliance.

5.2.3 Trial Blinding/Masking and Treatment Allocation

This is an open-label trial; therefore, the investigator and subject will know the treatment administered. This is a single arm, open-label study. All subjects will receive the combination of pembrolizumab and cabozantinib.

5.3 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. One exception is the use of corticosteroids during the study to treat an immune-mediated adverse event, as noted in Section 5.2.1.3, Table 3, and Section 5.4.1. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

5.3.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication should be recorded in the subject research chart including all prescription, over-the-counter (OTC), herbal supplements, and IV medications.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and Events of Clinical Interest (ECIs) as defined in Section 7.4.

5.3.2 Prohibited Concomitant Medications and Therapies

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab and cabozantinib
- Radiation therapy to a target lesion
    - Note: Palliative radiation therapy to a symptomatic non-target lesion, including the brain, may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology should be first discussed with and approved by the Principal Investigator.
    - Additionally, the use of physiologic doses of corticosteroids may be approved after consultation with the Principal Investigator.

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

5.4 Rescue Medications & Supportive Care

5.4.1 Supportive Care Guidelines for Pembrolizumab-Related Toxicities

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 to pembrolizumab, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 5.2.1 for dose modification.

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

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

- **Diarrhea/Colitis:**

  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

  - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
  - For **Grade 2 diarrhea/colitis,** administer oral corticosteroids.
  - For **Grade 3 or 4 diarrhea/colitis,** treat with intravenous steroids followed by high dose oral steroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or**

≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)

- For **T1DM** or **Grade 3-4** Hyperglycemia
  - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
  - Evaluate subjects with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

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

- **Hyperthyroidism or Hypothyroidism:**

  Thyroid disorders can occur at any time during treatment. Monitor subjects for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism
    - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

      Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hepatic:**
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.
- **Renal Failure or Nephritis:**
  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3-4** events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

  Table 6 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 6: 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 (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

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

5.4.2 Supportive Care Guidelines for Cabozantinib-Related Toxicities

The side effect profile of cabozantinib includes GI symptoms (such as nausea, vomiting, and diarrhea, mucositis/stomatitis), fatigue/asthenia, anorexia, weight loss, skin disorders including PPE syndrome, elevated liver function tests (including ALT and AST), increased pancreatic enzymes with rare cases of overt pancreatitis, thyroid function disorders, as well as side effects associated with inhibition of VEGF signaling. The latter of these include arterial and venous thrombotic events such as deep vein thrombosis (DVT), pulmonary embolism (PE), transient ischemic attack, and myocardial infarction, hypertension, hemorrhagic events, proteinuria, wound complications, and rare cases of GI perforation, fistulae formation and rectal/perirectal abscess, osteonecrosis, and reversible posterior leukoencephalopathy (RPLS).

- **Gastrointestinal Disorders:**
    - Diarrhea
        - Subjects should be instructed to notify their physician immediately at the first signs of poorly formed or loose stool or an increased frequency of bowel movements.
        - Administration of anti-diarrheal/ anti-motility agents is recommended at the first sign of diarrhea as initial management. Some subjects may require more than one antidiarrheal agent.
        - When therapy with antidiarrheal agents does not control the diarrhea to tolerable levels, cabozantinib treatment should be temporarily interrupted or dose reduced. Treatment may resume when acceptable per investigator decision.

- In addition, general supportive measures should be implemented including continuous oral hydration, correction of fluid and electrolyte abnormalities, small frequent meals, and stopping lactose-containing products, high fat meals, and alcohol.
- If diarrhea is high grade or persistent, treat as per diarrhea/colitis related to pembrolizumab.

- Nausea and vomiting
  - Antiemetic agents are recommended as clinically appropriate at the first sign of nausea and vomiting or as prophylaxis to prevent emesis, along with supportive care according to clinical practice guidelines.
  - The 5-HT3 receptor antagonists are recommended over chronic use of NK-1 receptor antagonists and dexamethasone (NK-1 receptor antagonists can induce or inhibit CYP3A4, and glucocorticoids induce CYP3A4 and thus could lower cabozantinib exposure.
- Stomatitis and Mucositis
  - Removal of local factors should be instituted as indicated, such as modification of ill-fitting dentures and appropriate care of gingivitis.
  - During treatment with cabozantinib, good oral hygiene and standard local treatments such as non-traumatic cleansing and oral rinses (e.g. with a weak solution of salt and baking soda) should be maintained.
  - Local treatment should be instituted at the earliest onset of symptoms.
  - Obtain bacterial/viral culture if oral infection is suspected and treat infection as indicated by local guidelines. When stomatitis interferes with adequate nutrition and local therapy is not adequately effective, dose reduction or temporary withholding of cabozantinib should be considered.

- **Hepatobiliary Disorders:**
  - Elevations of ALT, AST, and bilirubin have been observed during treatment with cabozantinib.
  - Subjects with elevation of ALT, AST, and/or bilirubin should have more frequent laboratory monitoring of these parameters.
  - Whenever possible, concomitant hepatotoxic medications should be avoided or discontinued in subjects who develop increased values of ALT, AST, or bilirubin.

- Dose reductions of study treatment should be considered in any subject who develops drug-related
  - Grade 2 elevated ALT, AST, or bilirubin lasting longer than 1 week.
  - Grade ≥ 3 elevated ALT, AST, or bilirubin.
  - ALT/AST elevations > 3 × ULN in combination with a bilirubin elevation > 2 × ULN require permanent treatment discontinuation.

- **Hematologic Disorders:**
  - Complete blood counts with differentials and platelets should be performed regularly.
  - Subjects with hematologic toxicities may require additional or more frequent laboratory monitoring of these parameters.
  - Febrile neutropenia or evidence of infection associated with neutropenia must be assessed immediately and treated appropriately and in a timely manner according to institutional guidelines.
  - Use of granulocyte colony-stimulating factor support for neutrophil recovery is allowed per investigator discretion and in accordance with accepted guidelines after the first incidence of clinically relevant cytopenia.
  - Dose reductions or dose interruptions for anemia are not mandated but can be applied as clinically indicated.
  - Supportive care such as red blood cell or platelet transfusions may be managed according to institutional guidelines.
- **Fatigue, Anorexia, and Weight Loss:**
  - Common causes of fatigue such as anemia, deconditioning, emotional distress (depression and/or anxiety), nutrition, sleep disturbance, and hypothyroidism should be ruled out and/or these causes treated according to standard of care.
  - Dose reduction of cabozantinib should be considered when general or pharmacological measures have not been successful in reducing symptoms. Dose interruption may be considered for Grade ≥ 3 fatigue despite optimal management, at the investigator's discretion.
  - Anorexia and weight loss should be managed according to local standard of care including nutritional support.

- **Skin Disorders:**
  - Palmar-plantar erythrodysesthesia syndrome (also known as hand-foot syndrome), skin rash (including blisters, erythematous rash, macular rash, skin exfoliation, dermatitis acneiform, and papular rash), pruritus, dry skin, and erythema have been reported in cabozantinib-treated subjects.
  - All subjects on study should be advised on prophylactic skin care.
  - Subjects with skin disorders should be carefully monitored for signs of infection.
  - Early signs of hand-foot syndrome could be tingling, numbness, and slight redness or mild hyperkeratosis. Early manifestations include painful, symmetrical red and swollen areas on the palms and soles.
  - Aggressive management of symptoms is recommended, including early dermatology or podiatry referral.

Table 7: Management of Cabozantinib-Related Palmar-Plantar Erythrodysesthesia (PPE) Syndrome

CTCAE v4.0 Grade	Action To Be Taken
1	Cabozantinib treatment may be continued at the current dose if PPE is clinically insignificant and tolerable. If clinically significant or intolerable, cabozantinib should be interrupted and/or reduced to the next lower dose level. Start urea 20% cream twice daily and clobetasol 0.05% cream once daily. Reassess weekly. Reassess at least weekly; if PPE worsens at any time or does not improve after 2 weeks, proceed to the intervention guidelines for Grade 2.
2	Cabozantinib treatment may be continued if PPE is tolerated. Cabozantinib should be dose reduced or interrupted if PPE is intolerable. Continue urea 20% cream twice daily and clobetasol 0.05% cream once daily and add analgesics (e.g., NSAIDs/GABA agonists) for pain control if needed. Reassess at least weekly; if PPE does not improve within 2 weeks or worsens or affects self-care, proceed to the intervention guidelines for Grade 3.

3	Interrupt cabozantinib treatment until severity decreases to Grade 1 or Grade 0. Continue treatment of skin reaction with clobetasol 0.05% cream twice daily and analgesics. Resume cabozantinib at reduced dose if PPE recovers to Grade 0 or 1. Discontinue cabozantinib treatment if intolerable PPE recurs after dose reduction or does not improve within 6 weeks.

- **Hypertension**:
  - Blood pressure should be monitored at each visit.

Table 8: *Management* ***of*** *Cabozantinib-Related* ***Hypertension***

Blood pressure or Condition	**Action to be Taken**
SBP 150-160 or DBP 100-110 mmHg	Optimize antihypertensive treatment by adding new or additional antihypertensive medications and/or increase dose of existing medications. Reduce cabozantinib treatment by one dose level if optimal antihypertensive therapy (usually to include 3 agents) does not result in BP < 150 mm Hg systolic or < 100 mm Hg diastolic. If subject is symptomatic, interrupt study treatment.
SBP > 160 or DBP > 110 mmHg	If optimized antihypertensive therapy (usually to include 3 agents) does not result in BP < 150 mm Hg systolic or < 100 mm Hg diastolic, cabozantinib treatment should be dose reduced further or interrupted. Interrupt cabozantinib treatment if upper limits of BP (≥ 160 mm Hg systolic or ≥ 110 mm Hg diastolic) are sustained and not adequately manageable or if BP is > 180 mm Hg systolic or > 120 mm Hg diastolic or if subject is symptomatic. Restart cabozantinib treatment at the most tolerable dose and re-escalate cabozantinib dose only if BP falls to and is sustained at < 140 mm Hg systolic and < 90 mm Hg diastolic.
Hypertensive crisis or hypertensive encephalopathy	Discontinue cabozantinib treatment.

- **Thromboembolic Events:**
  - Subjects who develop a PE or DVT should have cabozantinib treatment held until therapeutic anticoagulation with heparins (e.g., LMWH) is established.
  - Cabozantinib treatment may be resumed in subjects who are stable and have

uncomplicated PE or DVT and are deriving clinical benefit from cabozantinib treatment.

- Subjects with life-threatening PE or DVT should have study treatment discontinued unless toxicity can be managed and subject is deriving clear clinical benefit as determined by the treating physician and agreed by the Principal Investigator.
- Cabozantinib treatment should be discontinued in subjects who develop an acute myocardial infarction or any other clinically relevant arterial thromboembolic complication.

- **Proteinuria:**
  - If urinalysis shows proteinuria ≥ 3+, obtain spot urine protein creatinine ratio.

Table 9: Management of Cabozantinib-Related Proteinuria

Severity of Proteinuria (UPC Ratio)	**Action to be Taken**
UPC Ratio ≤ 1	No change in cabozantinib treatment or monitoring.
UPC Ratio > 1 to < 3.5	No change in cabozantinib treatment required. Consider confirming with a 24-hour protein assessment within 7 days. Repeat UPCR within 7 days and once per week. If UPCR < 1 on 2 consecutive readings, UPCR monitoring can revert to protocol-specific times.
UPC Ratio ≥ 3.5	Hold cabozantinib treatment pending repeat UPCR within 7 days and/or 24-hour urine protein. If ≥ 3.5 on repeat UPCR, continue to hold cabozantinib treatment and check UPCR every 7 days. If UPCR decreases to < 2, restart cabozantinib treatment at a reduced dose and monitoring of urine protein/creatinine should continue weekly until the UPCR decreases to < 1.
Nephrotic syndrome (e.g. proteinuria > 2 grams/day on 24 hour urine or urine protein creatinine ratio >3.5 AND serum albumin < 2 mg/dL AND edema)	Discontinue cabozantinib treatment.

- **Hypophosphatemia:**
  - Serum phosphorus should be monitored frequently while receiving cabozantinib.
  - Mild to moderate hypophosphatemia should be managed by oral replacement including food that are high in phosphate (diary items, meats, beans) and/or oral phosphate supplements according to standard clinical practice guidelines.

- **Thyroid Function Disorders:**
  - Changes in thyroid function tests (TFTs) and hypothyroidism have been reported with cabozantinib and other tyrosine kinase inhibitor treatment as a result of altered thyroid hormone regulation.
  - Management of thyroid dysfunction (e.g., symptomatic hypothyroidism) should follow accepted clinical practice guidelines.

- **Hemorrhagic Events:**
  - Discontinue cabozantinib treatment in subjects who have been diagnosed with a severe bleeding complication.

- **GI Perforation/Fistula and Non-GI Fistula Formation:**
  - Carefully monitor for episodes of abdominal pain, especially in subjects with known risk factors for developing GI perforation/fistula or non-GI fistula, to allow for early diagnosis.
  - Discontinue cabozantinib treatment in subjects who have been diagnosed with GI or non-GI perforation/fistula.

- **Osteonecrosis of the Jaw:**
  - Osteonecrosis of the jaw (ONJ) has been reported with use of anti-angiogenic drugs and bisphosphonates and denosumab in cancer subjects.
  - Subjects with any documented case of osteonecrosis should have study treatment discontinued, and appropriate clinical management should be initiated.

5.5 Diet/Activity/Other Considerations

5.5.1 Diet

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

5.5.2 Contraception

Pembrolizumab and/or cabozantinib may have adverse effects on a fetus in utero. Animal reproduction studies have not been conducted with pembrolizumab; however, blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss. These results indicate a potential risk, based on its mechanism of action, that administration of pembrolizumab during pregnancy could cause fetal harm, including increased rates of abortion or stillbirth. Human IgG4 is known to cross the placental barrier and pembrolizumab is an IgG4; therefore, pembrolizumab has the potential to be transmitted from the mother to the developing fetus. Pembrolizumab is not recommended during pregnancy unless the clinical benefit outweighs the potential risk to the fetus.

Furthermore, it is not known if pembrolizumab and/or cabozantinib have transient adverse effects on the composition of sperm.

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

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

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

OR

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

OR

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

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

(1) Practice abstinence[†] from heterosexual activity;

OR

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

Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

- Intrauterine device (IUD)
- Vasectomy of a female subject's male partner
- Contraceptive rod implanted into the skin

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

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

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

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential

will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.5.3 Use in Pregnancy

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

The 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 the Sponsor-Investigator. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor-Investigator and to Merck and followed as described above and in Section 7.7.

5.5.4 Use in Nursing Women

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

5.6 Subject Withdrawal/Discontinuation Criteria

5.6.1 Subject Withdrawal

Subjects may withdraw consent at any time for any reason or be taken off study treatment at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

5.6.2 Subject Discontinuation

A subject must be discontinued from the taken off study treatment for any of the following reasons:

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

- Confirmed radiographic disease progression

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, provided they meet all criteria for treatment beyond progression and have approval of the Principal Investigator (Section 5.7)

- Unacceptable adverse experiences as described in Section 5.2.1.2, 5.2.1.3, 5.2.1.3.1, and 5.2.1.3.2.
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Administrative reasons

5.6.3 Clinical Criteria for Early Trial Termination

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

- Quality or quantity of data recording is inaccurate or incomplete.
- Poor adherence to protocol and regulatory requirements.
- Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects.
- Plans to modify or discontinue the development of the study drug.

In the event of Merck's decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

Specific details regarding the procedures to be followed due to subject discontinuation or withdrawal from the study are provided in Section 7.1.4 – Other Procedures – Withdrawal/Discontinuation.

The End of Treatment/ Follow-up visit procedures are listed in Section 6 (Trial Schedule of Events) and Section 7.1.5 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected

for 90 days after the end of treatment as described in Section 7.2.5.3). Subjects who discontinue treatment for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up.

5.7 Treatment Beyond Disease Progression

Subjects may continue study treatment after standard RECIST v1.1 criteria for progressive disease are met provided they meet all the following criteria:

- Absence of symptoms and signs (including worsening of laboratory values, e.g., new or worsening hypercalcemia) indicating unequivocal progression of disease.
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
- Absence of tumor progression at critical anatomical sites such as the central nervous system, central airway, the great vessels, and other organs or tissues where tumor progression would be expected to result acutely in severe and/or irreversible disability or death.
- Subjects must provide written consent to acknowledge discussion with the treating investigator of the benefit-risk balance of continuing study treatment beyond radiographic progression.
- If radiographic disease progression is confirmed at a subsequent tumor assessment, subjects may be considered for continued study treatment at the investigator's discretion after discussion with the Principal Investigator, if they continue to meet the criteria above and have evidence of clinical benefit, as evidenced by improvement in one or more symptoms or signs attributable to the underlying cancer.

5.8 Subject Replacement Strategy

Any dose-escalation subject who does not complete the DLT assessment window for a reason other than a DLT will be considered non-evaluable for dose escalation decisions, as well as, the MTD and RP2D assessment and may be replaced by an additional subject at that same dose level.

A subject who has any component of study treatment held during the DLT assessment window for a reason other than a DLT such that administration of the next planned pembrolizumab dose is delayed by more than 7 days and/or ≥25% of the planned cabozantinib doses are missed, will be considered non-evaluable for dose-escalation decisions and the MTD assessment and may be replaced by an additional subject at that same dose level.

5.9 Known Potential Benefits

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

- To Participant: Potential benefit of improved efficacy of the combination of cabozantinib and pembrolizumab.
- To Society: Potential benefit of establishing benefit of this combination as a treatment option to future patients with metastatic renal cell carcinoma.

  Justify the importance of the knowledge gained: While there are survival benefits of cabozantinib monotherapy and nivolumab (an anti-PD-1 antibody similar to pembrolizumab currently approved for metastatic renal cell carcinoma) monotherapy, these treatments are not curative and resistance develops. The hope is that the combination would provide lead to more response rates and slower resistance to treatment, compared to each agent alone.

6.0 TRIAL SCHEDULE OF EVENTS CHART

Trial Period:	**Screening**	**Treatment Cycles[a]**							**End of Treatment/ Follow Up Visit**	**Survival Follow-Up[m]**
	Main Study Screening					To be repeated beyond 7 cycles			Safety Follow-up	Overall Survival
Treatment Cycle/Title:		1	2	3	4	5	6	7		Every 6 months
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	Within 30 days post treatment discontinuation	±1 month
Informed Consent	X									
Inclusion/Exclusion Criteria	X									
Demographics and Medical History	X									
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	
Pembrolizumab Treatment Administration[l]		X	X	X	X	X	X	X		
Cabozantinib Treatment Administration		X	X	X	X	X	X	X		
Post-study Anticancer Therapy Status									X	
Survival Status[m]									X	X[m]
Review Adverse Events	X	X	X	X	X	X	X	X	X	
Full Physical Examination	X	X	X	X	X	X	X	X	X	
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	
Height	X									
ECOG Performance Status	X	X	X	X	X	X	X	X	X	
12-lead EKG	X				X			X[k]	X	
Pregnancy Test – Urine[b]	X	X[j]	X	X	X	X	X	X		
PT/INR, aPTT, LDH	X									
CBC with Differential	X	X[j]	X	X	X	X	X	X	X	
Comprehensive Serum Chemistry Panel, including Phosphorus	X	X[j]	X	X	X	X	X	X	X	
Urinalysis	X	X[j]	X	X	X	X	X	X	X	
Total T3, Free T4, and TSH[i]	X				X			X	X	

Trial Period:	**Screening**	**Treatment Cycles[a]**							**End of Treatment/ Follow Up Visit**	**Survival Follow-Up[m]**
	Main Study Screening (Visit 2)					To be repeated beyond 7 cycles			Safety Follow-up	Overall Survival
Treatment Cycle/Title:		1	2	3	4	5	6	7		Every 6 months
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	Within 30 days post treatment discontinuation	±1 month
Tumor Imaging[c] (CT or MRI C/A/P +/- Whole Body Bone Scan [d])	X				X			X		
RECIST 1.1 and irRECIST radiology read[c]	X				X			X		
Archival Tumor Collection	X									
Optional Fresh Tumor Biopsies (baseline and post-treatment)	X[e]		X[e]							
• PD-L1 Testing	X		X							
• Immuno-Oncology Marker Testing	X		X							
Correlative Studies										
• Bone Turnover Markers[g] (in subjects with bone metastases only)		X	X		X			X[†]		

[a] Each treatment cycle = 3 weeks.

[b] Urine pregnancy test is required only in women of childbearing potential.

[c] CT or MRI CAP +/- bone scan and RECIST 1.1 assessments will be obtained at baseline and after every 3 cycles. irRECIST = immune-related response criteria. PET/CT is an acceptable alternative imaging modality. All scans can be performed ± 7 days from the scheduled date.

[d] Whole Body Bone Scan is required for subjects with known or suspected bone metastases. All scans can be performed ± 7 days from the scheduled date.

[e] The baseline optional fresh tumor biopsy should be obtained during the screening period, prior to C1D1 treatment. The post-treatment optional fresh tumor biopsy should be obtained approximately 3-6 weeks (during cycle 2). Subjects may consent for separately for either baseline and/or post-treatment biopsies.

[g] Bone turnover markers may include β C-terminal telopeptide (β-CTX), bone specific alkaline phosphatase, and procollagen type 1 amino-terminal propeptide (P1NP). †Bone turnover markers will be collected through cycle 7 but not beyond. Bone tumor markers are not required during the second course of treatment.

[i] Total T3 = Total thriiodothyronine, Free T4= T4 (thyroxine) Free

[j] Screening labs and pregnancy tests do not need to be repeated at C1D1 if done within 7 days of C1D1.

[k] EKG tests will be performed through cycle 7, and then only as clinically indicated.

[l] In the absence of disease progression, pembrolizumab may be administered for up to 35 cycles (first course). If the patient progresses after discontinuing pembrolizumab, they may resume dosing for up to 17 additional cycles (second course), providing they meet criteria for retreatment. See protocol section 5.2.1 for additional information.

[m] Survival status: patients will be followed for survival every 6 months (±1 month) for 3 years after completion of study treatment or until study discontinuation, whichever occurs first.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent Process

Consent forms describing in detail the study agent, study procedures, and risks are given to the subject and the Investigator must obtain a documented informed consent form (ICF) from each potential subject prior to participating in this clinical trial (i.e., starting intervention/ administration of study product). The Informed Consent Process will continue throughout the subject's participation in this clinical trial.

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

7.1.1.1.1 Informed Consent Form (ICF) and Documentation

ICFs will be IRB-approved and the subject will be asked to read and review the document. A designated study staff member will explain the research study to the subject and answer any questions that may arise. All subjects will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Subjects will have the opportunity to carefully review the written ICF and ask questions prior to signing. Subjects will have the opportunity to discuss the trial with their surrogates or think about it prior to agreeing to participate.

Consent will be documented on the ICF by the subject's dated signature along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form (ICF), any subsequent revised ICF and any written information provided to the subject will receive the IRB's approval in advance of use. The subject should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised and IRB approved ICF or addendum to the original ICF that captures the subject's dated signature.

The informed consent will adhere to IRB requirements, applicable laws and regulations and Sponsor requirements.

Subjects will sign the ICF prior to any procedures being done specifically for this trial.

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

7.1.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.2 Medical History

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

7.1.1.3 Prior and Concomitant Medications Review

7.1.1.3.1 Prior Medications

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

7.1.1.3.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.4 Disease Details and Treatments

7.1.1.4.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status including stage, histologic subtype (e.g. clear cell, non-clear cell, mixed, sarcomatoid, etc.), prior nephrectomy status, and site(s) of metastatic disease (e.g. bone, lung, brain, lymph node, etc.). Whenever possible, Memorial Sloan Kettering Cancer Center (MSKCC) renal cell carcinoma risk stratification will be documented.

7.1.1.4.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries. When available, data on response to and duration on prior treatments will be recorded.

7.1.1.4.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment within the 30 day follow up period. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30-day Safety Follow-up visit must occur before the first dose of the new therapy.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Schedule of Events Chart (Section 6) and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 12.3). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to section 7.3 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A physical exam should be performed during screening and during each study visit.

7.1.2.3 Vital Signs

The investigator or qualified designee will review vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Schedule of Events Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

7.1.2.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 12.2) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Schedule of Events Chart.

7.1.2.5 Tumor Imaging and Assessment of Disease

Radiographic tumor assessments will include a CT or MRI of the chest, abdomen, and pelvis (CAP). In subjects with known bone metastases, a technetium bone scan should also be obtained. If MRI is performed of the abdomen and pelvis at screening, then at least a non-contrast CT of the chest should be performed as well.

CT or MRI CAP +/- bone scan and RECIST 1.1 assessments will be obtained at baseline and after every 3 cycles. All scans can be performed ± 7 days from the scheduled date. The same imaging modalities should be used at screening and for subsequent tumor assessments. Radiographic response and disease progression will be determined using RECIST version 1.1 and immune-related response criteria (irRECIST).

PET/CT is an acceptable alternative imaging modality.

7.1.2.6 Tumor Tissue Collection

Archival tumor tissue is mandatory for enrollment in both the dose escalation and dose expansion cohorts. A subject with insufficient or unavailable archival tissue may be eligible, upon discussion with the Principal Investigator, if the subject is willing to consent to undergo a pretreatment core, punch, or excisional/incisional biopsy sample collection of the tumor.

In addition, subjects may consent for optional fresh tissue biopsies at baseline (during screening period) and/or post-treatment at approximately 3-6 weeks (during cycle 2) after initiation of study treatment.

These archival and fresh tumor specimens will be used for PD-L1 and/or other immune-oncology marker testing.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 10.

Table 10: Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin (β-hCG)[2]
Hemoglobin	Alkaline phosphatase	Glucose	
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Carbon Dioxide	Microscopic exam *(If abnormal results are noted)*	Total triiodothyronine (T3)
Absolute Neutrophil Count	Lactate dehydrogenase (LDH)[1]		Free thyroxine (T4)
Absolute Lymphocyte Count	Calcium	Urine pregnancy test [2]	Thyroid stimulating hormone (TSH)
	Chloride		
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

1 LDH only required at screening
2 Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.4 Other Procedures—Withdrawal/Discontinuation

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

7.1.5 Visit Requirements

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

7.1.5.1 Screening Period

All screening evaluations must be completed and reviewed to confirm that subjects meet all eligibility criteria before initiating study treatment. Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for subjects who are not subsequently enrolled will be maintained at the study site.

Screening and pre-treatment tests and evaluations will be performed within 28 days preceding Cycle 1 Day 1 (defined as the day of first dose of study treatment), unless otherwise specified. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to study entry may be used; such tests do not need to be repeated for screening.

See the study Schedule of Events (Section 6.0) for schedule of screening assessments.

7.1.5.2 Treatment Period

All visits must occur within ± 3 days from the scheduled date, unless otherwise noted. All assessments will be performed on the day of the specified visit unless a time window is specified. Assessments scheduled on the day of study treatment administration (Day 1) of each cycle should be performed prior to study drug infusion, unless otherwise noted. C1D1 laboratory assessments do not need to be repeated if screening labs were done within 7 days of C1D1.

See the study Schedule of Events (Section 6.0) for schedule of treatment period assessments.

7.1.5.3 End of Treatment/Safety Follow-Up Visit

The End of Treatment/Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment, or before the initiation of a new anti-cancer treatment, whichever comes first.

All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy (including single agent cabozantinib SOC) whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment (including single agent cabozantinib SOC) should also be followed and recorded.

7.1.5.4 Survival Follow-Up

Patients will be followed for survival every 6 months (±1 month) for 3 years after completion of study treatment or until study discontinuation, whichever occurs first.

7.2 Assessing and Recording Adverse Events

7.2.1 Definition of AEs

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

7.2.2 Assessment of AEs

An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Merck's product, is also an adverse event.
Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants

and children and onset of menses or menopause occurring at a physiologically appropriate time.

Merck product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by Merck for human use.

Adverse events may occur during the course of the use of Merck product in clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

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

7.2.3 Reporting of AEs

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

From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.4.1- *Definition and Assessment of SAEs*. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

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

7.3 Serious Adverse Events (SAE)

7.3.1 Definition and Assessment of SAEs

A serious adverse event is any adverse event occurring at any dose or during any use of Merck's product that:

- Results in death;
- Is life threatening;

- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is another important medical event.

- **Note:** In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.
  - Is a new cancer (that is not a condition of the study);
  - Is associated with an overdose.

Refer to Table 11 for additional details regarding each of the above criteria.

7.3.2 Immediate Reporting of SAEs

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.4.2.1-*Protocol Specific Exceptions to Serious Adverse Event Reporting* for additional details) that occurs to any subject must be reported within 24 hours to the Sponsor-Investigator and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.4.2.1-*Protocol Specific Exceptions to Serious Adverse Event Reporting* for additional details), whether or not related to the Merck product, must be reported within 24 hours to the Sponsor-Investigator and within 2 working days to Merck Global Safety. The SAE should also be submitted within 7 (for fatal or life-threatening events) or 15 (non-life-threatening events) calendar days of the sponsor investigator receiving notification of the occurrence to the Data and Safety Monitoring Committee (DSMC) at the University of Colorado Cancer Center.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time following consent through the end of the specified safety

follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck Global Safety.

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

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-661-6229 Merck will include a copy of all 15 Day Reports and Annual Progress Reports for their submissions as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. The Sponsor-Investigator of this study will cross reference the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission to the FDA, the IND application for this study. Additionally, investigators will submit a copy of these safety and annual progress reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 661-6229) at the time of submissions to the FDA.

7.3.2.1 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to Merck as described in Section 7.3.2 - *Immediate Reporting of AEs*, unless there is evidence suggesting a causal relationship between the drug and the event. Any such event will be submitted to the Sponsor-Investigator within 24 hours and to Merck Global Safety within 2 working days either by electronic or paper media. The SAE should be submitted within 7 (for fatal or life-threatening events) or 15 (non-life-threatening events) calendar days of the sponsor investigator receiving notification of the occurrence to the DSMC at the University of Colorado Cancer Center.

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

The Sponsor-Investigator will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the subjects in the trial. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to Merck Global Safety as a SAE within 2 working days of determination that the event is not progression of the cancer under study. The SAE should be submitted within 7 (for fatal or life-threatening events) or 15 (non-life-threatening events) calendar days of the sponsor investigator receiving notification of the occurrence to the DSMC at the University of Colorado Cancer Center.
Hospitalization related to convenience (e.g. transportation issues etc.) will not be considered a SAE.

7.4 Events of Clinical Interest (ECI)

7.4.1 Definition and Assessment of ECI

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and for this trial include:

1. An overdose of Merck product, as defined in Sections 7.5.1 - *Definition of an Overdose for This Protocol* and 7.5.2 - *Reporting of Overdose for this Protocol* 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.

7.4.2 Reporting ECIs

ECIs and must be reported within 24 hours to the Sponsor-Investigator and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229).

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor-Investigator and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 24 hours to the Sponsor-Investigator and within 24 hours to Merck Global Safety.

7.5 An Overdose for this Protocol

7.5.1 Definition and Assessment of an Overdose for this Protocol

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose).

No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

7.5.2 Reporting of an Overdose for This Protocol

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 24 hours to the Sponsor-Investigator and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220).

7.6 Reporting of Pregnancy and Lactation to the Sponsor and to Merck

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

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor-Investigator and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229).

7.7 Definition of Unanticipated Problems (UAP)

The Office of Human Research Protection (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This study will use the OHRP definition of UAP.

7.8 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

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

7.9 Sponsor-Investigator Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators, in accordance with all applicable global laws and regulations.

Table 11: Evaluating Adverse Events

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

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the subject's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours and to Merck within 2 working days to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours to the Sponsor and to Merck within 2 working days.	

	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units
Action taken	Did the adverse event cause Merck product to be discontinued?
Relationship to Merck Product	Did Merck product cause the adverse event? The determination of the likelihood that Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Merck product caused the adverse event (AE):
	Exposure — Is there evidence that the subject was actually exposed to Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course — Did the AE follow in a reasonable temporal sequence from administration of Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause — Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

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

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

The final study analysis will be based on subject data collected through study discontinuation. Analyses will be based on the safety-evaluable population, defined as all subjects who receive any amount of study treatment. In general, data will be summarized as warranted, and listings will be provided in place of tables when sample sizes are small. Summaries will be presented by the assigned dose regimen and designated treatment arm.

8.2 Statistical Analysis Plan

8.2.1 Analysis of Overall Conduct of Study

Enrollment and major protocol violations, study treatment administration, and reasons for subject discontinuations from the study treatment will be described and listed or summarized.

Demographic and baseline characteristics, such as age, sex, histology, prior nephrectomy status, site(s) of metastatic disease, prior treatments including response and duration, MSKCC renal cell carcinoma risk stratification, and baseline ECOG performance status will be summarized.

8.2.2 Analysis of Safety

Safety will be assessed through summaries of DLTs, adverse events, clinically significant changes in laboratory test results, clinically significant changes in vital signs and ECGs, and exposure to components of study treatment. All subjects who receive any amount of study treatment will be included in the safety analyses.

Adverse event data will be listed by dose cohort. Events occurring on or after treatment on Cycle 1, Day 1 will be summarized by AE term, NCI CTCAE v4.0 grade, and relationship to either pembrolizumab and/or cabozantinib.

Serious adverse events, including deaths, will be listed separately and summarized.

Adverse events leading to treatment discontinuation will be listed.

Adverse events meeting the criteria for DLT will be listed. Subjects who withdraw from the study prior to completing the DLT assessment window for reasons other than a DLT will be considered unevaluable for DLT assessments.

8.2.3 Analysis of Anti-Tumor Activity

Descriptive statistics will be used to summarize all demographic and analytic data. Continuous data will be summarized using means, standard deviation, range, etc. Categorical data will be summarized using frequency tables.

Tumor response analyses will be based on definitions of responses according to both RECIST v1.1 and immune-related response criteria (irRECIST).

Objective response is defined as a complete or partial response, as determined by investigator assessment using RECIST and irRECIST. Subjects with missing or no response assessments will be classified as non-responders. For the primary objective, a one-sided exact binomial test will be used to assess whether the ORR is significantly greater than 20% in subjects taking a combination of pembrolizumab and cabozantinib.

Clinical benefit rate (CR + PR +SD) and duration will also be recorded.

Among subjects with an objective response, duration of response will be defined as the time from first occurrence of a documented objective response until the time of documented disease progression or death from any cause during the study, whichever occurs first. For all other subjects, duration of objective response will be censored at the day of the last tumor assessment.

Progression-free survival (PFS) will be defined as the time from study treatment initiation (Cycle 1, Day 1) to the first occurrence of documented disease progression or death from any cause during the study, whichever occurs first. For subjects who do not have documented progressive disease or death during the study, PFS will be censored at the day of the last tumor assessment.

Overall survival (OS) will be defined as the time from study treatment initiation (Cycle 1, Day 1) to death from any cause. For subjects who do not have documented death during or after the study, OS will be censored at the day of known survival status.

In subjects with bone metastases, time to progression of bone metastases or skeletal related event (SRE, defined as pathologic fracture, spinal cord compression, and radiation to bone or surgery to bone related to cancer) will also be recorded from Cycle 1 Day 1 to the time of progression or SRE.

Progression-free survival, overall survival, duration of response/duration on treatment, and time to skeletal related event or bone progression will be assessed using Kaplan-Meier curves and hazard ratios. The clinical benefit rate and duration of clinical benefit will be summarized using descriptive statistics.

Among subjects who receive treatment beyond progression, duration on treatment will be recorded.

Response data may be listed, summarized in tables, and/or presented as a swimmer plot.

8.2.4 Analysis of Exploratory Endpoints

Bone biomarkers that are correlated with objective response will be identified using a Wilcoxon rank sum test comparing biomarker levels in those with and without objective response to treatment. The expression of PD-L1 and other immunologic biomarkers will be compared in biopsies before therapy, on-treatment, and at progression using a Wilcoxon signed-rank test on each pair of observations. As appropriate, expression levels will be dichotomized to meaningfully present versus not present.

8.2.5 Sample Size

The proposed study is a single-arm, phase I/II study of pembrolizumab in combination with cabozantinib in subjects with metastatic RCC. We will use a Simon two-stage design for the phase II portion this study based on the primary endpoint of objective response rate. The planned enrollment for this study is approximately 25-55 total subjects, to account for screen failures, in order to achieve 6-9 evaluable subjects in Phase I dose escalation and 20-38 evaluable subjects in Phase II dose expansion. Subjects from the Phase I part of the study who are treated at the RP2D may be included in the efficacy assessments in Stage I of the Phase II part of the study.

Phase I:
Any subject who does not complete the DLT assessment window for any reason other than a DLT will be considered non-evaluable for dose-escalation decisions and MTD and RP2D assessment and will be replaced by an additional subject at that same dose level.

Table 12 describes the probability of not observing any DLTs in 3 subjects, and the probability of observing fewer than two DLTs in 6 subjects for different underlying DLT rates.

Table 12: Probability of Observing DLTs for Different Underlying DLT Rates

Underlying DLT Rate	Probability of Observing No DLTs in 3 Subjects	Probability of Observing Fewer Than Two DLTs in 6 Subjects
0.10	0.73	0.89
0.20	0.51	0.66
0.33	0.30	0.36
0.40	0.22	0.23
0.50	0.13	0.11
0.60	0.06	0.04

For a given adverse event with a true rate of 10%, 5%, or 1%, the probability of observing at least one such adverse event in a given cohort of 6 subjects is 47%, 26.5%, and 5.8%, respectively.

Phase II:
The Simon's two-stage design will be implemented to test the null hypothesis that ORR ≤ 0.20 versus the alternative that ORR ≥ 0.50. After the enrollment of 20 evaluable patients in the first stage, the trial will be terminated if 2 or fewer respond. If the trial goes on to the second stage, a total of 38 patients will be studied. If the total number responding is greater than 12, the treatment is considered effective.

This two-stage design has an expected sample size of 34.29 and a probability of early termination of 0.206. If the drug is actually not effective, there is a 0.029 (satisfied the 0.05 type I error rate constraint) probability of concluding that it is. If the drug is actually effective, there is a 0.017 probability of concluding that it is not, which corresponding to a 98% power (satisfied the 90% power constraint).

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product- Pembrolizumab

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, Investigator's Brochure, and any applicable laws and regulations.

Clinical Supplies will be provided by Merck as summarized in Table 13.

Table 13: Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 50 mg	Lyophilized Powder for Injection
Pembrolizumab 100 mg/ 4mL	Solution for Injection

9.2 Cabozantinib

Cabozantinib (Cabometyx®) will be prescribed and obtained commercially as tablets through a specialty pharmacy, per standard of care.

Refer to the package insert for additional information.

9.3 Packaging and Labeling Information

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

9.4 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.5 Storage and Handling Requirements

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

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

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

9.6 Returns and Reconciliation

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

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

To maintain subject privacy, study drug accountability records, study reports, and communications will identify the subject by initials where permitted and/or by the assigned subject number. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Qualified representatives from the relevant regulatory agencies, the drug manufacturer (Merck), or its agents may inspect the subject/study records. Subject data obtained during the study may be presented in scientific publications, but at no time will subject names be used.

10.2 Conflict of Interest Policy and Compliance with Financial Disclosure Requirements

Independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed.by the University of Colorado Denver's (UCD) Office of Regulatory Compliance Conflict of Interest and Commitment Management (COIC) program. Persons with a perceived conflict of interest will have such conflicts managed in a way that is appropriate to their participation in the trial. Conflict of Interest management plans are project-specific and are reviewed at least annually. UCD has integrated the institutional conflict of interest management program with its existing program.

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). All investigators participating in this trial will also be required to complete a Financial Disclosure Form (FDF) to provide his/her financial interests in and/or arrangements with the Sponsor-Investigator, and/or a manufacturer of the investigational agent(s) being studied in this clinical trial. The submission of an FDF must be a complete and accurate certification and disclosure of financial interests held by the investigators.

10.3 Compliance with Law, Audit and Debarment

The Sponsor-Investigator will ensure that this study is conducted in full conformity with regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56. International Conference on Harmonisation (ICH) Guidance on Good Clinical Practice ([GCP] CPMP/ICH/135/95) may also be followed to the extent it has been adopted by and is in accordance with FDA regulations.

Clinical monitoring of all study site locations will be allowed periodically, in accordance with the CMP, to assess data quality and study integrity. On site, they will review study records and directly compare them with the original source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by auditors designated by the Sponsor-Investigator and by government inspectors who must be allowed access to CRFs, source documents, and all other study files. Sponsor-Investigator audit reports will be kept confidential.

COLORADO MULTIPLE INSTITUTIONAL REVIEW BOARD
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Project Title: **Creative Arts Therapy (CAT) in the Center for Cancer and Blood Disorders**

Principal Investigator: **Jennifer Raybin, RN, MSN, CPNP**

Co-Investigators: **Molly Hemenway, RN, CPNP**

Version Date: **5/10/2019**

I. Hypotheses and Specific Aims

The purpose of the study is to evaluate the effectiveness of Creative Arts Therapy (CAT) on pediatric patients undergoing chemotherapy in the Infusion Center at Children's Hospital Colorado Center for Cancer and Blood Disorders. Findings from a previous pilot study support the hypothesis that CAT may improve quality of life (QOL), resiliency, physical posture, and emotional response to pain of pediatric oncology patients undergoing chemotherapy.

Specific aims include:

a. Does CAT improve the child's reported QOL?
b. Is the child's resiliency enhanced by CAT?
c. Does CAT influence the physical posture of the child?
d. Does CAT impact the child's emotional response to pain?
e. Are patients, families, and staff satisfied with the CAT program?

II. Background and Significance

Although survival rates of children with cancer are improving, their QOL is known to be poorer than their healthy peers. As survival rates of pediatric cancer now approach 85%, the need for quality psychosocial care including creative arts has increased (Askins & Moore, 2008). Oncology patients are known to have significant morbidity during treatment as a result of the surgery, radiation and chemotherapy, but little is published on the day to day effects of treatment on the quality of life of pediatric oncology patients (Banks, 2008). Tremolada et al looked at parental perception of QOL in newly diagnosed children with leukemia and found that increasing the knowledge of QOL may improve communication and psychosocial care during initial treatment for leukemia (2010). In addition, quality of life among adolescents with cancer may be worse during treatment than for those not currently on therapy (Ward-Smith et al., 2007). Another study has shown that interventions to promote happiness may be a good predictor of QOL in adolescent cancer survivors (Bitsko et al., 2008).

It has been acknowledged that even the act of coming to the clinic weekly for chemotherapy infusions impacts on the patient's life. In addition, vincristine, a commonly used chemotherapy, is also well-known to cause significant morbidity (leg pain, numbness, tingling, and constipation) requiring dose-limiting regimes. Steroids are another common medication

with toxicities affecting QOL. Toxicities of steroids include weakness, sleep and mood disturbance, and pain with dose reduction (Sanford et al., 2008; Hinds et al., 2007).

Resilience is a subset of QOL that has been studied in pediatric chronic illness including cancer (Haase et al., 2004). Resilience has been defined as a characteristic that moderates stress and the ability to cope with change or misfortune (Wagnild & Young, 1993). Resilient individuals have positive outcomes in spite of adversity (Rew & Horner, 2003). Therefore nurses who understand resilience can promote those characteristics during times of illness or stress (Ahern et al., 2006). There is a paucity of literature directly studying resilience in pediatric oncology patients and further work is warranted.

Emotional response to pain is another subset of QOL that has been measured in this population. It is well known that pediatric oncology patients experience pain (Lervat, 2009). Experts recommend rigorous research using established measures to evaluate childrens' response to pain (McGrath et al., 2008). The Faces scale has been studied with children as young as 5 years to evaluate their emotional response to pain compared with their parents' perceptions (Breau et al., 2001). Pilot data on emotional response on the Faces scale has been shown to improve after group CAT (Madden et al., 2010).

Physical functioning and muscle strength are aspects of QOL that have been shown to be worse than healthy peers in children with cancer (Hartman et al., 2008). This aspect may also be affected by the central venous access lines placed in almost all pediatric cancer patients. Long-term central venous access is critical in pediatric cancer patients and the evolution of these devices has improved QOL in terms of pain and distress of venipuncture (Spagrud, 2008). The literature is rich with discussion of complications and risk of infection, but little is published about the effects on body image and QOL (Albanese, 1993; Nam, 2010). Anecdotally, patients have improved body awareness and posture (less kyphosis) after CAT. In addition, it has been postulated that increased kyphosis may correspond with psychosocial factors including anxiety, depression, and insecurity. Body awareness is a type of physical functioning that may be measured by kyphosis. Measuring posture with an inclinometer has been shown to be reliable, but further work is needed to establish validity (Lewis & Valentine, 2010). Piloting this tool may establish a way to physically measure an individual's sense of self by the way that he or she stands.

The use of complementary and alternative medicine (CAM) is one intervention that has been shown to improve QOL in this population. Current trends show increasing popularity of the use of CAM in even among children with cancer. Martel et al (2005) looked at prevalence of use of CAM in children. In their survey, almost 50% of the children used at least one type of CAM. Specifically to cancer, in 2009, Post-White et al used a survey of 281 patients to show that CAM was used in 59% of pediatric cancer patients versus 36% of general pediatric patients. The authors confirmed that children with cancer and other chronic illnesses use more CAM therapies than children seen in primary care clinics. Roth et al (2009) examined pediatric oncologists' perceptions of CAM and found that although they place importance in CAM, they lack time and knowledge to ask about patients' use of CAM. These authors recommend CAM research in pediatric oncology on modalities that could improve QOL.

CAT is a subset of CAM that may improve QOL. CAT is a broad term encompassing the modalities of dance/movement, music, art. Bringing creativity into health care is a current trend in oncology nursing and throughout the medical professions (Garland et al., 2007; Lane, 2006; Petterson, 2001; Strickland, 2008). There is a growing body of literature establishing the use

of CAT, but the studies use non-standardized tools, small sample sizes, adult populations, and non-rigorous designs. Much of the work on CAT in cancer patients studies adult populations using qualitative measures (Forzoni et al, 2010; Jones et al., 2009; Visser, et al, 2008; Bar-Sela, et al., 2007; Nainis et al., 2006). Other work looked at the family caregivers of patients with cancer and showed significantly reduced stress, anxiety, and increased positive emotions after a creative arts intervention (Walsh et al., 2004). Randomized controlled studies are in the literature and have shown improvement in QOL, but only for the population of women with breast cancer (Oster et al, 2006; Monti et al, 2006; Svensk et al, 2009; Thyme et al, 2009). Music was shown to decrease heart rate in children with leukemia, but the therapeutic aspects were not studied (Kemper et al., 2008). The literature is rich with other examples of types of music, art, movement therapies that may improve QOL in adult and pediatric oncology patients, but there are few rigorous studies to document the importance of CAT during the cancer treatment (Sencer et al, 2007; Dibell-Hope, 2000; O'Callaghan et al, 2007; Robb et al, 2003; Barrera, 2002; Hilliard, 2006).

Therefore, a pilot study of CAT on the QOL of pediatric brain tumor patients used a mixed-model approach with a randomized, controlled phase comparing CAT to a control. Pre- and post- measurements using the PedsQL showed statistically significant improvement on Parent report of child's hurt (problems with having a lot of pain), $p=0.03$ and Parent report of child's nausea (becoming nauseated while thinking about medical treatment), $p=0.0061$. The second non-randomized phase pre- and post- tested any child in group session of CAT. The subjects showed improved mood with statistical significance on the Faces Scale ($p < 0.01$), and patients were more excited ($p < 0.05$), happier ($p < 0.02$), and less nervous ($p < 0.02$) on the Emotional Responses Checklist (Madden et al, 2010).

Rationale

The pilot study was limited by the small sample size; therefore we propose a study with a larger sample size and broader inclusion criteria. We would also like to explore outcomes of resilience and body awareness measured by physical posture based on our observations during the pilot study.

Significance

Nurses have been shown to provide valuable information on QOL for this population (Klaassen et al, 2010). In addition, the pediatric oncology nurse is in a key position to incorporate the art and science of nursing to improve psychosocial treatment outcomes (Cantrell, 2007). Therefore this nursing research study will provide valuable insight to contribute to the body of knowledge of CAM for pediatric oncology patients. The use of CAM for pediatric oncology patients may improve QOL, resiliency, emotional response, and body awareness.

III. Preliminary Studies/Progress Report

See above regarding the previous pilot study. Small sample size limited the statistical significance.

IV. Research Methods

A. Outcome Measure(s)

1. Peds QL—Cancer module

The PedsQL 4.0 Cancer Module is evolved from the PedsQL 4.0 Generic Core Scale (Varni, 1998). The system employs a Parent-Proxy Report for ages 2-18 years and a companion Child Self-Report for children aged five years and older. Validity and reliability testing for both the Core Scale and Cancer Module has been extensive.

Reliability, assessed by internal consistency, yielded coefficient alphas ranging from .80-.90 across total and individual scales and are, thus, appropriate for the group comparisons planned in this study. The Cancer Module is a 27-item instrument that assesses eight subscales (Pain and hurt, nausea, procedural anxiety, treatment anxiety, worry, cognitive problems, perceived physical appearance, and communication). It is easily completed by parents in less than 10 minutes and reverse-scored and linearly-transformed in five minutes or less. Validity for both the Core Scale and the Cancer Module was established by expert panel review; similarly, construct validity for both measures was performed by comparing the responses of children with cancer across both measures to a group of healthy matched controls. In all cases, the Peds QL 4.0 Cancer Module was able to distinguish the responses of children with cancer from those of healthy children at a statistically significant level.

The instruments have been successfully employed in several small studies of children with cancer (Bhat, 2005; Meeske et al, 2004). The PedsQL has been shown to be the most responsive to change when compared with other measures of QOL used with children undergoing chemotherapy (Banks et al, 2008; Klaassen et al, 2010).

2. ***The Resilience Scale (RS)***

The RS-14 is a 14-item scale using a 7-point rating (1-7). The construct of resilience is measured by two factors: personal competence and acceptance of self and life. Wagnild and Young have completed psychometric testing that established internal consistency reliability and concurrent validity (Wagnild & Young, 1993). Many studies have validated that the scale may be used with samples of any age or ethnic background (Ahern et al, 2006), but it is written at a 6th grade level. The authors who developed the tool are currently using it in adolescents (personal communication, 5/25/10). Given that it is expected that half the population of this study will be teenagers, this tool will be used with subjects ages 12 and over to obtain initial data on CAT's effect on resilience.

3. ***Faces Scale***

The Faces Scale has been used for evaluating emotional responses to pain on children 3-17 years old. It is a one page form with nine faces in order of happy to upset. Numerical values are given to each face as determined by childrens' perspectives for an affective value by asking 200 children to directly scale the feelings depicted by the faces. Consistent rating was measured by children over 5 years regardless of age, gender, or health status (McGrath, 1990). The scale is a facial affective scale and has been integrated as a routine measure for management of acute, recurrent, and chronic pain (McGrath, 1990; McGrath et al., 1996). For children less than 3 years old, parents will be asked to complete the Faces Scale. Although this scale has been used for emotional response to pain, it is felt to be an appropriate measure for the emotional response to the discomfort and anxiety in the infusion room.

4. ***Postural Measurement***

Thoracic kyphosis will be measured using two gravity dependent inclinometers (Isomed Inc.). Spinal processes will be determined by palpation by a registered nurse or pediatric nurse practitioner. The feet of the inclinometers will be placed over the spinal processes thought to be at T1, T2 and T12, L1. The measurements will be taken in relaxed standing and measured 3 times in succession. Clinical assessment of the thoracic kyphosis angle is considered essential in postural examination, but can be time

consuming when measured radiographically (Lewis, 2010). Lewis and Valentine studied intra-rater reliability in subjects with and without symptoms and found measurements of less than 1.7 degrees should be considered measurement error. The test-re-test reliability established excellent intra-rater reliability. Although validity of this measure is less studied, the measurement is thought to provide guidance of how much change of the kyphoscoliosis angle is a real consequence of intervention over time (Lewis, 2010).

5. Patient/Family Surveys

A brief ten minute written survey will be administered to subjects to ascertain level of satisfaction with the program.

B. Description of Population to be Enrolled: Study Design and Research Methods

1. Population

The Center for Cancer and Blood Disorders (CCBD) at Children's Hospital Colorado sees approximately 240 new Oncology patients each year. Approximately 45% of these patients receive vincristine, a chemotherapy agent that is known to affect physical functioning. In addition, about 25% of these patients receive steroids, another medication known to affect physical functioning and quality of life. About half of the new patients each year are anticipated to fit the inclusion criteria. Therefore, we expect approximately 100 eligible subjects per year, with a 50% attrition rate, for a total sample size of 100 subjects over a two year period.

Enrollment for this study was reached in 2019. At this time, an additional 10 patients will be allowed to enroll on study to help supplement the data.

2. Eligibility Criteria

Inclusion

- Center for Cancer and Blood Disorders (CCBD) patient with Oncology or Neuro-oncology diagnosis
- No more than 2 previous sessions of CAT as an outpatient in the CCBD
- English speaking
- Receiving outpatient chemotherapy, biotherapy, or transfusions in the infusion center approximately weekly for at least 3 months.
- Ages 3 to 18 years

Exclusion

- Hematology or other patients in the infusion center
- Patients who have previously received more than 2 sessions of CAT in the infusion center
- Non-English speaking patients

3. Study Design

A repeated measures design will be used with each patient serving as his/her own control.

Any Oncology patient in the CCBD who has not previously received more than two sessions of CAT in the outpatient unit and who will be receiving approximately weekly infusions of at least one hour in the infusion center will be identified by a research assistant. The study will be explained to the patient/family and informed consent will

be obtained by the principal investigator or the research assistant. A demographic form will be completed including the information of diagnosis, age, treatment, educational level of parents, zip code, prior experience with art, music, movement.

The intervention will consist of approximately weekly CAT in the infusion center during cancer therapy. The interventionist is a Master's prepared, licensed dance/movement therapist who is experienced in music and art therapies as well. The CAT includes dance/movement such as playing with a parachute, simple yoga breathing and postures, and work with physioballs. The music includes singing, listening to music, and playing instruments. The art consists of drawing, finger painting, working with clay. The CAT may occur in individual sessions in private infusion rooms, or in groups in the middle of the infusion center. The CAT is not only a distraction, but also a therapeutic process addressing the stressors of cancer and its treatment. The "dose" of CAT will be recorded (number and type of sessions) and will be factored into the analysis.

The subjects and/or parents will be tested with all instruments before the intervention, and approximately every 30 days for no less than 3 months and a maximum participation of 6 months. Treatment time points will be at least 30 days apart. Because some subjects are not scheduled to come into the clinic every 30 days for SOC appointments, they are unable to complete 3 sessions of CAT in a 3 month time period. For those subjects who are scheduled to come into clinic every 1-2 months for SOC appointments, study participation may take up to 6 months. This 6 month time period would allow for the completion of 4 different time points of CAT.

The testing will take place in an exam room after vital signs have been completed upon intake to the clinic. The trained research assistant, trained RN, or PI will administer the questionnaires. The PedsQL includes a subject report (ages 5 and over) and a parent report. The Resilience Scale is a self-report and will be used for ages 12 and over. The Faces Scale will use parent report for ages less than 5 and self-report for ages 5 and over. In order to confirm consistency, the posture measure will be completed by the PI (nurse practitioner) or registered nurse on the study after training with the manual included with the inclinometer tool.

Off Study Criteria

1. Subject discontinues CAT
2. Unable to complete 4 time points in 6 months

C. Description, Risks and Justification of Procedures and Data Collection Tools

The anticipated risks include psychological distress incurred by completing the outcome measure questionnaires as well as the therapeutic process. This risk will be minimized by the presence of the Master's prepared, experienced dance/movement therapist. The patients' social workers through the clinic will be available during the intervention as well.

D. Potential Scientific Problems

Based on the pilot data, the anticipated scientific problem is slow accrual due to unforeseen events during the traumatic time of a new diagnosis in pediatric oncology. We are unable to randomize because CAT is standard of care for any patient in the infusion center and therefore we feel it is unethical to deny CAT to a control arm. Therefore, we will compare the subjects to themselves over time to look at longitudinal changes of CAT.

E. Data Analysis Plan

The primary outcome is Peds QL at approximately 3 months; secondary outcomes will be the Resilience Scale, Faces Scale, and postural measurement at approximately 3 months. A repeated measures analysis of variance will be used to analyze the primary and secondary outcomes. We will also use the repeated measures analysis of covariance with the addition of covariates, depending on their statistical significance, such as gender, age, cancer diagnosis, and previous exposure to arts/music/dance. All of the analysis will be adjusted for baseline measures.

We expect to recruit 100 patients, we also expect patients will be equally distributed in the following 3 categories: receiving low (0-3), intermediate (4-6) and high (7+) CAT sessions due to the nature of each patient's random visits. Power analysis was done based on pair-wised T-Test with these assumptions for simplicity. With 33 patients in each group, assuming 80% power and 0.017 significance level of alpha after Bonferroni ad justification of multiple comparisons, we will observe a minimum effect size of 0.813. This is to say that 80% of the Peds QL scores in the lower session CAT group will be below the average of scores in the higher session CAT group. Thus, what we would expect to see in the positive dose-response relationship.

We will also conduct subgroup analysis by age group if the sample size is large enough since Peds QL is designed by age group.

F. Summarize Knowledge to be Gained

Integrative and holistic therapies are being used throughout healthcare. We know that families are using alternative therapies without rigorous evidence documenting their worth. We therefore strive to build a body of literature showing evidence that CAT helps children with cancer feel better.

G. Appendices

1. PedsQL
2. Resilience Scale
3. Faces Scale
4. Inclinometer information
5. Patient/Family Survey

H. References:

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COMIRB
APPROVED
15-May-2019

Study Title: **Creative Arts Therapy (CAT) in the Center for Cancer and Blood Disorders**

Principal Investigator: **Jennifer Raybin, RN, MSN, CPNP**

COMIRB No: **10-1028**
Version Date: **5/10/2019**

In this form, we use the words "you" and "your." If you are reading this form and deciding for someone else, the words 'you' and 'your' refer to that other person, not to you.

You are being asked to be in a research study. This form provides you with information about the study. A member of the research team will describe this study to you and answer all of your questions. Please read the information below and ask questions about anything you don't understand before deciding whether or not to take part.

Why is this study being done?

This study plans to learn more about how creative arts therapy will affect your quality of life during your treatment for cancer.

You are being asked to be in this research study because you will be receiving outpatient therapy in the Center for Cancer and Blood Disorders for the next few months.

Other people in this study

Up to 110 people from Children's Hospital Colorado will participate in the study.

What happens if I join this study?

If you decide to join this study:

- Before the study starts, you will be asked to complete a demographic form with a member of the study team. This will help us find out more about you, your therapy, and what kind of experience you have had with art, music, and movement.
- You will be asked to complete the following measurements before the study starts and then 3 more times over a three to six month period (depending on how often you come to the clinic for your regularly scheduled visits). You will complete these with a member of the study team to assess the effect of creative arts therapy on your quality of life during your treatment for cancer:
    - **PedsQL** – This is a survey that asks questions about your level of pain and hurt, anxiety, worry, problems with thinking, your physical appearance, and communication. This survey has 27 questions and should take less than 10

minutes each time to complete. Your parent may be asked to complete a portion of this survey.
    - **Resilience Scale** – This is a scale that measures how well you are able to cope with the changes in your life that have come with your cancer diagnosis and treatment. This scale has 25 items and should take less than 10 minutes to complete.
    - **Faces Scale** – This is a scale that measures your emotional response to your treatment for cancer. This scale has 9 items and should take less than 5 minutes to complete.
    - **Posture Measurement** – A member of the study staff will measure the angle of your back three times during each of these visits. This should take less than 10 minutes to complete.
    - **Patient/Family Survey** – This is a survey that asks questions about your parent's satisfaction with the creative arts therapy program. This survey has 13 questions and should take less than 10 minutes to complete.
- Once you have completed these four visits over three to six months, you will be finished with this study.

You will be allowed to do creative arts therapy during your clinic visits as many times as it is offered and as much as you would like to participate. This study will not limit the number of times you can do creative arts therapy, and it will not require you to do more creative arts therapy visits than you want to do. We will track how many times you receive creative arts therapy over a three-month period in the clinic.

What are the possible discomforts or risks?

Discomforts you may experience while in this study include some stress you may feel while completing the measurements. If you feel this stress, please let the study staff know.

Other possible risks include the risk of the loss of confidentiality of your protected health information; however, the chance of such a loss is small. Children's Hospital Colorado has procedures in place to keep your information private. No identifiable information about you will be published or presented at scientific meetings.

What are the possible benefits of the study?

This study is designed for the researcher to learn more about how creative arts therapy affects children who are receiving treatment for cancer.

This study is not designed to treat any illness or improve your health.

Who is paying for this study?

This study is being paid for by a grant from The Daisy Foundation.

Will I be paid for being in the study?

You will not be paid to be in the study.

Will I have to pay for anything?

It will not cost you anything to be in the study.

Is my participation voluntary?

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

If you leave this study, you will still receive your normal medical care.

If there are any new findings during the study that may affect whether you want to continue to take part, you will be told about them.

Can I be removed from this study?

The study doctor may decide to stop your participation without your permission if the primary investigator thinks that being in the study may cause you harm, or for any other reason.

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

If you have an injury while you are in this study, you should call Jennifer Raybin, RN, CPNP immediately. Her phone number is 720-777-3407.

We will arrange to get you medical care if you have an injury that is caused by this research. However, you or your insurance company will have to pay for that care.

Who do I call if I have questions?

The researcher carrying out this study is Jennifer Raybin, RN, CPNP. You may ask any questions you have now. If you have questions, concerns, or complaints later, you may call Jennifer Raybin at 720-777-3407. You will be given a copy of this form to keep.

You may have questions about your rights as someone in this study. You can call Jennifer Raybin with questions. You can also call the Colorado Multiple Institutional Review Board (COMIRB) at 303-724-1055.

Who will see my research information?

Children's Hospital Colorado has rules to protect information about you. Federal and state laws including the Health Insurance Portability and Accountability Act (HIPAA) also protect your privacy. This part of the consent form tells you what information about you may be collected in this study and who might see or use it.

The institution involved in this study is Children's Hospital Colorado.

CHCO shares a medical record system with the Barbara Davis Center and PedsConnect; therefore it is also possible that your information could be viewed by healthcare professionals at these organizations.

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

We will see, use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside Children's Hospital Colorado and its affiliate hospitals may not be covered by this promise.

We will do everything we can to keep your records a secret. It cannot be guaranteed.

The use and disclosure of your information has no time limit. You can cancel your permission to use and disclose your information at any time by writing to the study's Primary Investigator at the name and address listed below. If you do cancel your permission to use and disclose your information, your part in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in this study.

Primary Investigator Name: Jennifer Raybin RN, CPNP
Primary Investigator Address: Children's Hospital Colorado
13123 E. 16th Ave. B115
Aurora, CO 80045

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

- Federal offices such as the Food and Drug Administration (FDA) that protect research subjects like you.
- People at the Colorado Multiple Institutional Review Board (COMIRB)
- Jennifer Raybin, RN, CPNP and her team of researchers.
- The Daisy Foundation, who is the organization paying for this research study.
- Officials at Children's Hospital Colorado who are in charge of making sure that we follow all of the rules for research
- The Clinical Investigations Shared Resources at the University of Colorado Cancer Center who also make sure that we follow all of the rules for research

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

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

The investigator (or staff acting on behalf of the investigator) will also make *all or some* **of the following health information about me available to:**

- The Cancer Clinical Trials Office at the University of Colorado Cancer Center

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

- Name and Demographic Information (age, sex, ethnicity, address, phone number, etc.)
- Name and demographic portions of my previous and current medical records that are relevant to this study, including but not limited to Diagnosis(es), History and Physical, Laboratory or tissue studies, radiology studies, procedure results
- Research visit and research test records
- The results of your Peds QL, Resilience Scale, Faces Scale, postural measurements, and Patient/Family Survey.

What happens to Data that is collected in this study?

Scientists at Children's Hospital Colorado involved in this study work to find the causes and cures of disease. The data collected from you during this study is important to this study and to future research. If you join this study:

- The data is given by you to the investigators for this research and so no longer belongs to you.
- Both the investigators and any sponsor of this research may study your data collected from you.
- If data is in a form that identifies you, Children's Hospital Colorado may use it for future research only with your consent or IRB approval.
- Any product or idea created by the researchers working on this study will not belong to you.
- There is no plan for you to receive any financial benefit from the creation, use or sale of such a product or idea.

Agreement to be in this study

I have read this paper about the study or it was read to me. I understand the possible risks and benefits of this study. I know that being in this study is voluntary. I choose to be in this study: I will get a copy of this consent form.

Signature: _____ Date:_____
Subject (if 18 years old); OR Parent/Guardian

Print Name: _____

Signature: _____ Date:_____
Subject (Ages 13-17, in addition to Parent Signature)

Consent form explained by: _____ Date:_____

Print Name: _____

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act of 2007 (FDAAA), as the Sponsor of this trial, this trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, and will be properly registered at http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

10.5 Quality Management System

By signing this protocol, the Sponsor-Investigator agrees to be responsible for implementing and maintaining a quality management system with written development procedures and to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

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

10.6 Data Management

10.6.1 Monitoring and Oversight

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

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

Per the CU Cancer Center Institutional DSM Plan, SAEs and UAPs are reported to the DSMC,

IRB and the sponsor investigator per protocol. All SAEs and UAPs are to be reported to the DSMC within 7 (for fatal or life-threatening events) or 15 (non-life-threatening events) calendar days of the sponsor investigator receiving notification of the occurrence.

Each subject's treatment outcomes will be discussed by the site PI and appropriate staff at regularly scheduled meetings. Data regarding number of subjects, significant toxicities, dose modifications, and treatment responses will be discussed.

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

10.6.2 Quality Control and Quality Assurance

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

Site monitoring visits will be performed by the CU Cancer Center Clinical Monitor on a regular basis, pursuant to the Clinical Monitoring Plan (CMP), incorporated herein by reference. The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of the monitoring reports. During these visits, information recorded on the CRFs will be verified against source documents. Additional computer programs that identify selected protocol deviations, out-of-range data, and other data errors within the electronic data entry may also be used to help monitor the study. As necessary, requests for data clarification or correction will be sent to the PI.

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

10.7 Institutional Review Board

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

11.0 REFERENCES

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12.0 APPENDICES

12.1 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

12.2 Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

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

RECIST version 1.1* will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

* As published in the European Journal of Cancer:

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

12.4 Immune Response modification to Response Evaluation Criteria in Solid Tumors (irRECIST) for Evaluating Response in Solid Tumors

irRECIST* will also be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per irRECIST, CT is the preferred imaging technique in this study.

* As published in Clinical Cancer Research:

Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Can Res 2009;15:7412−20.

- Unidimensional measurements (longest diameter) have been shown to have less variability.
- PD thresholds for irRECIST and RECIST are aligned, allowing for comparisons to be made between trials and to historical data

12.4.1 Baseline Assessment Using irRECIST

Step 1. Identify the index target lesions (unidimensional, >/= 10mm, five lesions total, two lesions per organ).

Step 2. Add the sum of all target lesions.

12.4.2 Post-Baseline Assessments Using irRECIST

Step 1. Identify the index target lesions.

Step 2. Add the sum of all target lesions. New lesions are incorporated in the total tumor burden measurement.

Step 3. Assess response per criteria in table below.

Step 4. Wait up to 12 weeks to confirm PD to account for flare.

	Response Criterion
Immune-mediated complete response (irCR)	Complete disappearance of all lesions (whether measurable or not, and no new lesions).
Immune-mediated partial response (irPR)	Decrease in tumor burden ≥ 30% relative to baseline.
Immune-mediated stable disease (irSD)	Criteria for irCR, irPR, and irPD are not met; does not require confirmation.
Immune-mediated progressive disease (irPD)	Increase in tumor burden ≥ 20% relative to nadir (minimum 5 mm) confirmed by a consecutive assessment ≥ 12 weeks from the date first documented.

COMIRB
APPROVED
For Use
09-Nov-2019
09-Jul-2020

Principal Investigator:	**Elaine Lam, MD**
COMIRB No:	**16-2300**
Version Date:	**July 17, 2019**
Study Title:	Phase I/II Study of Pembrolizumab and Cabozantinib in Patients with Metastatic Renal Cell Carcinoma

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You are being asked to be in a research study. This form provides you with information about the study. A member of the research team will describe this study to you and answer all of your questions. Please read the information below and ask questions about anything you don't understand before deciding whether or not to take part.

Why is this study being done?

This study plans to learn more about a combination of drugs called pembrolizumab and cabozantinib, and how they work together to treat your type of cancer. Pembrolizumab works by stimulating the immune system to target the cancer cells. Cabozantinib blocks some of the ways that tumor cells grow and spread. Pembrolizumab is approved by the U.S. Food and Drug Administration (FDA) to treat other types of cancers. Cabozantinib is approved by the FDA to treat your type of cancer. This is considered an "investigational" study, which means that this combination of drugs has not been approved by the FDA.

You are being asked to be in this research study because you have been diagnosed with locally advanced, recurrent, or metastatic renal cell carcinoma.

Pembrolizumab and cabozantinib will be called "study drugs" when referenced together throughout the rest of this consent form.

Other people in this study

This study has two parts. The first part is a dose escalation, also called Phase I. The second part is an expansion, also called Phase II. The part of the study you are being asked to participate in will be described in the next section of this consent form.

Up to 46 people from your area will participate in the Phase II part of this study. Up to 55 people will participate in both parts of this study.

What happens if I join this study?

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

There are 2 parts to this study. If you decide to participate in this study, you will be in Part II:

Part II – Phase II
Expansion group (cohort) – In this part of the study, we are looking at how safe combination of study drugs is and how well they work together to treat your type of cancer.

By signing this consent form you will be taking part in Part II of this study, which has 3 sections:

- Before starting the study (Screening)
- During the study (Treatment)
- End of study (After treatment follow-up)

There are also optional parts of this study. These optional procedures are voluntary and are not required. You can still take part in the main study if you choose not to take part in the optional study procedures. You will be given the choice later in this consent form to decide if you would like to take part in these optional procedures.

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

Study Procedures:

Below are the study procedures and schedule of events (when each procedure will take place) for Part II of this study. Some procedures are the same as you would receive as standard of care treatment of your disease even if you did not take part in this trial. If you have had some of these procedures recently, they may not need to be repeated. Some procedures are required only for this research study and will be called “research” procedures.

The time points when these study procedures will take place are specified in the next section called “Study Visits”.

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

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

- **Physical Examination**
  A physical examination will be completed as part of your standard of care. We will also assess if the study drug is affecting your body functions including lungs, heart, abdomen, extremities, skin, head (eyes, ears, nose, hair, etc.) and neurologically.

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

- **Positron Emission Tomography (PET)/Computed Tomography (CT)**
  Computed tomography scans use x-rays to make detailed pictures of parts of the body and the structures inside the body. Positron emission tomography creates computerized pictures of organs and tissues in the body.

- **MRI**
  Magnetic resonance imaging is a test that uses a magnetic field and pulses of radio wave energy to make pictures of organs and structures inside the body.

- **Whole body bone scan**
  A bone scan is a nuclear imaging procedure. In nuclear imaging, tiny amounts of radioactive materials (tracers) are injected into a vein and are taken up in varying amounts at different sites in the body. Areas of the body where cells and tissues are repairing themselves most actively take up the largest amounts of tracer. Nuclear images highlight these areas, suggesting the presence of abnormalities associated with disease or injury. A bone scan includes both an injection and the actual scan.

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

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

- **Other Medications**
  Your study doctor will let you know which other medications you can and cannot take while taking part in this study. From the time you first receive the study drugs through 30 days after the last dose, we will record other medications you may be taking.

- **Review Adverse Events**
  Some risks have been identified because of the disease process or through use of the study drugs themselves and these will be followed very closely by the Principal Investigator and study staff. More information will be provided in the Risk area of this consent.

- **Tumor Biopsy – Optional**
  You will have the **option** later in this consent form to participate in two tumor biopsies. If you agree to participate in the **optional** biopsies, either a core biopsy or a punch biopsy will be taken from your tumor. A numbing medication will be applied to the area of the biopsy before the procedure. In a core biopsy, a hollow needle is inserted through the skin into the tumor. A small "core" of tissue is removed using the needle. Your doctor may use ultrasound or x-ray equipment to guide the needle to the correct position. In a punch biopsy, a small circular blade is rotated through the skin into the tumor. A small sample of tissue is removed using the blade. This procedure leaves a small wound that is closed with sutures.

Study Visits:

1. SCREENING

After you sign this consent form you will have the following done to see if you can be in this study:

- Review your medical and cancer history
- Physical exam
- Vital signs including height and weight
- ECOG performance status

- Blood tests:
  - Complete blood count (CBC) including types – white cells, red cells and platelets (differential)
  - Comprehensive serum chemistry panel
  - Thyroid tests (T3, FT4 and TSH)
  - Blood clotting (PT/INR and aPTT)
- Review of medications
- EKG – **research**
- Urine pregnancy test (women of childbearing potential only)
- Urinalysis
- Tumor imaging by PET/CT or MRI. This may include a whole-body bone scan.
- Archival tumor collection – **research**
- Tumor biopsy – **optional research procedure**

2. TREATMENT

During the Treatment portion of this study, you will receive the study drugs. The study drugs are given in "cycles". You will have a study visit at the beginning of each cycle. One cycle is 3 weeks long.

The following procedures will be done at every Treatment visit:

- Review of medications
- Review of adverse events
- Physical exam
- Vital signs including weight
- Performance status
- Urine pregnancy test (women of childbearing potential only)
- Blood draw, including:
  - CBC and differential
  - Comprehensive serum chemistry panel
- Urinalysis
- Receive study drugs – **research**

Cycle 1

- All the procedures in the group above
- Blood draw, including the tests above and:
  - Bone turnover markers (subjects with bone metastases only) - **research**

Cycle 2

- All the procedures in the group above
- Tumor biopsy – **optional research procedure**
- Blood draw, including the tests above and:
    - Bone turnover markers (subjects with bone metastases only) – **research**

Cycle 3

- All the procedures in the group above

Cycle 4

- All the procedures in the group above
- EKG – **research**
- Blood draw, including all the tests above and:
    - Thyroid tests (T3, FT4 and TSH)
    - Bone turnover markers (subjects with bone metastases only) – **research**
- Tumor imaging by PET/CT or MRI. This may include a whole-body bone scan.

Cycle 5

- All the procedures in the group above

Cycle 6

- All the procedures in the group above

Cycle 7

- All the procedures in the group above
- EKG – **research**
- Blood draw, including all the tests above and:
    - Thyroid tests (T3, FT4 and TSH)
    - Bone turnover markers (subjects with bone metastases only) – **research**
- Tumor imaging by CT or MRI. This may include a whole-body bone scan.

If you continue to receive study treatment beyond 7 cycles, Cycles 5-7 will be repeated.

3. AFTER TREATMENT FOLLOW-UP

After you stop receiving the study treatment, you will have a safety follow-up visit within 30 days. The following procedures will be done at this end-of-study visit:

- Review of medications
- Review of adverse events
- Review of any anticancer therapies you have taken or are taking after the study.
- Physical exam
- Vital signs including weight
- Performance and survival status
- EKG – **research**
- Blood draw, including:
    - CBC and differential
    - Comprehensive serum chemistry panel
    - Thyroid tests (T3, FT4 and TSH)
- Urinalysis

How long will I be on the study?

You may take part in this study for as long as you tolerate the study treatment and your disease is stable or improving. You may continue to receive treatment with the study drugs until your disease progresses or you have an unacceptable drug-related side effect.

If your study doctor feels that you are still receiving a clinical benefit from the study drugs when your disease progresses, you may be able to continue treatment with the study drugs. If this is an option for you, you will be given a separate consent form and an opportunity to ask questions.

What are the possible discomforts or risks?

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

You should talk to your study doctor about any side effects or discomfort you may have.

The study doctor may give you some medicine that will help with some side effects. The study doctor may also interrupt or discontinue the study drug.

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

Based on animal studies and/or other studies with similar types of drugs, side effects or discomforts you may experience while in this study include**:**

Risks of the Study Drugs

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

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

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

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

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

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

- Joint pain
- Rash
- Fever
- Back pain
- Pain in your belly
- Loss of skin color

- Not enough thyroid hormone so you may feel tired, gain weight, feel cold, have infrequent or hard stools
- Low level of salt in the blood that may cause you to feel tired, confused, have a headache, muscle cramps, or an upset stomach

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

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

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

- Inflammation of the nerves that may cause
  - Pain
  - Weakness or tingling in the hands and feet, and may spread to the legs, arms and upper body leading to severe muscle weakness and possible temporary paralysis
- Inflammation of the muscles so you may feel weak or have pain in the muscles, sometimes referred to as myasthenic syndrome
- Inflammation of the pancreas (a gland in your abdomen that controls sugar levels) so you may:
  - Have severe upper belly pain that may move to the back
  - Feel sick to your stomach
  - Have vomiting that gets worse when you eat

- Inflammation of the eye so you may have:
  - Redness
  - Blurred vision
  - Sensitivity to light
  - Eye pain
  - See floaters
  - Headaches
- Inflammation of the liver that may make you:
  - Feel sick to your stomach and vomit
  - Feel like not eating
  - Feel tired
  - Have a mild fever
  - Have pain in the right side of your belly
  - Have yellow eyes and skin
  - Have dark urine
- Inflammation of the pituitary gland (a gland in the head) which may cause you to:
  - Feel sick to your stomach or have headaches
  - Have changes in your behavior
  - Have Double vision
  - Have few to no menstrual cycles
  - Have Weakness
  - Vomit
  - Have Dizziness or fainting
- Adrenal glands (glands on top of the kidneys) that may not produce enough hormone which could cause:
  - Tiredness
  - Weight loss
  - Muscle weakness
  - Feeling faint
  - Joint, muscle, and belly aches
  - Nausea
  - Vomiting
  - Loose or watery stools
  - Fever
  - Salt craving
  - Darkening of the skin like a suntan
- Type 1 Diabetes, a condition that can cause too much sugar in the blood, which may make you:
  - Feel thirstier than usual
  - Frequently urinate

  - Lose weight
  - Need regular insulin shots
- Inflammation of the kidney, so you may:
  - Pass less urine
  - Have cloudy or bloody urine
  - Have swelling
  - Have low back pain
- Inflammation of the middle layer of your heart (myocarditis), that may cause your heart to have difficulty pumping blood throughout your body, which can cause:
  - Chest pain
  - Shortness of breath
  - Swelling of the legs
  - Fast or irregular heartbeat (that may cause dizziness or fainting)
  - **Death**
- Inflammation of the thyroid gland, an organ that makes and stores thyroid hormones. This condition may lead to change in your:
  - Heart rate
  - Blood pressure
  - Body temperature
  - Metabolism (the rate at which food is converted into energy)
- A condition that may make you feel weak and tired and might have drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, or difficulty breathing.
- The formation of small clusters of immune cells (called granulomas) in parts of your body such as your lymph nodes, eyes, skin, or lungs.
- Inflammation of the brain with confusion and fever, which may also include:
  - Disorientation
  - Memory problems
  - Seizures (fits)
  - Changes in personality and behavior
  - Difficulty speaking
  - Weakness or loss of movement in some parts of your body
  - Loss of consciousness

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

- Inflammation of the joints which may include joint pain, stiffness and/or swelling.

- Severe responses of the immune system that cause the body to attack its own blood cells, spleen, liver, lymph nodes, skin and brain. This may include fever, rash, inflammation of the liver, yellowing of the skin, an enlarged liver and spleen, low blood counts, and enlarged lymph nodes. The nervous system may also be affected and cause confusion, seizures, and even coma.

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

Cabozantinib

Common side effects (in more than 20 out of 100 people)

- Diarrhea
- Nausea
- Vomiting
- Stomach pain and inflammation
- Constipation
- Abdominal pain
- Fatigue
- Decreased appetite
- Hand-foot syndrome (redness, swelling, and pain on the palms and soles of the feet)
- Rash – you should report any unusual rash to your study doctor immediately
- High blood pressure
- Weight loss
- Changes in taste
- Hypothyroidism

Less common side effects (in 5 to 20 out of 100 people)

- Upset stomach
- Inflammation of the mouth and esophagus, which may make it painful or difficult to eat and drink
- Loss of energy
- Dry skin
- Headache
- Dizziness
- Difficulty breathing

- Cough
- Low red blood cell count (anemia), which may make you feel tired, weak, or short of breath
- Changes in hearing
- Pain in your hands, feet, arms, or legs
- Muscle spasms
- Joint pain
- High levels of protein in your urine

Rare, but serious side effects (in fewer than 5 out of 100 people)

- Severe bleeding (hemorrhage), which can be life-threatening
- Development of holes in the stomach or intestines, which can be life-threatening
- Blood clots
- Severe high blood pressure, which can lead to stroke
- A syndrome called Reversible Posterior Leukoencephalopathy Syndrome, which includes symptoms of headache, confusion, seizures, and loss of vision.

Hypoglycemia (low blood sugar) has been reported in drugs similar to cabozantinib occurring in 5-20 out of 100 people. This side effect is more commonly seen in patients with diabetes who are on insulin therapy. This side effect has occurred in one participant at our site and could possibly be related to cabozantinib.

These drugs are being studied in combination, which means there is potential for increased frequency or higher severity of certain side effects.

Risks of the Study Procedures

Risks of Having an IV Inserted in Your Vein

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

Risks of Having Blood Taken

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

Risks of Biopsy

In this study, if you agree to participate in the optional biopsy procedures, we will take 1 or 2 biopsies from you. There are some risks to taking a biopsy. There is a small chance that you could get an infection where the needle goes in. You may also experience redness, swelling, minor bleeding or bruising at the site where the cut was made or the needle inserted. You may experience mild to moderate pain at the site of the needle puncture. There is also a small chance that you could have an allergic reaction to the numbing medicine. After your skin heals up, you may have a small scar where we take the samples. If an X-ray is used to help place the needle, you will be exposed to additional radiation. The amount of radiation you receive during each biopsy procedure is approximately equal to the radiation you would receive in about 4 years in your normal environment.

The core biopsy procedure has some additional risks, depending on where your tumor is located. If you have a biopsy of a solid organ, like your liver or a kidney, or of a lymph node, there is a risk of pain, bleeding, and infection. There is a risk of damage to nearby structures or organs, and a small risk of tract seeding (spreading cancer along the tract that is created by the needle during the biopsy). There is a risk of injury due to positioning of the needle, and a small risk of heart or lung problems. If you have a lung biopsy, there is a risk of air getting into the space around your lung that would require a tube to be placed in between your ribs to draw the air out. If this tube is placed, some additional risks include damage to other nearby structures, including the lung, a prolonged air leak, and a possible need for additional tubes or procedures. There is a small risk of death from complications of a biopsy.

Risks of having an EKG

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

Risks of Magnetic Resonance Imaging (MRI)

In this study we may take an MRI of your chest, abdomen, and pelvis, The MRI machine uses powerful magnetic waves to take pictures inside the body. The

waves themselves are not harmful, but they can cause metal to heat up and electronics to stop working.

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

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

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

<u>Risks of Positron Emission Tomography (PET)/Computed Tomography (CT)</u>

As part of this study we may perform a PET/CT scan of your chest, abdomen, and pelvis (CAP). PET is a way of taking pictures of your body using tracers that are radioactive. The actual scanning done by PET is a form of radiation. CT is also a way of taking detailed pictures inside your body by using X-rays. X-rays are a type of radiation.

You get some radiation from your environment. You get radiation from bricks and concrete, from some foods, and from radon gas, which is an invisible gas that seeps out of the ground. The amount of radiation that PET/CT scans will deliver to your body (give you) is about the same as you would get from living in your environment for 5 years.

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

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

<u>Risks of Bone Scan</u>

If your cancer has spread to your bones, we will perform a bone scan of your whole body. A bone scan is a way of seeing if there are any problems with the way your bones are growing.

To do the bone scan we will need to inject a radioactive tracer into your blood stream. You will get some radiation from this tracer.

Your natural environment has some radiation in it. It comes from the outer space, from soil, rocks, bricks and concrete, from some foods, and from radon gas, which is an invisible gas that seeps out of the ground. The amount of radiation that this procedure will give you is about the same as you would get from your environment in 1 year.

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

Risks Associated with Pregnancy

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

Women who are able to get pregnant must use effective birth control while taking pembrolizumab and for at least 4 months after the last dose of pembrolizumab.

Before you begin study treatment, your doctor will discuss acceptable forms of birth control with you.

Risk of Loss of Confidentiality

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

The study may include risks that are unknown at this time.

What are the possible benefits of the study?

This study is designed for the researcher to learn more about the effects of the study drugs on your disease. However, there is no guarantee that your health will improve if you join this study. Also, there could be risks to being in this study. If there are risks, these are described in the section describing the discomforts or risks.

Are there alternative treatments?

There may be other ways of treating your cancer. Instead of taking part in this study:

- You may choose to receive treatment with another experimental therapy.
- You may choose to receive treatment with another approved therapy.
- You may choose to receive comfort/palliative care.
- You could also choose to get no treatment at all.

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

Who is paying for this study?

Merck & Co, Inc. is providing a grant of funding support for this study. Merck manufactures the study drug Pembrolizumab and will provide this drug for the study. This research is being conducted by Dr. Elaine Lam. The research study will only pay for procedures not considered standard of care.

Will I be paid for being in the study?

You will not be paid to be in the study.

Will I have to pay for anything?

The drug manufacturer, Merck, will pay for the cost of the study drug Pembrolizumab. The funding for this study will also pay for any tests or procedures that are related to the research study, including the optional tumor biopsies.

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

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

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

Is my participation voluntary?

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

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

If there are any new findings during the study that may affect whether you want to continue to take part, you will be told about them.

Can I be removed from this study?

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

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

If you have an injury while you are in this study, you should immediately call the study doctor at your hospital:

- University of Colorado Hospital, Dr. Elaine Lam. Her phone number is (720) 848-0170.

- Poudre Valley Health System (UCHealth North), Dr. Steven Schuster. His number is (970) 493-6337. This number is answered 24 hours a day.
- UCHealth Memorial Hospital (UCHealth South), Dr. Geetika Srivastava. Her phone number is (719) 365-6568. This number is answered 24 hours a day.

We will arrange to get you medical care if you have an injury that is caused by this research. However, you or your insurance company will have to pay for that care.

Who do I call if I have questions?

The primary researcher carrying out this study is Dr. Lam. However, Dr. Schuster is the lead site researcher carrying out this study at Poudre Valley Health System (UCHealth North), and Dr. Srivastava is the lead site researcher carrying out the study at Memorial Hospital (UCHealth South). You may ask any questions you have now.

If you have questions, concerns, or complaints later, you may call Dr. Lam at 720-848-0170, Dr. Schuster at (970) 493-6337, or Dr. Srivastava at (719) 365-6568.

You will be given a copy of this form to keep.

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

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

Optional Study Procedures

These are the optional parts of this study. **Remember, no matter what you decide to do about these optional parts of the study, you may still take part in the main study.** If you decide to withdraw your consent for the optional parts, you can continue to take part in the main study, unless you withdraw your consent for the main study as well.

Following each optional procedure is a statement asking if you want to participate in the optional procedure. Please read the statement and think about your choice. After reading the sentence, please check “Yes” or “No” and initial next to your choice. If you have any questions, please talk to your doctor or nurse.

1. Optional Consent for Baseline Tumor Biopsy
   As part of this study, you are being asked if you would like to participate in **optional** tumor biopsies. If you have a tumor from which a core or punch biopsy can be obtained and you agree to this procedure, a small sample of your tumor tissue will be taken before you begin study treatment. This tumor tissue will be used for research on the study drugs and how they impact tumor cells. If you agree to this procedure, you will be given a separate hospital consent form to review and sign before having the biopsy.

   I give my permission for a biopsy of my tumor to be taken before I begin study treatment.

   ☐ Yes ☐ No ☐ N/A (re-consenting – my previous selection has not changed)

   _____Initials

2. Optional Consent for Treatment Tumor Biopsy
   As part of this study, you are being asked if you would like to participate in **optional** tumor biopsies. If you have a tumor from which a core or punch biopsy can be obtained and you agree to this procedure, a small sample of your tumor tissue will be taken approximately 3-6 weeks after you begin study treatment, during Cycle 2. This tumor tissue will be used for research on the study drugs and how they impact tumor cells. If you agree to this procedure, you will be given a separate hospital consent form to review and sign before having the biopsy.

   I give my permission for a biopsy of my tumor to be taken during Cycle 2 of the study treatment.

   ☐ Yes ☐ No ☐ N/A (re-consenting – my previous selection has not changed)

   _____Initials

Who will see my research information?

The University of Colorado Denver (UCD) and its affiliated hospital(s) have rules to protect information about you. Federal and state laws including the Health Insurance Portability and Accountability Act (HIPAA) also protect your privacy. This part of the

consent form tells you what information about you may be collected in this study and who might see or use it.

The institutions involved in this study include:

- University of Colorado Denver
- University of Colorado Hospital
- Poudre Valley Health System (UCHealth North)
- UCHealth Memorial Hospital (UCHealth South)

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

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

We will do everything we can to maintain the confidentiality of your personal information but confidentiality cannot be guaranteed.

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

Elaine Lam, MD
University of Colorado Denver
Anschutz Medical Campus
12801 East 17th Avenue
Mail Stop 8117
Aurora, CO 80045

Steven Schuster, MD
Poudre Valley Hospital
2121 E. Harmony Road
Suite 170
Fort Collins, CO 80528

Geetika Srivastava, MD

UCHealth Memorial Hospital
525 Bob Peters Grove
Colorado Springs, CO 80909

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

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

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

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

The investigator (or staff acting on behalf of the investigator) will use your information for the research outlined in this consent form. They will also make some of the following health information about you collected in this study available to: QualTek Molecular Laboratories, a lab company performing some of the tumor testing.

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

- Name and demographic information (age, sex, ethnicity, address, phone number, etc.
- Portions of your previous and current medical records that are relevant to this study, including but not limited to diagnoses, history and physical, laboratory or tissue studies, radiology studies, procedure results.
- Research visit and research test records.
- Tissue samples and the data with the samples.

What happens to data, tissue, blood and specimens that are collected in this study?

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

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

HIPAA Authorization for Optional Additional Study Procedures

In this form, you were given the option to agree to additional, optional research procedures. You must also give us your permission, under HIPAA rules, to use and disclose the information collected from these optional procedures, as described above.

If you decline to give us permission to use and disclose your information, you cannot take part in these optional procedures, but you can still participate in the main study. Please initial next to your choice:

_____ I give permission for my information, from the optional procedures I have agreed to above, to be used and disclosed as described in this section.

_____ I **do not** give permission for my information for any optional procedures to be used and disclosed; I understand that I will not participate in any optional procedures.

[SIGNATURES ON NEXT PAGE]

Agreement to be in this study and use my data

I have read this paper about the study or it was read to me. I understand the possible risks and benefits of this study. I understand and authorize the access, use and disclosure of my information as stated in this form. I know that being in this study is voluntary. I choose to be in this study: I will get a signed and dated copy of this consent form.

Signature: _____ Date: _____

Print Name: _____

Consent form explained by: _____ Date: _____

Print Name: _____

A signature line for a witness is required for consent of non-reading subjects and consent using a short form.

Witness Signature: _____ Date: _____

Witness Print Name: _____

Witness of Signature

Witness of consent process