UCSF Helen Diller Family Comprehensive Cancer Center

A Phase II Study of Perioperative Pembrolizumab-Based Therapy in Patients with Locally Advanced or Metastatic Renal Cell Carcinoma Prior to Cytoreductive Nephrectomy or Metastasectomy

Protocol Number: CC #197017

Merck Protocol Number: 3475-800

Study Drugs: Pembrolizumab, Axitinib, TBD

Version Number: 1.9
Version Date: 01/30/2024

IND Number: 144040

Principal Investigator (Sponsor-Investigator)
David Oh, MD, PhD
University of California San Francisco
Helen Diller Family Comprehensive Cancer Center
[redacted]

Statistician
Li Zhang, PhD

Revision History

Version 1.9	Dated 01/30/2024
Version 1.8	Dated 02/23/2023
Version 1.7	Dated 06/08/2022
Version 1.6	Dated 01/13/2022
Version 1.5	Dated 03/18/2021
Version 1.4	Dated 12/07/2020
Version 1.3	Dated 07/15/2020
Version 1.2	Dated 01/02/2020
Version 1.1	Dated 07/03/2019
Version 1.0	Dated 03/14/2017

Protocol Signature Page

1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Institutional Review Board (IRB), and Data Safety Monitoring Committee (DSMC).

2. I will conduct the study per applicable IRB requirements, Federal regulations, and state and local laws to maintain the protection of the rights and welfare of study subjects.

3. I certify that I, and the study staff, have received the requisite training to conduct this research protocol.

4. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I agree to conduct the protocol per Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), and with local regulatory requirements. Per the FDA Modernization Act, I will ensure the registration of the trial on the www.clinicaltrials.gov website.

5. I agree to keep adequate and accurate records per IRB policies, Federal, state, and local laws and regulations.

UCSF Principal Investigator / Study Chair

_____

Printed Name

_____ _____

Signature Date

Abstract

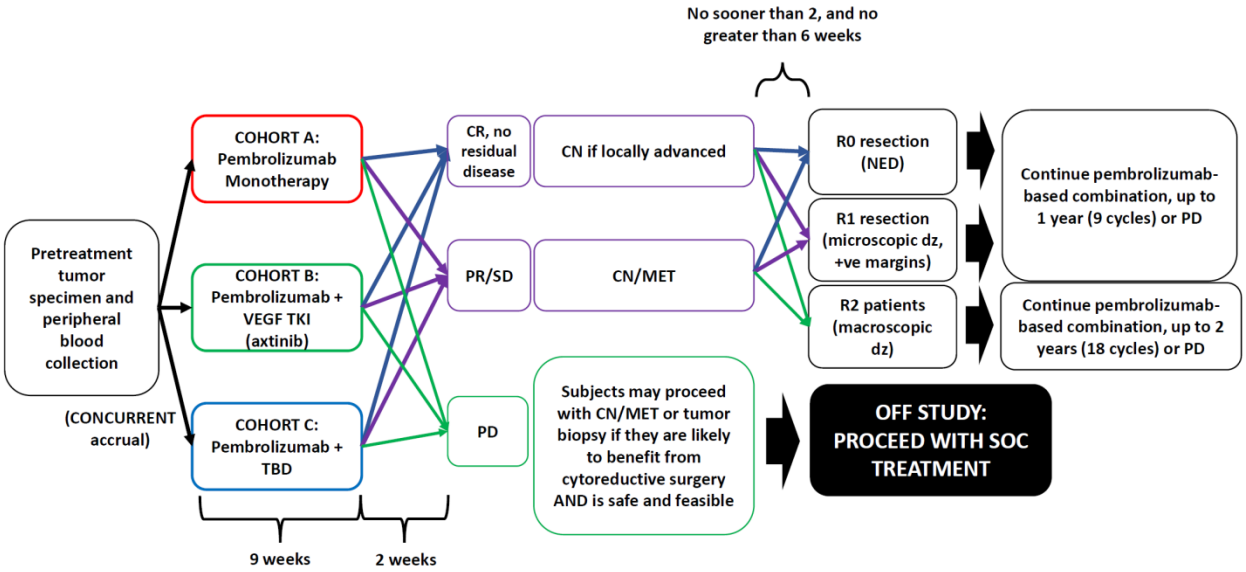
Title	A Phase II Study of Perioperative Pembrolizumab-Based Combination Therapy in Patients with Locally Advanced or Metastatic Renal Cell Carcinoma Prior to Cytoreductive Nephrectomy or Metastasectomy
Patient population	• Treatment-naïve • Locally advanced or metastatic renal cell carcinoma (RCC; clear cell component) • Planned cytoreductive nephrectomy (CN) and/or metastasectomy (MET)
Rationale for Study	Recent studies show that combining anti-programmed cell death 1 (PD-1) with other targeted therapies increase response rates compared to checkpoint inhibitor monotherapy. However, the mechanisms of response and resistance to PD-1/programmed cell death ligand 1 (PD-L1)-based combination therapies remain unclear.
Primary Objective	• To determine the impact of pembrolizumab-based combination therapy on the composition, phenotype, and function of tumor-infiltrating immune cells (TIICs) in subjects with advanced RCC undergoing CN/MET.
Secondary and Correlative Objectives	Secondary • To determine the clinical efficacy of preoperative pembrolizumab-based combination therapy in subjects with advanced RCC undergoing CN/MET • To explore the clinical efficacy of continued pembrolizumab-based therapy following CN/MET in subjects with advanced RCC ○ Subjects who achieve a complete response (CR) prior to or following CN/MET, a partial response (PR), or stable disease (SD) will receive continued pembrolizumab-based combination therapy up to 1-2 years (9-18 cycles) depending on their resection status • To determine the safety and tolerability of pembrolizumab-based combination therapy in subjects with advanced RCC undergoing CN/MET Correlative • To explore the relationship between changes in TIICs and clinical efficacy in subjects with advanced RCC treated with pembrolizumab-based combination therapy • To characterize changes in the frequency and number of circulating T cells induced by pembrolizumab-based combination therapy in subjects with advanced RCC • To determine the impact of pembrolizumab-based combination therapy on the composition and phenotype of the tumor microenvironment

	(including tumor and stromal cells) in subjects with advanced RCC • To determine whether locally advanced versus metastatic RCC exhibit differences in immune composition or phenotype at baseline and in response to pembrolizumab-based therapy • To determine the change in T cell repertoire within the tumor and blood induced by pembrolizumab-based combination therapy in subjects with advanced RCC • To explore molecular profiles to identify potentially predictive biomarkers for subjects with advanced RCC treated with immunotherapy
Study Design	• Prospective, phase II • Single center • Open label • Multi-cohort study, with concurrent enrollment (nonrandomized) ○ Cohort A: Pembrolizumab monotherapy ○ Cohort B: Pembrolizumab + axitinib ○ Cohort C: Pembrolizumab + TBD (agent to be determined) • Additional cohorts may be added after discussion with Study Steering Committee and mutual agreement between the Principal Investigator (PI)/Sponsor and Merck; see schema below.
Number of subjects	Up to 84 subjects in total will be enrolled. Up to twelve subjects will be enrolled into the pembrolizumab monotherapy cohort (Cohort A). The first 6 subjects accrued to Cohort A will be evaluated in a safety lead-in for the safety of pembrolizumab prior to planned CN/MET. Once 6 subjects are enrolled in Cohort A, the pembrolizumab-based combination cohorts will open to concurrent enrollment. A minimum of 4 and a maximum of 36 subjects may be enrolled into each pembrolizumab-based combination cohort.
Duration of Therapy	PREoperative therapy: 3 cycles (9 weeks; see study schema below) CN/MET: • Surgery will occur 2 weeks following completion of the preoperative treatment period • Subjects with locally advanced disease who achieve radiographic CR during the preoperative treatment period will proceed with CN followed by postoperative therapy as described below. POST-operative therapy:

	• Subjects will begin postoperative therapy no sooner than 3 weeks and no later than 6 weeks following CN/MET, to allow for postoperative recovery (adequate wound healing and recovery from any postoperative complications, as determined by the treating surgeon). • Subjects who achieve R0 resection (NED, negative margins) or R1 resection (microscopic disease, positive margins) after preoperative treatment will receive continued pembrolizumab-based combination therapy for up to 9 cycles following CN/MET, or until disease progression, death, unacceptable toxicity, or withdrawal from study, whichever occurs first. • Subjects who achieve R2 resection (macroscopic disease after surgery) after preoperative treatment, or who do not undergo nephrectomy after achieving pre-operative radiographic CR, will receive continued pembrolizumab-based combination therapy for up to 18 cycles following CN/MET, or until disease progression, death, unacceptable toxicity, or withdrawal from study, whichever occurs first. Subjects with progressive disease (PD) during preoperative therapy: Subjects may still undergo CN/MET under study if the study investigator and treating physician determine that the subject will benefit from cytoreductive surgery. Subjects unlikely to benefit from CN/MET, or in whom CN/MET is not feasible due to PD or safety reasons, will be required to provide a tumor biopsy, unless deemed unsafe or delays appropriate standard of care. These subjects will discontinue study participation after CN/MET or tumor biopsy. Subjects in whom cytoreductive surgery or tumor biopsy is not feasible or safe, or will lead to delay in standard of care, will discontinue study participation immediately. Subjects with PR/SD who cannot undergo CN/MET for any reason following therapy: In rare cases, subjects who were deemed eligible for CN/MET prior to study participation and have PR/SD after preoperative therapy may not be able to undergo CN/MET (for example, due to adverse events). These subjects will be required to provide a tumor biopsy, unless deemed unsafe or delays appropriate standard of care. Subjects may continue study treatment until disease progression, death, unacceptable toxicity, or withdrawal from study. Subjects in whom tumor biopsy is not collected will not be evaluable for the primary endpoint.

Duration of Follow up	Subjects with R0 or R1 resection who complete 9 cycles of either pembrolizumab monotherapy or pembrolizumab combination therapy, or subjects with R2 resection who complete 18 cycles of either pembrolizumab monotherapy or pembrolizumab combination therapy, will be followed for up to 1 year, or until disease progression, death, or withdrawal from study, whichever occurs first. Subjects who discontinue study participation due to PD will return for the mandatory Safety Follow-up visit 30 days (+7 days) after the final study treatment. All adverse events (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 anticancer therapy, whichever occurs first. Serious AEs that occur within 90 days of the end of treatment should also be followed and recorded.
Duration of study	Each cohort is expected to reach primary completion 36 months after opening to accrual.
Study Drugs	Pembrolizumab (Investigational, intravenous [IV]; all cohorts) Axitinib (Standard of care, by mouth [PO]; Cohort B) Additional study drugs for Cohort C and each subsequent cohort may be added at a later time.
Safety Assessments	Safety assessments will include AEs (including AEs related to surgery) and clinical laboratory evaluations.
Efficacy Assessments	Clinical efficacy assessments: • Objective response rate • Rate of R0 resection • Disease/Progression-free survival (DFS/PFS; rate at 1-year and 2-years, and median)
Unique Aspects of this Study	The perioperative approach proposed in this study provides a unique opportunity to evaluate the *in vivo* immunologic impact of pembrolizumab-based therapy in subjects with advanced RCC. Paired tissue collection (pre- and post-treatment) enables rich scientific correlatives.

Study Schema



- Patient population: Treatment-naïve, advanced (locally advanced or metastatic) RCC subjects, with clear cell component on histology, who have planned CN and/or MET surgery.
- Preoperative treatment: 3 cycles (9 weeks); each cycle is 21 days in duration.
  - Cohort A: Each cycle consists of pembrolizumab monotherapy (200 mg Q3W) given on Day 1 of each cycle. Total duration of therapy: 9 weeks.
  - Cohort B: Each cycle consists of pembrolizumab (200 mg Q3W) given on Day 1 of each cycle, and axitinib (5 mg PO twice daily [BID]) taken on days 1-21. Axitinib dose may be titrated per standard of care (SOC) after first 3 weeks. Total duration of therapy: 9 weeks.
  - Cohort C: To be decided later after consideration by the Study Steering Committee, Sponsor, and Merck.
- There will be a 2-week break after preoperative therapy, prior to CN and/or MET.
- For subjects experiencing unequivocal disease progression during the preoperative treatment period in whom CN/MET is unlikely to provide clinical benefit, core biopsies may be performed prior to the subject discontinuing study participation, if in the judgment of the treating physician, the biopsy would not delay appropriate standard of care and is safe and feasible.
- Subjects will begin postoperative therapy no sooner than 3 weeks and no later than 6 weeks following CN/MET.
- Subjects who achieve R0 resection (NED, negative margins) or R1 resection (microscopic disease, positive margins) after preoperative treatment will receive continued pembrolizumab-based combination therapy (42-day cycles) for up to 9 cycles following CN/MET.
- Subjects who achieve R2 resection (macroscopic disease after surgery) after preoperative treatment, or who do not undergo nephrectomy after achieving pre-operative radiographic

CR, will receive continued pembrolizumab-based combination therapy (42-day cycles) for up to 18 cycles following CN/MET.

List of Abbreviations

AE	adverse event
ACE	angiotensin-converting-enzyme
ADL	activities of daily living
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APaT	All Patients as Treated
AST	aspartate aminotransferase
BCG	Bacillus Calmette–Guérin
BID	Twice daily
BUN	blood urea nitrogen
CBC	complete blood cell (count)
CD	Cluster of differentiation
CN	Cytoreductive nephrectomy
CR	complete response
CRF	case report form
CT	computed tomography
CTCEA	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CTMS	Clinical Trial Management System
DFS	disease-free survival
DILI	drug induced liver injury
DLT	Dose-limiting toxicity
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECOG	Eastern Cooperative Oncology Group
ERC	Ethics Review Committee
FACS	fluorescence-activated cell sorting
FDA	United States Food and Drug Administration

List of Abbreviations

FNA	Fine needle aspirate
FSH	Follicle stimulating hormone
FT4	Free thyroxine
GCP	Good Clinical Practice
GEP	Gene expression profile
GI	Gastrointestinal
HCV	hepatitis C virus
HDFCCC	Helen Diller Family Comprehensive Cancer Center
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonization
Ig	immunoglobulin
IHC	immunohistochemistry
IND	investigational new drug application
IRB	Institutional Review Board
IV	Intravenous(ly)
KN	KEYNOTE
LD	Longest diameter
LDH	lactate dehydrogenase
mAb	Monoclonal antibody
MET	metastasectomy
mRCC	Metastatic renal cell carcinoma
MRI	magnetic resonance imaging
MSI	microsatellite instability
mTOR	Mammalian target of rapamycin
NCI	National Cancer Institute

List of Abbreviations

NSAE	Non-serious adverse event
NSCLC	Non-small cell lung cancer
ORR	objective response rate
OS	Overall survival
PBMC	peripheral blood mononuclear cell
PBPK	Physiologically based pharmacokinetics
PD	disease progression
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PFS	Progression-free survival
PI	Principal investigator
PK	Pharmacokinetic(s)
PO	*Per os* (by mouth, orally)
PR	partial response
PRC	Protocol Review Committee (UCSF)
PTT	partial thromboplastin time
q3 months	Every 3 months
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q6W	Every 6 weeks
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RTK(I)	receptor tyrosine kinase (inhibitor)
SAE	Serious adverse event
SD	Stable disease
T3	triiodothyronine

List of Abbreviations

TCR	T-cell receptor
TIICs	Tumor-infiltrating immune cells
TKI	Tyrosine kinase inhibitor
TSH	Thyroid stimulating hormone
ULN	upper limit of normal
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
WBC	white blood cell
WES	whole genome sequencing

Table of Contents

List of Tables

1 Introduction

1.1 Background on Indication

It is estimated that there are more than 60,000 new cases of kidney cancer and over 14,000 deaths due to kidney cancer in the US each year[1], with the majority of cases being renal cell carcinoma (RCC). Tyrosine kinase inhibitors (TKIs) and allosteric mammalian target of rapamycin (mTOR) inhibitors have been the standard of care for subjects with advanced RCC for the past decade. Approved agents for advanced RCC in this class include axitinib in the second-line setting, which showed a progression free survival (PFS) benefit versus sorafenib in a randomized phase III trial [2], lenvatinib in combination with everolimus after one prior line of anti-angiogenic therapy, which demonstrated PFS and overall survival (OS) benefit over everolimus alone in an open-label phase II study [3], and more recently cabozantinib both after at least one line of anti-antiangiogenic therapy, where it showed an OS benefit over everolimus [4], and also in the first line, where it showed a PFS benefit versus sunitinib for intermediate- and poor-risk disease [5]. Unfortunately, approximately 20% of subjects never experience clinically significant benefit, and treatment-related resistance eventually emerges in the remainder of subjects [2-4]. Median overall survival (OS) for subjects with metastatic RCC (mRCC) is estimated to be approximately 22 months [5] in the TKI era.

More recently, checkpoint inhibitors have become standard of care treatments in this disease. Immunotherapy has long demonstrated its role in the treatment of RCC, including the experience with high-dose interleukin-2 (IL-2) [6]. The current era of immunotherapy with programmed cell death 1 (PD-1) and PD-1 ligand 1 (PD-L1) directed antibodies promises even greater rewards. Nivolumab (Opdivo®, Bristol Myers Squibb) received regulatory approval in the second line-setting in 2015, demonstrating survival benefit compared to everolimus in subjects who are refractory to previous TKI therapy in the CheckMate 025 study [[7]. Pembrolizumab as monotherapy has also demonstrated activity for previously untreated, advanced clear cell RCC; however, with a confirmed objective response rate of 34% [12], this is a population of patients in whom further therapeutic advances can be made.

Combination approaches using checkpoint inhibition as the backbone may hold the key to capturing a greater number of responders, resulting in a greater clinical impact. The combination of ipilimumab added to nivolumab received regulatory approval in 2018 for the first-line treatment of intermediate to poor risk [5] metastatic clear cell RCC. The CheckMate 214 study of nivolumab plus ipilimumab (3 mg/kg and 1 mg/kg, respectively) vs sunitinib was positive for its co-primary end points of objective response rate (42% vs 27%, p<0.0001), PFS (median 11.6 vs 8.4 mo., HR 0.82, p=0.0331), and OS (median NR vs 26 mo., HR 0.63, p<0.0001); in addition, 9% of patients receiving the combination achieved a complete response [13]. IMmotion151 (NCT02420821), a phase III study of atezolizumab plus bevacizumab vs sunitinib also reported positive results, with the combination therapy improving PFS in PD-L1+ subjects with metastatic, untreated ccRCC (median 11.2 vs 7.7mo, HR 0.74, p=0.02)[8]. More recently, combinations of VEGFR TKIs with checkpoint inhibitors have been tested. These involve the TKI axitinib with the anti-PD-L1 antibody avelumab or the anti-PD-1 antibody pembrolizumab, which showed promising response rates (55 and 73%, respectively) in phase Ib trials [15, 16]. These combinations have now been approved in the front-line RCC setting based on phase III trials. For the avelumab/axitinib combination, this was based on data which demonstrated improved ORR (51.4% vs 25.7%) and PFS (13.8 vs 8.4 mos., HR 0.61, p<0.001) with the combination compared to sunitinib [17]; the pembrolizumab/axitinib approval was based on data showing that the combination achieved an

ORR of 59.3% versus 35.7% and HR for overall survival of 0.53 versus sunitinib [18], as will be described in greater detail below. There are multiple, additional, ongoing phase III studies of immunotherapy-based combination approaches, including: pembrolizumab plus lenvatinib versus lenvatinib plus everolimus versus sunitinib (NCT02811861); and cabozantinib plus nivolumab versus sunitinib (NCT03141177).

To develop the most promising combinations, we must first understand the mechanistic underpinnings for response and resistance to immunotherapy-based combinations, which is currently lacking. Thus, we propose a perioperative study of pembrolizumab-based combination approaches in subjects with advanced RCC. Pre- and post-treatment tissue will be collected in all subjects to interrogate the in vivo immunologic impact of these treatments.

1.2 Background on the Compounds

1.2.1 Pembrolizumab

Pembrolizumab is a potent humanized IgG4 monoclonal antibody (mAb) with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. KEYTRUDA® (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the IB.

1.2.1.1 Pharmaceutical and Therapeutic Background on Pembrolizumab

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [9]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of cluster of differentiation 8 positive (CD8+) T cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T cells (Tregs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and RCC. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [10, 11].

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 cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [12, 13].

The structure of murine PD-1 has been resolved [14]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV type) domain responsible for ligand binding and a cytoplasmic tail 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, and an immunoreceptor tyrosine-based switch motif. Following T cell

stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T cell signaling cascade [13, 15-17]. The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [18, 19]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in RCC.

1.2.1.2 Preclinical and Clinical Trial Data

Refer to the IB for detailed Preclinical and Clinical data.

Clinical Trials Testing Pembrolizumab in Renal Cell Carcinoma

There are multiple clinical trials investigating pembrolizumab in the treatment of advanced RCC. These include results with pembrolizumab monotherapy described above [12], as well as the combination of pembrolizumab with axitinib, which will be described in further detail below [18]. The BTCRC-GU14-003 study is a phase Ib trial of pembrolizumab in combination with bevacizumab in advanced RCC. There are phase III studies comparing the efficacy of pembrolizumab-based combination therapies (pembrolizumab and axitinib; pembrolizumab and lenvatinib) vs sunitinib that are ongoing.

1.2.2 Axitinib

Axitinib is a TKI that potently targets the vascular endothelial growth factor (VEGF) receptors (as well as platelet-derived growth factor (PDGF) receptors and KIT) [20]. In a phase III study in patients with advanced RCC refractory to first-line therapy, axitinib demonstrated superior progression-free survival (PFS) compared to sorafenib, leading to regulatory approval in this indication around the world [21]. One of the novel aspects of axitinib compared to other TKIs that was demonstrated in this study was the ability to titrate dose individually, including dose escalation. Patients started on a dose of 5 mg by mouth (PO) twice daily (BID); in patients with well controlled blood pressure and without Grade >2 adverse events (AEs), dose increases up to 7 mg and 10 mg PO BID were allowed.

Axitinib has been studied in the first-line setting for patients with advanced RCC [22]. In an international, randomized phase II trial, patients with treatment-naïve advanced RCC were treated with axitinib at the standard initial dosing of 5 mg BID during a 4-week lead-in period. Those without Grade 3/4 AEs and well controlled blood pressure were then randomized to either masked dose titration (to 7 mg BID, and then 10 mg BID if tolerated) or placebo dose titration. One hundred twelve patients were randomized (1:1). The ORR in the dosed titration group was 54%, vs 34% in the placebo titration group (p=0.019); interestingly, the ORR in patients who could not be randomized due to toxicities was 59%. The results of this study not only demonstrated the feasibility of axitinib in the first-line setting, but further supported the importance of individualized dose-titration of axitinib in select patients.

1.2.2.1 Axitinib and Pembrolizumab

A notable result that was recently reported was the combination of axitinib with pembrolizumab versus sunitinib in an open-label phase III trial for patients with treatment-naïve advanced RCC [18]. The estimated percentage of patients alive at 12 months was significantly higher with axitinib + pembrolizumab (89.9% versus 78.3%, HR 0.53), as was median PFS (15.1 versus 11.1 months, HR 0.69), with an objective response rate of 59% with axitinib + pembrolizumab. Grade 3 or higher adverse events of any cause were seen in 76% of patients receiving axitinib + pembrolizumab, with 63% of patients experiencing a Grade 3 or higher adverse event attributed to the combination therapy. Most frequent treatment-related adverse events (>=Grade 3) were hypertension (21%), elevations in alanine aminotransferase (12%), diarrhea (7%), and elevations in aspartate aminotransferase (7%). Adverse events regardless of attribution led to discontinuation of either drug (31%), discontinuation of both drugs (11%), interruption of either drug (70%), and dose reduction of axitinib (20%).

1.3 Rationale for the Proposed Study

1.3.1 Rationale for a Perioperative Study in Subjects Eligible for CN/MET

Historical studies have demonstrated the clinical efficacy of CN in association with immunotherapy. In SWOG-8949, advanced RCC subjects treated with CN in addition to interferon-alpha (IFN-α) had a significant improvement in OS (11 vs 8 months) compared to those treated with IFN-α alone [23]. Similar results were seen in a European Organisation for Research and Treatment of Cancer (EORTC) study (same treatment as SWOG study), with a significant improvement in OS in favor of CN in addition to immunotherapy [24]. The clinical benefit of CN appears to persist in the TKI era as well; results from the International Metastatic Renal Cell Carcinoma Database Consortium showed a median OS of 20.6 months for subjects who underwent CN vs 9.5 months for those who received only systemic therapy [25].

Furthermore, small studies of MET in select patient populations with limited tumor burden, either upfront or as consolidation (in addition to either systemic TKI or immunotherapy), may provide additional clinical benefit [26, 27]. No prospective studies exist, but multiple retrospective analyses, both in the pre-TKI and TKI era, have demonstrated the significant clinical benefit of MET, particularly in cases where a complete (R0) resection could be achieved [28-32].

Finally, the efficacy and safety of perioperative treatment for subjects with metastatic and advanced RCC prior to CN has been shown in multiple prospective studies. Perioperative TKI treatment has demonstrated tumor shrinkage in the range of 13-22%, with a significant proportion of subjects who were previously deemed unresectable able to proceed with surgical resection [27, 33-36]. Just as importantly, there does not appear to be increased risk of overall surgical morbidity or mortality associated with perioperative therapy. One specific concern is the risk of delayed wound healing in subjects receiving TKI therapy; the results of existing studies are conflicting, as some studies have shown delayed wound healing in up to 20-25% of subjects, while other studies have shown no evidence of delayed wound healing.

1.3.1.1 Rationale for Fixed Dose Pembrolizumab

The planned dose of pembrolizumab for this study is 200 mg Q3W followed by 400 mg Q6W.

Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type.

A 400 mg Q6W dosing regimen of pembrolizumab is expected to have a similar benefit-risk profile as 200 mg Q3W, in all treatment settings in which 200 mg Q3W pembrolizumab is currently appropriate [37]. Specifically, the dosing regimen of 400 mg Q6W for pembrolizumab is considered adequate based on modeling and simulation (M&S) analyses, given the following rationale:

- Pharmacokinetic (PK) simulations demonstrating that in terms of pembrolizumab exposures:
  - Average concentration over the dosing interval (C_{avg}) (or area under the curve [AUC]) at 400 mg Q6W is similar to the approved 200 mg Q3W dose, thus bridging efficacy between dosing regimens.
  - Trough concentrations (C_{min}) at 400 mg Q6W are generally within the range of those achieved with 2 mg/kg or 200 mg Q3W in the majority (>99%) of patients.
  - Peak concentrations (C_{max}) at 400mg Q6W are well below the C_{max} for the highest clinically tested dose of 10 mg/kg Q2W, supporting that the safety profile for 400 mg Q6W should be comparable to the established safety profile of pembrolizumab.
  - Exposure-response (E-R) for pembrolizumab has been demonstrated to be flat across indications, and OS predictions in melanoma and non-small cell lung cancer (NSCLC) demonstrate that efficacy at 400 mg Q6W is expected to be similar to 200 mg or 2mg/kg Q3W, given the similar exposures; thus, 400 mg Q6W is expected to be efficacious across indications.

1.3.2 Overarching Objective

Here we propose perioperative therapeutic combinations, with pembrolizumab (KEYTRUDA, Merck) as the treatment backbone, in patients with locally advanced or metastatic RCC who are eligible for CN or MET. The study will include multiple treatment cohorts into which subjects will be accrued, and after 9 weeks of preoperative therapy, subjects will undergo CN or MET. Paired tumor specimens (pre- and on-treatment) will be collected for molecular analysis and allow for unprecedented translational investigation of combination immune therapeutic approaches in human mRCC specimens. Subjects who experience clinical benefit (CR, PR, or SD) during the preoperative treatment period will be offered continued pembrolizumab-based therapy (400 mg Q6W) following CN or MET.

1.4 Correlative Studies

1.4.1 Correlative Studies Background

Correlative science to understand the biologic and immunologic impact of pembrolizumab-based therapy in advanced RCC, and to identify candidate biomarkers of response, resistance, or toxicity, is an integral part of this study. Sample collection for the correlative studies are outlined in the Procedure Manual. Correlative studies may include but are not limited to:

- Clinical correlatives:
  - Pathologic response rate and R0 resection rates
  - Clinical efficacy of continued pembrolizumab-based therapy
- Scientific correlatives:
  - Changes in tumor-infiltrating immune cells (TIICs)
  - Changes in frequency and numbers of circulating T cells
  - Comprehensive assessment of the tumor microenvironment
  - Transcriptional profiling of tumor microenvironment constituents
  - Changes in T cell repertoire
  - Molecular profiling to explore biomarkers of response
  - Change in neoepitope burden
- Correlative research will be performed on:
  1. Baseline primary and/or metastatic biopsies.
  2. CN and/or MET specimens.
     - If CN or MET is not feasible, post-treatment tumor core biopsies should be performed when safe and feasible to allow acquisition of adequate specimens for correlative studies
  3. Serial blood samples.
  4. Archival tumor samples originally obtained prior to study consent (when available).

1.4.2 Biomarker Research

Cancer immunotherapies represent an important and novel class of antitumor agents. However, the mechanism of action of these exciting new therapies is not completely understood and much

remains to be learned regarding how best to leverage these new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer immunotherapy and other treatments administered, as well as determinants of AEs in the course of our clinical studies. These efforts may identify novel predictive/PD biomarkers and generate information that may better guide single-agent and combination therapy with immuno-oncology drugs. To identify novel biomarkers, biospecimens (ie, blood components, tumor material) will be collected to support analyses of cellular components (eg, protein, DNA, RNA, metabolites) and other circulating molecules. Investigations may include but are not limited to:

Tumor PD-L1 Expression

To date, tumor PD-L1 expression had not proven itself as a reliable predictive biomarker of response in mRCC. In the phase III CheckMate 025 study, responses to nivolumab were identical in the PD-L1 negative and positive groups. More recently, the preliminary analysis of the ongoing phase II study of atezolizumab and bevacizumab in treatment-naïve mRCC (NCT01984242) was reported. In the atezolizumab monotherapy arm, again, there was no significant difference in response rate between the PD-L1 negative and positive groups. However, in the atezolizumab/bevacizumab combination arm, the response rate of PD-L1 positive subjects was much higher[38]. Thus in this study, we propose an investigation of tumor PD-L1 expression as a potential biomarker in subjects who receive combination checkpoint inhibitor/VEGF-inhibitor therapy.

Immune-related Gene Expression Profile (GEP)

Intratumoral expression levels of select genes will be analyzed using an analytically validated platform. Association between the immune-related GEP and response to pembrolizumab has been established using these genes in melanoma and in cancers from clinical studies KN012 (head and neck, bladder, and gastric cancers) and KN028 (ovarian, esophageal, and other cancers). Data from these cohorts has been used to derive a GEP, which combines the expression levels of several key genes into a single scalar score [40]. The pattern of association in the esophageal cohort of KN028 using a prototype GEP suggested the ability to identify patients who may not respond to pembrolizumab by identifying tumors that have low values of the GEP. The GEP includes genes from immune-regulatory pathways and a GEP score will be tested for association with response to pembrolizumab in retrospective fashion. The relationship between GEP and the probability of response will be used to develop cut-offs that may have high clinical utility.

Tumor and Blood RNA Analyses

Both genome-wide and targeted mRNA expression profiling and sequencing in tumor tissue and in blood may be performed to define gene signatures that correlate to clinical response to treatment with pembrolizumab or other immunotherapies. Pembrolizumab induces a response in tumors that likely reflects an inflamed/immune phenotype. Specific immune-related gene sets (ie, those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Individual genes related to the immune system may also be evaluated (eg, IL-10). MicroRNA profiling may also be pursued as well as exosomal profiling.

Proteomics and IHC using blood or tumor

Tumor and blood samples from this study may undergo proteomic analyses (eg, PD-L1 IHC). PD-L1 protein level in tumor sections, assessed by IHC, has been shown to correlate with response to pembrolizumab in patients with NSCLC, and an IVD device has been developed for use with pembrolizumab in NSCLC. Preliminary data indicates that this association may also be true in additional cancer types (ie, triple negative breast cancer, head and neck, and gastric). Additional tumor or blood-derived proteins may also correlate with response to pembrolizumab. Therefore, tumor tissue may be subjected to proteomic analyses using a variety of platforms that could include but are not limited to immunoassays and liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for pembrolizumab therapy.

Genetic (DNA) analyses from tumor

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (ie, mutations, methylation status, microsatellite instability). Key molecular changes of interest to immuno-oncology drug development include the mutational burden of tumors and the clonality of T-cells in the tumor microenvironment. Increased mutational burden (sometimes referred to as a 'hyper-mutated' state) may generate neo-antigen presentation in the tumor microenvironment. To conduct this type of research, it is important to identify tumor-specific mutations that occur across all genes in the tumor genome. Thus, genome-wide approaches may be used for this effort. Note that in order to understand tumor-specific mutations, it is necessary to compare the tumor genome with the germline genome. Microsatellite instability may also be evaluated as this is an important biomarker for some cancers (ie, colorectal cancer). Circulating tumor DNA and/or RNA may also be evaluated from blood samples.

Germline (blood) genetic analyses (e.g., single-nucleotide polymorphism [SNP] analyses, whole exome sequencing, whole genome sequencing)

This research may evaluate whether genetic variation within a clinical study population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or AEs, the data might inform optimal use of therapies in the patient population. Furthermore, it is important to evaluate germline DNA variation across the genome in order to interpret tumor-specific DNA mutations. Finally, MSI may be evaluated as this is an important biomarker for some cancers (ie, colorectal cancer).

Planned Genetic Analysis

Genetic variation may impact a patient's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and Institutional Review Board (IRB)/Ethics Review Committee (ERC) allow, a sample will be collected for DNA analysis from consenting subjects.

DNA samples will be used for research related to the study treatment(s), the disease under study and related diseases. They may also be used to develop tests/assays including diagnostic tests

related to the disease under study, related diseases, and study drug(s). Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).

DNA samples will be analyzed for variation across the entire genome. Analyses may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to understand study disease or related conditions.

Microbiome Analysis of Stool

Stool samples will be collected and a stool questionnaire will be completed to assess the microbiome associated with clinical activity. This research may help identify factors predictive of pembrolizumab response and resistance and novel targets for cancer immunotherapy.

1.4.3 Future Biomedical Research Specimen Collection

The investigator will conduct Future Biomedical Research on specimens consented for future biomedical research during this clinical trial.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for FBR is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. Decisions on Future Biomedical Research will be made by the Joint Steering Committee.

1.4.3.1 Future Biomedical Research Samples

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

- Leftover tumor for future research
- Leftover DNA and RNA from Correlative Studies
- Leftover plasma and serum from Biomarker Studies
- Leftover peripheral blood mononuclear cells (PBMC) from whole blood from correlative studies
- Microbiome

2 Objectives and Endpoints of the Study

2.1 Objectives

2.1.1 Primary

- To determine the impact of pembrolizumab-based therapy on the composition, phenotype, and function of tumor-infiltrating immune cells (TIICs) in subjects with advanced RCC undergoing CN/MET

2.1.2 Secondary

- To determine the clinical efficacy of preoperative pembrolizumab-based therapy in subjects with advanced RCC undergoing CN/MET

- To explore the clinical efficacy of continued pembrolizumab-based therapy following CN/MET in subjects with advanced RCC

    - Subjects who achieve R0 resection (NED, negative margins) or R1 resection (microscopic disease, positive margins) after preoperative treatment will receive continued pembrolizumab-based combination therapy for up to 1 year (9 cycles) following CN/MET, or until disease progression, death, unacceptable toxicity, or withdrawal from study, whichever occurs first.

    - Subjects who achieve R2 resection (macroscopic disease after surgery) after preoperative treatment, or who do not undergo nephrectomy after achieving pre-operative radiographic CR, will receive continued pembrolizumab-based combination therapy for up to 2 years (18 cycles) following CN/MET, or until disease progression, death, unacceptable toxicity, or withdrawal from study, whichever occurs first.

- To determine the safety and tolerability of pembrolizumab-based therapy in subjects with advanced RCC undergoing CN/MET

2.1.3 Exploratory

2.1.3.1 Clinical

- To explore the clinical efficacy of preoperative pembrolizumab-based therapy in subjects with advanced RCC, by pathologic response

2.1.3.2 Scientific

- To explore the relationship between changes in TIICs and clinical efficacy in subjects with advanced RCC treated with pembrolizumab-based therapy

- To characterize changes in the frequency and number of circulating T cells induced by pembrolizumab-based therapy in subjects with advanced RCC

- To determine the impact of pembrolizumab-based therapy on the composition and phenotype of the tumor microenvironment (including tumor and stromal cells) in subjects with advanced RCC

- To determine whether locally advanced versus metastatic RCC exhibit differences in immune composition or phenotype at baseline and in response to pembrolizumab-based therapy

- To determine the change in T cell repertoire within the tumor and blood induced by pembrolizumab-based therapy in subjects with advanced RCC

- To explore molecular profiles to identify potentially predictive biomarkers for subjects with advanced RCC treated with immunotherapy

2.2 Endpoints

2.2.1 Primary

- The proportion of subjects with ≥2-fold increase in the number of TIICs between pre- and post-treatment tumor specimens.

2.2.2 Secondary

- The clinical efficacy of preoperative pembrolizumab-based therapy in subjects with advanced RCC will be assessed by ORR, defined as CR or PR per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, modified to allow a maximum of 10 target lesions or 5 target lesions per organ.

- The clinical efficacy of continued pembrolizumab-based therapy in subjects with advanced RCC will be assessed as follows:

    - In subjects who obtain CR or PR/SD with R0 resection and are treated 1 year of pembrolizumab-based therapy:

        - 1-year and 2-year disease-free survival (DFS) rate, and median DFS

    - In subjects who obtain PR/SD and have residual disease following CN/MET and are treated with 1 year of pembrolizumab-based therapy:

        - 1-year and 2-year PFS rate, and median PFS

- Safety will be assessed and reported using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0

    - Surgical complications will be assessed according to the Clavien-Dindo classification (Appendix 3)

2.2.3 Exploratory

2.2.3.1 Clinical

- Pathologic response
  - Clinical to pathologic downstaging rate following preoperative therapy, including CR rate
  - R0 resection rate, following preoperative therapy

2.2.3.2 Scientific

- The relationship between clinical efficacy (by above measures) and changes in TIICs (by above measures will be explored).
- The changes in frequency and numbers of circulating T cells will be assessed by flow cytometry.
- Comprehensive assessment will be performed to explore the tumor microenvironment, including PD-L1 status. Transcriptional profiling of tumor microenvironment constituents (including T cell subsets, tumor, stroma) in pre- and post-treatment specimens will be analyzed.
- Changes in the T cell repertoire will be explored via high resolution T cell receptor (TCR) sequencing, in both blood and tumor specimens.
- Molecular profiling of pre- and post-treatment tumor and normal tissue to explore biomarkers of response. Neoepitope burden will be assessed.
- These correlative objectives will also be explored in subjects who continue pembrolizumab-based therapy following CN and/or MET; subjects will be consented to tissue collection at the time of disease progression
- Exploratory qualitative comparisons will be conducted between subjects with locally advanced versus metastatic disease for the above measures.

3 Study Design

3.1 Characteristics

This is an open-labeled, single center, phase II study, in which eligible subjects will be treated with pembrolizumab-based therapy. The treatment cohorts will be accrued concurrently once 6 patients are enrolled in Cohort A (see study schema). Subjects with advanced RCC (locally advanced or metastatic) in whom CN/MET is feasible are eligible for this study. Eligible subjects must also have evaluable pre-treatment tumor specimen adequate for analysis, or consent to tumor specimen collection prior to enrollment.

Subjects enrolled into Cohort A will receive pembrolizumab monotherapy (200 mg Q3W). The objective of this monotherapy cohort is to determine the safety of pembrolizumab in subjects with

advanced RCC undergoing CN/MET. Of particular interest are surgical complications. The first 6 subjects accrued to Cohort A will be evaluated in a safety lead-in for the safety of pembrolizumab prior to planned CN/MET. For the first 6 patients in the safey lead-in, if ≥2 subjects experience Grade IV and V surgical complications according to the Clavien-Dindo classification (Appendix 3), the study will be halted to accrual. Given the complexity of surgery, it will be difficult to attribute surgical complications to the preoperative administration of pembrolizumab. Thus, the occurrence of these events may not require an early end to the study, but will be discussed amongst members of the Joint Steering Committee, Merck, and the Sponsor to consider whether the study can re-open to accrual.

After 6 patients are enrolled into Cohort A, Cohort B will open to concurrent enrollment where subjects will receive pembrolizumab in combination with axitinib. The pembrolizumab-based combination for cohort C has not yet been determined. Cohort C will be determined by discussion between the Joint Steering Committee, Merck, and the Sponsor, based on emerging data regarding promising combination approaches.

Enrolled subjects will begin their assigned preoperative pembrolizumab-based therapy (200 mg Q3W). After 9 weeks (3 × 3-week cycles of treatment), subjects will be assessed for response per RECIST 1.1 criteria (Section 7.1). Subjects will then proceed as follows:

- Subjects who achieve CR during the preoperative treatment period and have locally advanced disease will proceed with CN.

- Subjects with PR/SD during the preoperative treatment period will proceed with CN/MET.

- Subjects with PD during the preoperative treatment period who, in the opinion of the treating physician and principal investigator, are likely to benefit from CN/MET AND in whom surgery is safe and feasible, may proceed with CN/MET on study. Subjects in whom CN/MET is unlikely to provide benefit OR surgery is not safe and feasible, may proceed with tumor biopsy on study, if safe and feasible. Subjects will withdraw from study participation following CN/MET or tumor biopsy. If CN/MET and tumor biopsy are not safe and feasible and not in the best interests of the subject, the subject will withdraw from study participation immediately. The risk of disease progression during the preoperative treatment period is 10% [18]. The use of anti-PD-1 antibodies has now become standard of care. As a result, participants are receiving treatment that is deemed standard of care.

- Subjects with PR/SD in whom CN/MET is not safe and feasible: in rare cases, subjects who were deemed eligible for CN/MET prior to study participation and have PR/SD to preoperative therapy may not be able to undergo CN/MET (for example, due to adverse events). These subjects will be required to provide a tumor biopsy, unless deemed unsafe or delays appropriate standard of care, in lieu of CN/MET. Subjects may continue study treatment with pembrolizumab 400 mg Q6W for up to 1 year (9 cycles), or until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs first. The chance of experiencing severe toxicities related to study drug(s) that might preclude or delay surgery is less than 5%.

Following CN/MET, post-operative therapy for patients who achieved pre-operative CR/PR/SD will proceed as follows:

- Subjects with an R0 resection (NED, margins negative) or R1 resection (microscopic disease, margins positive) will continue receiving their assigned pembrolizumab-based combination therapy (with pembrolizumab dosing as 400 mg Q6W) for up to 9 cycles or until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs first.

- Subjects with an R2 resection (macroscopic disease after surgery), or who had a pre-operative CR but did not undergo CN, will continue receiving their assigned pembrolizumab-based combination therapy (with pembrolizumab dosing as 400 mg Q6W) for up to 18 cycles or until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs first.

- The first dose of study treatment following CN/MET may be no sooner than 3 weeks and no later than 6 weeks following surgery, to allow for postoperative recovery (adequate wound healing and recovery from any postoperative complications) as assessed by the treating surgeon. Subjects who cannot resume therapy within 42 days for any reason will discontinue study participation, any exception will be discussed with the PI and approved on a case-by-case basis.

At the time of disease progression (or death, unacceptable toxicity, or withdrawal of consent, whichever occurs first) on postoperative pembrolizumab-based therapy, subjects will discontinue study participation. Prior to study discontinuation, all subjects will be consented for an additional optional tissue collection.

3.2 Number of Subjects

Up to 84 subjects in total will be enrolled. Up to twelve subjects will be accrued into Cohort A, with the first 6 subjects undergoing a safety lead-in to evaluate the safety of pembrolizumab monotherapy and potential surgical complications as assessed per the Clavien-Dindo classification (Appendix 3). After six (6) subjects have been enrolled into Cohort A, up to 36 evaluable subjects will be accrued concurrently to each pembrolizumab-based combination cohort. based on group sequential design. See section 8.2.1 for details regarding sample size determination.

3.3 Eligibility Criteria

Subjects must have baseline evaluations performed prior to the first dose of study treatment and must meet all of the inclusion and none of the exclusion criteria. In addition, subjects must be thoroughly informed about all aspects of the study, including the study visit schedule, and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from subjects prior to enrollment. The following criteria apply to all subjects enrolled onto the study unless otherwise specified.

3.3.1 Inclusion Criteria

1. Histologically confirmed RCC with a clear cell component.

2. Locally advanced or metastatic disease (primary intact or status post nephrectomy with recurrent disease)

3. Planned CN and/or MET.

4. Must have a tumor lesion amenable to biopsy at pre-treatment and subjects must consent to acquisition of fresh tumor specimens obtained using the following approaches:

    i. Core biopsy

    ii. Nephrectomy

    iii. Metastasectomy (MET)

    Note: Subjects who undergo nephrectomy or metastasectomy prior to study enrollment must still have measurable disease (RECIST 1.1) that is amenable to cytoreductive nephrectomy or metastasectomy to be eligible for study participation.

    iv. FNA specimens are not acceptable

5. Measurable disease per RECIST 1.1 as assessed by the investigator. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

6. Subject (or legally acceptable representative if applicable) must provide written informed consent for the trial.

7. ≥18 years of age on day of signing informed consent.

8. Performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale (Appendix 1).

9. Adequate organ function as defined in Table 1; all screening labs should be performed within 10 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System	**Laboratory Value**
Hematological	
Absolute neutrophil count (ANC)	≥1,500/μL
Platelets	≥100,000/μL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR**	≤1.5 × upper limit of normal (ULN) **OR**

System	Laboratory Value
Measured or calculated[a] creatinine clearance (CrCl) (GFR can also be used in place of creatinine or CrCl)	≥60 mL/min for subject with creatinine levels >1.5 × institutional ULN
Hepatic	
Serum total bilirubin	≤1.5 × ULN **OR** Direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 ULN
AST (SGOT) and ALT (SGPT)	≤2.5 X ULN
Albumin	≥2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 × ULN unless subject is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

10. Negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication (Day 1) (female subjects of childbearing potential). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

11. Male and female subjects of childbearing potential must be willing to use an adequate method of contraception* as outlined in Section 6.6, 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 subject.

3.3.2 Exclusion Criteria

1. RCC WITHOUT a clear cell component
2. Prior systemic therapy for the treatment of RCC
3. No measurable disease (e.g. only bone metastases)
4. Not a candidate for CN and/or MET

5. Currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment.

   Note: Subjects who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks since the last dose of the previous investigational agent.

6. Diagnosis of immunodeficiency or receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

7. Known history of active TB (Bacillus Tuberculosis).

8. Severe hypersensitivity (≥Grade 3) to pembrolizumab/axitinib or any of their excipients.

9. Prior systemic anti-cancer mAb, targeted small molecule therapy, or radiation therapy within 2 weeks prior to the first dose of study treatment (Day 1).

   Note: Subjects must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Subjects with ≤Grade 2 neuropathy may be eligible.

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

   Subjects must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.

10. Known additional malignancy that is progressing or has required active treatment within the past 2 years.

    Note: Subjects with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (e.g., breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

11. Known active CNS metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are radiologically stable, i.e., without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability.

12. 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 not considered a form of systemic treatment and is allowed.

13. History of (non-infectious) pneumonitis that required treatment with steroids or has current pneumonitis.

14. Active infection requiring systemic therapy.

15. Any arterial thromboembolic events, including but not limited to myocardial infarction, transient ischemic attack, cerebrovascular accident, or unstable angina, within 6 months prior to randomization.

16. Uncontrolled or poorly controlled hypertension despite standard medical therapy.

17. Serious or non-healing wound, ulcer, or bone fracture within 28 days of study enrollment.

18. 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.

19. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

20. 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.
21. Any prior therapy with an anti–PD-1, anti–PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T cell receptor (e.g., CTLA-4, OX-40, and CD137).
22. Known history of human immunodeficiency virus (HIV) infection. No HIV testing is required unless mandated by local health authority.
23. Known history of Hepatitis B (defined as Hepatitis B surface antigen reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection. No testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.

24. Live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

25. History of grade 3-4 gastrointestinal (GI) bleeding within 12 weeks prior to study enrollment

26. Solid organ or hematologic transplant.

27. Encephalopathy in the last 6 months. Those subjects on rifaximin or lactulose to control their encephalopathy are not allowed.

28. Evident ascites on physical examination.

Note: Medically controlled ascites and ascites detectable on imaging studies only is allowed.

29. Female of childbearing potential who has a positive urine pregnancy test within 72 hours prior to allocation. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

30. Has had an allogenic tissue/solid organ transplant.

3.4 Duration of Therapy

The preoperative treatment regimen consists of 3 cycles (9 weeks) of treatment (as described under "Treatment Plan," in Section 5). Following CN and/or MET (or biopsy if CN and/or MET is not feasible), all subjects will be offered the option of continuing pembrolizumab-based therapy (400 mg Q6W) as described in Section 3.1 unless the subject meets any of the discontinuation/withdrawal criteria outlined in Section 6.3.

3.5 Duration of Follow Up

Duration of follow up:

- Those subjects who complete preoperative therapy and achieve either CR/PR/SD with R0 or R1 resection, and complete 9 cycles of continued pembrolizumab-based combination therapy (with pembrolizumab dosing as 400 mg Q6W) will be followed for up to 12 additional months, or until disease progression, death, unacceptable toxicity or withdrawal of consent, whichever occurs first.

- Those subjects who complete preoperative therapy and achieve either CR/PR/SD with R2 resection, or achieve a pre-operative CR but do not undergo CN, and complete 18 cycles of continued pembrolizumab-based combination therapy (with pembrolizumab dosing as 400 mg Q6W) will be followed for up to 12 additional months, or until disease progression, death, unacceptable toxicity or withdrawal of consent, whichever occurs first.

- Subjects who experience disease progression will have the mandatory safety follow-up visit 30 days (+7 days) after the last dose of study treatment. 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 anticancer therapy, whichever occurs first. Serious AEs that occur within 90 days of the end of treatment should also be followed and recorded.

- Subjects removed from study for any reason other than disease progression, death, or AEs will have a mandatory safety follow-up visit within 30 days for the final study treatment.

3.6 Randomization Procedures

There will be no randomization. After enrolling six (6) subjects into cohort A as per Section 5.1, enrollment will proceed concurrently into the remaining treatment cohorts.

3.7 Study Timeline (Primary Completion)

Each cohort is expected to reach primary completion 36 months after opening to accrual..

4 Study Drugs

4.1 Description, Supply and Storage of Investigational Drugs

4.1.1 Pembrolizumab

Details on the preparation and administration of pembrolizumab are provided in the Pharmacy Manual. Refer to the package insert for complete information. Refer to the IB for additional information on pembrolizumab.

Classification

PD-L1 inhibitor, immunotherapy

Mechanism of Action

Pembrolizumab (MK-3475) is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. For more details, see Section 1.2.1 and the IB.

Contraindications

Immunodeficiency, autoimmune diseases requiring treatment with disease modifying agents, corticosteroids or immunosuppressive drugs, active infections.

Availability

Pembrolizumab will be provided to subjects enrolled on this study by Merck.

Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

For all trial sites, the local country Merck personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by Merck.

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 study treatments in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by Merck, as summarized in Table 2.

Table 2 Product Descriptions

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

Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, Merck 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.

4.1.2 Axitinib

Please refer to the prescribing information for information and administration of the drug.

Classification

VEGF-targeting TKI

Mechanism of Action

Axitinib is a TKI indicated for the treatment of advanced RCC after failure of one prior systemic therapy. It inhibits multiple receptor tyrosine kinases, including VEGFR-1, VEGFR-2, and VEGFR-3.

Contraindications

There are no specific contraindications listed in the manufacturer's United States labeling.

Availability

Commercial supply of axitinib will be provided to subjects on this study by UCSF.

Storage and Handling

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

Axitinib is available as 1 mg and 5 mg tablets.

Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, Merck 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.

Returns and Reconciliation

The investigator is responsible for keeping accurate records of 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.

4.2 Drug Accountability

The Investigational Pharmacist will manage drug accountability records.

4.3 Drug Ordering

UCSF will obtain pembrolizumab directly from Merck as study supply. Commercial drug will be supplied by UCSF.

Axitinib will be obtained as commercial supply.

4.4 Packaging and Labeling of Study Drugs

Study drugs will be labeled by sponsor prior to receipt at UCSF. Prior to administration or dispensing of drug, UCSF Investigational Drug Pharmacy will affix an appropriate clinical label with patient identifiers per UCSF institutional standards, adhering to applicable local and federal laws.

5 Treatment Plan

5.1 Dosage and Administration

In all subjects, pembrolizumab will be administered as a flat dose of 200 mg for 3 cycles prior to surgery and 400 mg for 9 or 18 cycles after surgery, as an IV infusion. The Pharmacy manual

contains specific instructions for the preparation of pembrolizumab infusion fluid as well as the administration of the infusion solution.

On Day 1 of each cycle, pembrolizumab will be administered once as a 30-minute IV infusion. Every effort will be made to keep infusion timing as close to 30 minutes as possible. However, given the variability of infusion pumps, a window of -5 minutes and +10 minutes is permitted (i.e. infusion time is 30 minutes: -5 min/+10 min).

The treatment to be used during the study is outlined below in Table 3 and Table 4.

Table 3 Neoadjuvant Treatment Regimen Per Cohort

Cohort	Drug/Dose	Dose Frequency	Route of Administration	Schedule	Dose Levels
A/B/C	Pembrolizumab 200 mg	Q3W	IV	Day 1 of each 21-day cycle (Q3W)	N/A
B	Axitinib 5 mg titratable	BID	PO	Days 1-21 of each 21-day cycle	DL -2: 1 mg BID DL -1: 3 mg BID DL 1: 5 mg BID DL 2: 7 mg BID DL 3: 10 mg BID
C	TBD (agent to be determined)	TBD	TBD	TBD	TBD

Abbreviations: BID = twice daily; DL = dose level; IV = intravenous; N/A = not applicable; PO = by mouth; Q3W = every 3 weeks; TBD = to be determined

Table 4 Adjuvant Treatment Regimen Per Cohort

Cohort	Drug/Dose	Dose Frequency	Route of Administration	Schedule	Dose Levels
A/B/C	Pembrolizumab 400 mg	Q6W	IV	Day 1 of each 42-day cycle (Q6W)	N/A
B	Axitinib 5 mg titratable	BID	PO	Days 1-42 of each 42-day cycle	DL -2: 1 mg BID DL -1: 3 mg BID DL 1: 5 mg BID

Cohort	Drug/Dose	Dose Frequency	Route of Administration	Schedule	Dose Levels
					DL 2: 7 mg BID DL 3: 10 mg BID
C	TBD (agent to be determined)	TBD	TBD	TBD	TBD
Abbreviations: BID = twice daily; DL = dose level; IV = intravenous; N/A = not applicable; PO = by mouth; Q6W = every 6 weeks; TBD = to be determined.					

5.1.1 Cohort A: Pembrolizumab Monotherapy

Up to twelve subjects will be enrolled into Cohort A. The first 6 subjects accrued to Cohort A will be evaluated in a safety lead-in for the safety of pembrolizumab prior to planned CN/MET. After six (6) subjects are enrolled into Cohort A, the pembrolizumab-based combination cohorts will open to concurrent enrollment.

Administer pembrolizumab doses according to Table 3 and Table 4. See section 5.2 for details regarding dose modifications and dosing delays.

During neoadjuvant treatment, subjects will receive 3 cycles of pembrolizumab (200 mg Q3W), given on Day 1 of each 21-day cycle. Of particular interest are surgical complications (Appendix 3). For the first 6 patients in the safey lead-in, if ≥2 subjects experience Grade IV and V surgical complications according to the Clavien-Dindo classification (Appendix 3), or if ≥2 subjects experience a delay in surgery beyond the specified 14-21 day window following the end of the preoperative treatment period (that is, 14-21 days from Cycle 3, Day 21; delays for scheduling, operating room scheduling or patient preference are not included), the study will be halted to accrual. Given the complexity of surgery, it will be difficult to attribute surgical complications to the preoperative administration of pembrolizumab. Thus, the occurrence of these events may not require an early end to the study, but will be discussed amongst the members of the Joint Steering Committee, Merck, and the Sponsor to determine whether study can re-open to accrual.

5.1.2 Cohort B: Pembrolizumab + Axitinib

5.1.2.1 Safety Lead-In

The first 6 subjects accrued to Cohort B will be evaluated to test the safety of the combination of pembrolizumab and axitinib. All 6 subjects in Cohort B will be followed for 28 days after surgery for excessive post-operative complications before additional subjects are enrolled to each combination cohort. If ≤1 subject experience Grade IV/V surgical complications per the Clavien-Dindo classification (Appendix 3), then 11 additional evaluable subjects will be accrued to the cohort. If ≥2 subjects experience Grade IV/V surgical complications, or if ≥2 subjects experience a delay in surgery beyond the specified 14-21 day window following the end of the preoperative treatment period (that is, 14-21 days from Cycle 3, Day 21; delays for scheduling, operating room scheduling or patient preference are not included), then the cohort will be halted to accrual, and the safety data reviewed to modify the protocol as appropriate, including changes in dose level

(Section 5.1). If the cohort is re-opened with a change in dose level, an additional 6 subjects will be accrued to evaluate safety. If ≤1 subject experience a Grade IV/V surgical complication, then 11 additional subjects will be accrued to the cohort at the reduced dose. If ≥2 subjects experience a Grade IV/V surgical complication, the cohort will be terminated for lack of safety. Therefore, a minimum of 4, and a maximum of 36 subjects may be accrued into Cohort B.

5.1.2.2 Treatment Plan

Administer pembrolizumab and axitinib doses according to Table 3 and Table 4. On Day 1 of each cycle, administer axitinib after the subject completes their pembrolizumab infusion. Axitinib may be administered as soon as the pembrolizumab infusion is completed. Additional details regarding the treatment plan are provided below.

Preoperative treatment period (3 cycles):

Subjects will begin treatment with pembrolizumab 200 mg Q3W, administered on Day 1 of each 21-day cycle. Axitinib will be self-administered twice daily. After 3 cycles of therapy, subjects will have a 2-week treatment break prior to CN and/or MET.

During the preoperative treatment period, subjects who experience toxicities requiring study discontinuation will proceed immediately to CN and/or MET, as soon as it is determined to be safe and feasible per the treating physicians and PI. Subjects who experience toxicities requiring dose delays must be able to resume treatment within 42 days of the prior dose of pembrolizumab. Subjects unable to resume treatment within 42 days of the prior dose of pembrolizumab must discontinue treatment participation.

CN/MET:

CN/MET will be performed per institutional standard of care, 14 to 21 days following the end of the preoperative treatment period (14-21 days from Cycle 3, Day 21).

Post-CN/MET treatment:

Following CN/MET (or continued therapy in metastatic subjects who achieve CR during the preoperative treatment period), subjects will be offered the option to continue treatment on study as summarized in Section 3.1 (see Section 6.3 for exceptions).

The first dose of post-CN/MET therapy will be no sooner than 21 days, and no later than 42 days, following CN/MET, based on adequate postoperative recovery (including wound healing), as assessed by the treating physicians. Subjects with metastatic disease who achieve CR during the preoperative treatment period (obviating the need for metastasectomy) will continue with their pembrolizumab-based therapy without a break allowing for surgery and recovery. Subjects will receive pembrolizumab 400 mg Q6W, administered on Day 1 of each 42-day cycle.

- In subjects who continue on the combination of pembrolizumab and axitinib as continued therapy following CN/MET (or following CR during preoperative therapy in metastatic patients), axitinib dose-titration (as well as dose modification and delays) should be managed by the treating physician per standard of care.

- Subjects treated with the combination of pembrolizumab and axitinib may experience AEs attributable to axitinib that require holding or discontinuing axitinib. Dose delays or discontinuation of axitinib should be managed per standard of care. In cases where axitinib must be discontinued permanently due to toxicity, subjects may remain on study and receive pembrolizumab monotherapy. In cases where axitinib is held due to toxicity:

- Subjects who resume axitinib within 42 days may continue to receive combination therapy

- Subjects who do not resume axitinib within 42 days may remain on study and receive pembrolizumab monotherapy (400 mg Q6W), and axitinib must be discontinued for the remainder of the study duration

- Subjects treated with the combination of pembrolizumab and axitinib may also experience AEs attributable to pembrolizumab that require holding or discontinuing pembrolizumab. Dose delays, modifications, and discontinuations are discussed in Section 5.2. In cases where pembrolizumab must be discontinued due to toxicity, subjects may remain on study and receive axitinib monotherapy. In cases where pembrolizumab is held due to toxicity:

    - Subjects who resume adjuvant pembrolizumab within 42 days may continue to receive combination therapy; subjects will begin treatment with pembrolizumab 400 mg Q6W, administered on Day 1 of each 42-day cycle. The total duration of adjuvant pembrolizumab (either 9 cycles for R0/R1 resection, or 18 cycles for R2 resection) reflects the total number of pembrolizumab doses administered, even if doses are withheld for toxicity and then pembrolizumab is resumed. Subjects who do not resume adjuvant pembrolizumab within 42 days may remain on study and receive axitinib monotherapy, and pembrolizumab must be discontinued for the remainder of the study duration

5.1.3 Cytoreductive Nephrectomy and/or Metastasectomy

All subjects participating in this study must have been deemed eligible for CN and/or MET prior to study enrollment, as determined by the treating surgical team(s). It is strongly recommended that this decision be made through a Multidisciplinary Tumor Board, although this may not always be feasible.

CN and/or MET will be performed 14 to 21 days after the third and final cycle of preoperative pembrolizumab-based therapy. Tissue collection procedures will be outlined in an accompanying Laboratory Manual.

5.1.4 Continuation of Pembrolizumab-based Therapy Following CN/MET

Following CN/MET, post-operative therapy for patients who achieved pre-operative CR/PR/SD will proceed as follows (see Section 6.3):

- Subjects with an R0 resection (NED, margins negative) or R1 resection (microscopic disease, margins positive) will continue receiving pembrolizumab-based combination therapy (with pembrolizumab dosing as 400 mg Q6W) for up to 9 cycles or until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs first.

- Subjects with an R2 resection (macroscopic disease after surgery), or who had a pre-operative CR but did not undergo CN, will continue receiving pembrolizumab-based combination therapy (with pembrolizumab dosing as 400 mg Q6W) for up to 18 cycles or until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs first.

- Subjects will begin their first post-operative treatment no sooner than 21 days and no later than 42 days following CN and/or MET.

All subjects will be consented for optional tissue and blood collection at the time of disease progression.

5.2 Dose Modifications and Dosing Delays

5.2.1 Pembrolizumab

5.2.1.1 Dose Modification and Toxicity Management for Immune-related AEs Associated with Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immune-related response. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation.

Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 5.

Table 5 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations and IO Combinations

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. Pembrolizumab monotherapy, coformulations, or IO combinations 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 pembrolizumab monotherapy, coformulations or IO combinations has been withheld, study intervention may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 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
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
AST or ALT Elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 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 to 2 mg/kg	

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
			prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective 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, 3 or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis:	Grade 2	Withhold	• Administer corticosteroids	• Monitor changes of renal

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
grading according to increased creatinine or acute kidney injury	Grade 3 or 4	Permanently discontinue	(prednisone 1 to 2 mg/kg or equivalent) followed by taper	function
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	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (which was previously myocarditis Grade 1 using CTCAE v4.0)	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal. **Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.** [a] AST/ALT: >3.0 to 5.0 × ULN if baseline normal; >3.0 to 5.0 × baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 × ULN if baseline normal; >1.5 to 3.0 × baseline if baseline abnormal [b] AST/ALT: >5.0 to 20.0 × ULN, if baseline normal; >5.0 to 20.0 × baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 × ULN if baseline normal; >3.0 to 10.0 × baseline if baseline abnormal [c] AST/ALT: >20.0 × ULN, if baseline normal; >20.0 × baseline, if baseline abnormal; bilirubin: >10.0 × ULN if baseline normal; >10.0 × baseline if baseline abnormal [d] The decision to withhold or permanently discontinue pembrolizumab monotherapy, coformulations or IO combinations is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab monotherapy, coformulations, or IO combinations may be resumed. [e] Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).				

5.2.1.2 Toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion-reactions, including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of infusion completion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 6.

Table 6 Pembrolizumab Infusion Reaction Dose modification and 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 therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	**Stop Infusion.** 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 1 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 study drug treatment**	Subject may be premedicated 1.5 h (±30 minutes) prior to infusion of pembrolizumab with: • Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). • Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic).

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: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Subject is permanently discontinued from further study drug treatment.**	No subsequent dosing

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NCI = National Cancer Institute; NSAIDs = non-steroidal anti-inflammatory drugs; PO = by mouth.

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.

For further information, please refer to the CTCAE v5.0 at http://ctep.cancer.gov

5.2.1.3 Other Allowed Dose Interruptions for Pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention. However, study intervention is to be restarted within 3 weeks for Q3W or 6 weeks for Q6W (21 days or 42 days) of the originally scheduled dose and within 42 or 84 days of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the participant's study record.

5.2.2 Axitinib

Dose levels for axitinib is described in Table 3.

Dosing modifications/delays should be managed per standard of care at the discretion of the treating physician.

5.3 Monitoring and Toxicity Management

Each subject receiving pembrolizumab-based therapy will be evaluable for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical findings, and spontaneous reports of adverse events reported to the investigator by subjects.

Each subject will be assessed periodically for the development of any toxicity as outlined in Section 6. Toxicity will be assessed according to the NCI CTCAE v5.0. Dose adjustments will be made according to the system showing the greatest degree of toxicity.

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2, (Table 5). Where appropriate, these guidelines include the use of oral or IV 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 of the event, it is determined not to be related to pembrolizumab, the Investigator does not need to follow the treatment guidance. Refer to Table 5 in Section 5.2 for guidelines regarding dose modification and supportive care.

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

6 Study Procedures and Observations

6.1 Schedule of Procedures and Observations

The study-specific assessments are detailed in this section and outlined in Section 6.2. Screening assessments must be performed within 28 days prior to the first dose of investigational product. Any results falling outside of the reference ranges may be repeated at the discretion of the investigator. All on-study visit procedures are allowed **a window of ±3 days** unless otherwise noted. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

A written, signed, ICF and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the subject and a copy will be filed in the medical record. The originals will be kept on file with the study records.

All subjects who are consented will be registered in OnCore®, the UCSF HDFCC Clinical Trial Management System (CTMS). The system is password protected and meets HIPAA requirements.

6.1.1 Pretreatment Period

6.1.1.1 Screening

The Screening procedures and assessments must be completed within 28 days of the first dose of pembrolizumab-based therapy.

Screening procedures and assessments:

- Demographics
- Complete medical history
- Baseline conditions assessment
- Complete physical examination
- Baseline medications taken within 14 days of Day 1. For stool correlative analysis, it should be noted if antibiotics were taken within 90 days before the first dose of study drug(s).
- Vital signs, height, and weight
- ECOG performance status within 7 days of Cycle 1 Day 1
- Laboratory assessments (within 10 days of treatment initiation):
    - Complete blood count (CBC) with differential and platelet count

- Blood chemistry assessment, including:
  - Alkaline phosphatase (ALP), aspartate aminotransferase/alanine aminotransferase (ALT/AST), total bilirubin, calcium, phosphorus, blood urea nitrogen (BUN), creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate, uric acid, lactate dehydrogenase (LDH)
- Thyroid function tests: thyroid-stimulating hormone (TSH), free thyroxine (FT4), triiodothyronine (T3)
- Coagulation assessment (prothrombin time [PT], partial thromboplastin time [PTT], and international normalized ratio [INR])
- Urinalysis (including microscopic exam if abnormal results are noted)

- Serum or urine pregnancy test within 72 hours prior to the start of study drug
- Imaging evaluation (computed tomography [CT] chest, abdomen and pelvis; magnetic resonance imaging [MRI] if CT is contraindicated; IV contrast given unless contraindicated; Bone scan if clinical indicated; MRI brain if clinically indicated), for tumor assessment
- Request of archival specimen originally obtained prior to consent for banking (formalin-fixed paraffin-embedded [FFPE] tumor specimen, if available)
- Biopsy of primary or metastatic lesion (see Section 3.3.1, Inclusion Criteria)
- Blood for correlative studies (including immune monitoring)
- Correlative Studies Stool Collection

6.1.2 Treatment Period

Subjects who experience unequivocal disease progression without clinical benefit during the preoperative treatment period or withdraw consent will be removed from the study (see Sections 6.1.3 and 6.1.3.2). Subjects who have unacceptable toxicities during the pre-operative treatment period or decline continued therapy will discontinue treatment but continue to be followed on study (Section 6.3).

6.1.2.1 Preoperative Therapy, Cycle 1 Day 1

Preoperative Cycle 1 Day 1, week 1 (±3 days) study procedures:

- Directed physical examination
- Vital signs and weight
- ECOG performance status

- Evaluation of AEs
- Concomitant medications
- CBC with differential and platelet count**
- Blood chemistry assessment**, including:
    - ALP, ALT/AST, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate, uric acid, LDH
- Coagulation assessment (PT, PTT, INR)**
- Blood for correlative studies (including immune monitoring)
- Treatment:
    - Cohort A:
        - Pembrolizumab 200 mg IV (Day 1)
    - Cohort B:
        - Pembrolizumab 200 mg IV (Day 1)
        - Axitinib (Days 1-21); 5mg BID PO

**Note: Laboratory evaluations may be omitted if they were already performed within 7 days of Cycle 1, Day 1

6.1.2.2 Preoperative Therapy, Cycle 2 Day 1

Preoperative Cycle 2 Day 1, week 4 (±3 days) study procedures:

- Directed physical examination
- Vital signs and weight
- ECOG performance status
- Evaluation of AEs
- Concomitant medications
- CBC with differential and platelet count
- Blood chemistry assessment, including:

- ALP, ALT/AST, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate, uric acid, LDH

- Thyroid Function Tests: TSH, FT4, T3
- Blood for correlative studies (including immune monitoring)
- Urinalysis, (including microscopic exam, if abnormal results are noted)
- Treatment:
  - Cohort A:
    - Pembrolizumab 200 mg IV (Day 1) Q3W
  - Cohort B:
    - Pembrolizumab 200 mg IV (Day 1) Q3W
    - Axitinib (Days 1-21). Dose titration per "Treatment Plan" in select patients, see Section 5.1.

6.1.2.3 Preoperative Therapy, Cycle 3 Day 1

Preoperative Cycle 3 Day 1, week 7 (±3 days) study procedures:

- Directed physical examination
- Vital signs and weight
- ECOG performance status
- Evaluation of AEs
- Concomitant medications
- CBC with differential and platelet count
- Blood chemistry assessment, including:
  - ALP, ALT/AST, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate, uric acid, LDH
- Blood for correlative studies
- Treatment:
  - Cohort A:

- Pembrolizumab 200 mg IV (Day 1)

- Cohort B:
  - Pembrolizumab 200 mg IV (Day 1)

6.1.2.4 Axitinib (Days 1-21). Dose titration per "Treatment Plan" in select patients, see Section 5.1.Preoperative Visit, Week 10

Preoperative visit, week 10 (±3 days) study procedures:

- ECOG performance status
- Evaluation of AEs
- Concomitant medications
- Imaging evaluation (CT chest, abdomen and pelvis; MRI if CT is contraindicated; IV contrast given unless contraindicated; Bone scan if clinical indicated; MRI brain if clinically indicated) must be performed after the final cycle and prior to CN and/or MET.
- Correlative studies stool collection

6.1.2.5 Cytoreductive Nephrectomy and/or Metastasectomy

Complete the following tests within 14 days of CN and/or MET:

- CBC with differential and platelet count
- Blood chemistry assessment, including:
- ALP, ALT/AST, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate, uric acid, LDH
- Thyroid Function Tests: TSH, FT4, T3
- Coagulation assessment (PT, PTT, INR)
- Immune parameter assessments
- Urinalysis, (including microscopic exam, if abnormal results are noted)

Subjects will undergo CN and/or MET no sooner than 2 weeks following the final cycle of preoperative pembrolizumab-based therapy. The final cycle of preoperative therapy concludes after the conclusion of the last day (21st day) of the 3rd cycle of pembrolizumab-based therapy. A window of 7 days will be allowed for surgical planning and scheduling (thus, CN and/or MET will occur 14 days [+7 days] following the final cycle of preoperative therapy). Complete the following procedures on the day of surgery:

- CN and/or MET (performed per standard of care).
- Tissue collection for study purposes (see Laboratory Manual for details).
- Pathology assessment (as clinically indicated, per standard of care).

The subject may be consented for core tumor biopsies if CN and/or MET cannot be performed following preoperative pembrolizumab-based therapy for any reason, including:

- Unequivocal disease progression
- AEs
- Development of a concurrent, unrelated medical illness that deems subject inoperable
- Subject withdrawal of consent
- Investigator or surgeon deems inoperable for any reason
- Subjects may be consented for multiple tumors to be biopsied if safe and feasible.
- Subjects who achieve a radiographic CR and have locally advanced disease will proceed with CN.

Subjects who become ineligible for CN and/or MET while on study, and do not consent to provide a tumor biopsy (if safe and feasible), will be removed from study. See section 8.2.2 for details regarding replacement policy.

6.1.2.6 Postoperative Therapy, Day 1 of Each Cycle

Following CN/MET, continuation of pembrolizumab-based therapy for patients who achieved pre-operative CR/PR/SD will proceed as follows:

- Subjects with an R0 resection (NED, margins negative) or R1 resection (microscopic disease, margins positive) will continue receiving their assigned pembrolizumab-based combination therapy for up to 9 cycles or until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs first
- Subjects with an R2 resection (macroscopic disease after surgery), or who had a pre-operative CR but did not undergo CN, will continue receiving their assigned pembrolizumab-based combination therapy for up to 18 cycles or until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs first.
- Subjects may resume therapy following CN/MET as soon as 21 days following surgery (subjects with metastatic disease who have a CR during the preoperative period and therefore do not undergo MET will have no interruption in their therapy). Prior to resuming therapy, the subject must be evaluated by their surgeon and appropriate wound healing must be documented. Subjects with wound healing complications that have not resolved with 42 days of CN and/or MET will discontinue study participation. Any subject who

cannot resume study therapy within 42 days of CN/MET will discontinue study participation.

Perform the following study procedures on Day 1 of each cycle (±3 days) unless stated otherwise:

- Directed physical examination
- Vital signs and weight
- ECOG performance status
- Evaluation of AEs
- Concomitant medications
- CBC with differential and platelet count
- Blood chemistry assessment, including:
    - ALP, ALT/AST, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate, uric acid, LDH
- Thyroid Function Tests: TSH, FT4, T3
- Blood for correlative studies (including immune monitoring) at week 15 only
- Urinalysis (including microscopic exam, if abnormal results are noted
- Treatment:
    - All cohorts, metastatic disease and achieved CR:
        - Pembrolizumab 400 mg IV (Day 1) Q6W
    - Cohort A (all other subjects continuing therapy):
        - Pembrolizumab 400 mg IV (Day 1) Q6W
    - Cohort B (all other subjects continuing therapy):
        - Pembrolizumab 400 mg IV (Day 1) Q6W
        - Axitinib (Days 1 - 42). Dose titration per standard of care
- Imaging evaluation (CT chest, abdomen and pelvis; MRI if CT is contraindicated; IV contrast given unless contraindicated; Bone scan if clinical indicated; MRI brain if clinically indicated) for tumor assessment will be performed every 2 cycles (as indicated in study flow chart [Section 6.2])

6.1.3 Post-Treatment Period

6.1.3.1 End-of-Treatment

The following study procedures should be completed within 7 days of the last dose of study drug or discontinuation:

- Directed physical examination
- Vital signs and weight
- ECOG performance Status
- Evaluation of AEs
- Concomitant medications
- Urinalysis (including microscopic exam if abnormal results are noted)
- CBC with differential and platelet count
- Blood chemistry assessment, including:
    - ALP, ALT/AST, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate, uric acid, LDH
- Thyroid function tests: TSH, FT4, T3
- Imaging evaluation (CT chest, abdomen and pelvis; MRI if CT is contraindicated; IV contrast given unless contraindicated; Bone scan if clinical indicated; MRI brain if clinically indicated), for tumor assessment. If prior scan was done within 6 weeks, does not have to repeated (per physician discretion)
- Newly obtained (biopsy) tissue collection (subjects will require additional consent) at the time of disease progression.
- Blood for correlative studies (including immune monitoring)
- Correlative Studies Stool Collection

6.1.3.2 Safety Follow-Up

The mandatory Safety Follow-up Visit should be conducted 30 days (+7 days) after the last dose of study treatment or before initiation of a new anticancer 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 anticancer therapy, whichever occurs first. Serious AEs (SAEs) that occur within 90 days of the end of treatment or before initiation of a new anticancer treatment should also be followed and recorded.

The following procedures will be performed at the Safety Follow-up Visit:

- Directed physical examination
- Vital signs and weight
- ECOG performance Status
- Evaluation of AEs
- Concomitant medications
- Urinalysis (including microscopic exam if abnormal results are noted)
- CBC with differential and platelet count
- Blood chemistry assessment, including:
    - ALP, ALT/AST, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate, uric acid, LDH
- Thyroid function tests: TSH, FT4, T3

6.1.3.3 1-Year Follow-Up

Those subjects who complete preoperative therapy and achieve either CR/PR/SD with R0 or R1 resection, and complete 1 year (9 cycles) of continued pembrolizumab-based therapy will be followed for up to 1 additional year (12 months), or until disease progression, death, unacceptable toxicity or withdrawal of consent, whichever occurs first.

Those subjects who complete preoperative therapy and achieve either CR/PR/SD with R2 resection, or achieve a pre-operative CR but do not undergo CN, and complete 2 years (18 cycles) of continued pembrolizumab-based therapy (400 mg Q6W) will be followed for up to 12 additional months, or until disease progression, death, unacceptable toxicity or withdrawal of consent, whichever occurs first.

During the 1-year follow-up period, the following procedures will be performed every 12 weeks(±14 days) from the date of last dose of study treatment or discontinuation:

- Directed physical examination
- Vital signs and weight
- ECOG performance status
- Evaluation of AEs
- Concomitant medications

- CBC with differential and platelet count
- Blood chemistry assessment, including:
    - ALP, ALT/AST, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate, uric acid, LDH
- Thyroid Function Tests: TSH, FT4, T3
- Urinalysis (including microscopic exam, if abnormal results are noted)
- Imaging evaluation (CT chest, abdomen and pelvis; MRI if CT is contraindicated; IV contrast given unless contraindicated; Bone scan if clinical indicated; MRI brain if clinically indicated) for tumor assessment will be performed as specified in study flow chart [Table 7])

6.2 Trial Flow Chart

Table 7: Schedule of Activities

Trial Period:	**Screening Phase**	**Preoperative Treatment Period Visit Number**				**CN/ MET**	**Postoperative Continued Treatment Visit Number[f]**				**Post-Treatment**		
							Up to 9 cycles[q] OR Up to 18 cycles[r]						
	Screening	1 (W1)	2 (W4)	3 (W7)	4 (W10)	(W12)	5 (W15)[v]	6 (W21)	7 (W27)	8-40 (W33-125)	END OF TX[k]	Safety F/U	F/U for subjects who complete 1Y[q] or 2Y[r] of continued TX
Scheduling Window:	-28d to -1d	D1	D1 ±3d	D1 ±3d	D1 ±3d	+7d	D1 ±3d	D1 ±3d	D1 ±3d	D1 ±3d	At DC[w] +7d	30d after DC[w] +7d	Q12W after DC[w] ±7d, for up to 1Y
Administrative Procedures													
Informed Consent	X												
Inclusion/Exclusion Criteria	X												
Demographics/Medical History and Baseline Conditions Assessment	X												
Prior and Concomitant Medication Review	X[o]	X	X	X	X	X	X	X	X	X	X	X	X

Trial Period:	**Screening Phase**	**Preoperative Treatment Period Visit Number**				**CN/ MET**	**Postoperative Continued Treatment Visit Number[f]**				**Post-Treatment**		
							Up to 9 cycles[q] OR Up to 18 cycles[r]						
	Screening	1 (W1)	2 (W4)	3 (W7)	4 (W10)	(W12)	5 (W15)[v]	6 (W21)	7 (W27)	8-40 (W33-125)	END OF TX[k]	Safety F/U	F/U for subjects who complete 1Y[q] or 2Y[r] of continued TX
Scheduling Window:	-28d to -1d	D1	D1 ±3d	D1 ±3d	D1 ±3d	+7d	D1 ±3d	D1 ±3d	D1 ±3d	D1 ±3d	At DC[w] +7d	30d after DC[w] +7d	Q12W after DC[w] ±7d, for up to 1Y
Clinical Procedures/Assessments													
Review Adverse Events		X	X	X	X	X[d]	X	X	X	X	X	X	X
Complete Physical Examination	X												
Directed Physical Exam		X	X	X		X	X	X	X	X	X	X	X
Vital Signs, Height[s], and Weight	X	X	X	X		X	X	X	X	X	X	X	X
ECOG Performance Status	X[a]	X	X	X	X	X[d]	X	X	X	X	X	X	X
Laboratory Procedures/Assessments													
Pregnancy Test – Urine or Serum β-HCG[e]	X												

Trial Period:	**Screening Phase**	**Preoperative Treatment Period Visit Number**				**CN/ MET**	**Postoperative Continued Treatment Visit Number[f]**				**Post-Treatment**		
							Up to 9 cycles[q] OR Up to 18 cycles[r]						
	Screening	1 (W1)	2 (W4)	3 (W7)	4 (W10)	(W12)	5 (W15)[v]	6 (W21)	7 (W27)	8-40 (W33-125)	END OF TX[k]	Safety F/U	F/U for subjects who complete 1Y[q] or 2Y[r] of continued TX
Scheduling Window:	-28d to -1d	D1	D1 ±3d	D1 ±3d	D1 ±3d	+7d	D1 ±3d	D1 ±3d	D1 ±3d	D1 ±3d	At DC[w] +7d	30d after DC[w] +7d	Q12W after DC[w] ±7d, for up to 1Y
PT/INR and aPTT[x]	X	X[c]				X[d]							
CBC with Differential and Platelet Count[x]	X	X[c]	X	X		X[d]	X	X	X	X	X	X	X
Comprehensive Serum Chemistry Panel[b,x]	X	X[c]	X	X		X[d]	X	X	X	X	X	X	X
Urinalysis[n,x]	X		X			X[d]	X		X	X	X	X	X
T3, FT4, and TSH[x]	X		X			X[d]	X		X	X	X	X	X
Study Treatment													
Pembrolizumab		X	X	X			X	X	X	X			
Axitinib (Cohort B Only)		X	X	X			X	X	X	X			
CN/MET						X							
Efficacy Measurements													
Tumor Imaging[j]	X				X		X			X[g]	X[h,i]		X[h,i]

Trial Period:	**Screening Phase**	**Preoperative Treatment Period Visit Number**				**CN/ MET**	**Postoperative Continued Treatment Visit Number[f]**				**Post-Treatment**		
							Up to 9 cycles[q] OR Up to 18 cycles[r]						
	Screening	1 (W1)	2 (W4)	3 (W7)	4 (W10)	(W12)	5 (W15)[v]	6 (W21)	7 (W27)	8-40 (W33-125)	END OF TX[k]	Safety F/U	F/U for subjects who complete 1Y[q] or 2Y[r] of continued TX
Scheduling Window:	-28d to -1d	D1	D1 ±3d	D1 ±3d	D1 ±3d	+7d	D1 ±3d	D1 ±3d	D1 ±3d	D1 ±3d	At DC[w] +7d	30d after DC[w] +7d	Q12W after DC[w] ±7d, for up to 1Y
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood and Stool													
Archival or Newly Obtained Tissue Collection	X[t]					X[u]					X[m]		
Correlative Studies Blood Collection (including immune monitoring)	X	X	X	X		X	X				X		
Correlative Studies Stool Collection and Questionnaire	X				X						X		

Abbreviations: aPTT = activated partial thromboplastin time; β-HCG = beta human chorionic gonadotropin; CBC = complete blood count; DC = discontinuation; ECOG = Easter Cooperative Oncology Group; FT4 = free thyroxine; F/U = follow-up; INR = international normalized ratio; PT = prothrombin time; Q12W = every 12 weeks; SD = stable disease; T3 = triiodothyronine; TSH = thyroid stimulating hormone; Tx = treatment; D = day; W = week; Y = year.

a. To be done within 7 days of Cycle 1 Day 1

b. Includes alkaline phosphatase (ALP), aspartate aminotransferase/alanine aminotransferase (ALT/AST), total bilirubin, calcium, phosphorus, blood urea nitrogen (BUN), creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate, uric acid, lactate dehydrogenase (LDH)

c. Laboratory evaluations may be omitted if they were already performed within 7 days of Cycle 1, Day 1

d. Window for these specific assessments is within the 14 days prior to CN and/or MET

e. Women of childbearing potential require a negative urine test within 72 hours prior to the first dose of study treatment. Serum test is only required if urine test is positive or is not evaluable. Additional urine pregnancy testing can be conducted if required by local regulations or clinically indicated.

f. Administered for up to 1 year (9 cycles) (for patients who undergo CN/MET with R0 or R1 resection), or up to 2 years (18 cycles) (for patients who undergo CN/MET with R2 resection or who had a pre-operative CR but did not undergo CN), or until death, disease progression, unacceptable toxicity, or withdrawal of consent.

g. To be done every 2 cycles (i.e., about every 3 months) during postoperative pembrolizumab-based treatment

h. If prior scan was done within 6 weeks, does not have to repeated (per physician discretion)

i. Those subjects who undergo CN/MET with R0 or R1 resection who complete 1 year (9 cycles) of postoperative pembrolizumab-based therapy, or those patients who undergo CN/MET with R2 resection or who had a pre-operative CR but did not undergo CN and complete 2 years (18 cycles) of postoperative pembrolizumab-based therapy, will have scans Q12W for up to 12 additional months, or until disease progression, death, unacceptable toxicity or withdrawal of consent, whichever occurs first.

j. Imaging evaluation (CT chest, abdomen and pelvis; MRI if CT is contraindicated; IV contrast given unless contraindicated; Bone scan if clinical indicated; MRI brain if clinically indicated), for tumor assessment

k. In subjects who complete postoperative pembrolizumab-based therapy: end of treatment visit will be performed within 7 days of the last dose of study drug or discontinuation

l. In subjects who complete postoperative pembrolizumab-based therapy: additional safety follow-up visit is not necessary; the follow-up visit will be done during the 12 month follow-up period

m. At the time of disease progression (subjects will require additional consent)

n. Urinalysis (including microscopic exam if abnormal results are noted)

o. Record baseline medications taken within 14 days of Cycle 1 Day 1. For stool correlative analysis, it should be noted if antibiotics were taken within 90 days before the first dose of study drug(s).

p. To be done within 72 hours prior to the start of study drug

q. Subjects with an R0 resection (NED, margins negative) or R1 resection (microscopic disease, margins positive) will continue receiving their assigned pembrolizumab-based therapy for up to 9 cycles or until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs first. They will then enter the 1-Year Follow-Up Period.

r. Subjects with an R2 resection (macroscopic disease after surgery), or who had a pre-operative CR but did not undergo CN, will continue receiving their assigned pembrolizumab-based therapy for up to 18 cycles or until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs first. They will then enter the 1-Year Follow-Up Period.

s. Record height at screening only

t. Newly obtained tissue will be a fresh biopsy of primary or metastatic lesion at study baseline and must be collected from all enrolled subjects. Archival tissues will be prior tissues from primary or metastatic lesions that were originally obtained prior to study consent (where available).

u. Subject may be consented for core tumor biopsies if CN and/or MET cannot be performed following preoperative pembrolizumab-based therapy. See section 6.1.2.4 for details.

v. The first dose of study treatment following CN/MET may be no sooner than 3 weeks and no later than 6 weeks following surgery, to allow for postoperative recovery (adequate wound healing and recovery from any postoperative complications) as assessed by the treating surgeon. Subjects who cannot resume therapy within 42 days for any reason will discontinue study participation

w. The timing of the End of Treatment, Safety Follow-Up and every 12 week visits during the 1-Year Follow-Up Period is relative to the last dose of study drug dosing or discontinuation.

x. These specific screening laboratory assessments (CBC with Differential and Platelet Count, Comprehensive Serum Chemistry Panel, PT/INR and aPTT, T3, FT4, and TSH, urinalysis) should be performed within 10 days of treatment initiation.

6.3 Discontinuation/Withdrawal Criteria

6.3.1 Discontinuation of Study Treatment

Discontinuation of study treatment does not represent withdrawal from the study.

As certain data on clinical events beyond study treatment discontinuation may be important to the study, they must be collected through the subject's last scheduled follow-up, even if the subject has discontinued study treatment. Therefore, all subjects who discontinue study treatment prior to completion of the protocol-specified treatment period regimen will still continue to participate in the trial as specified in Sections 6.1.3 and 6.1.3.2.

Subjects may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a subject may be discontinued from study treatment by the investigator or Merck if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Sections 6.1.3 and 6.1.3.2.

A subject must be discontinued from study treatment but continue to be monitored (see Sections 6.1.3 and 6.1.3.2) in the study for any of the following reasons:

- The subject or subject's legally acceptable representative requests to discontinue study treatment
- There is evidence of unequivocal disease progression without evidence of clinical benefit during the adjuvant treatment period (i.e., postoperative pembrolizumab-based therapy)
- There is(are) unacceptable AE(s), which requires discontinuation from study treatment at that time (the subject may still be consented to post-treatment tissue collection, if safe and feasible)
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the investigator
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Any AE requiring discontinuation outlined in Section 5.2
- Subject has a confirmed positive serum pregnancy test
- For subjects who are discontinued from study treatment but continue to be monitored in the trial, all visits and procedures, as outlined in the trial flowchart (Section 6.2), should be completed.

6.3.2 Withdrawal from the Study

A subject must be withdrawn from the study if the subject or subject's legally acceptable representative withdraws consent from the study.

A subject must be withdrawn from the study if there is evidence of unequivocal disease progression without evidence of clinical benefit during the preoperative treatment period. Subjects with PD during the preoperative treatment period who, in the opinion of the treating physician and principal investigator, are likely to benefit from CN/MET AND in whom surgery is safe and feasible, may proceed with CN/MET on study. Subjects in whom CN/MET is unlikely to provide benefit OR surgery is not safe and feasible, may still be consented to core tumor biopsy on study, if safe and feasible and, in the judgment of the treating physician, the biopsy will not delay appropriate standard of care. Subjects will withdraw from study participation following CN/MET or tumor biopsy. If CN/MET and tumor biopsy are not safe and feasible and not in the best interests of the subject, the subject will withdraw from study participation immediately.

If a subject withdraws from the study, they will no longer receive study treatment or be followed at scheduled protocol visits.

6.3.3 Lost to Follow-up

If a subject fails to return to the clinic for a required study visit and/or if the site is unable to contact the subject, the following procedures are to be performed:

- The site must attempt to contact the subject and reschedule the missed visit. If the subject is contacted, the subject should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the subject at each missed visit (e.g., phone calls and/or a certified letter to the subject's last known mailing address or locally equivalent methods). These contact attempts should be documented in the subject's medical record.

  Note: A subject is not considered lost to follow-up until the last scheduled visit for the individual subject. The amount of missing data for the subject will be managed via the pre-specified data handling and analysis guidelines.

6.4 Usage of Concurrent/Concomitant Medications/Vaccinations

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Merck Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on study treatment requires the mutual agreement of the investigator, Merck, and the subject.

6.4.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over the counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. For stool correlative analysis, it should be noted if antibiotics were taken within 90 days before the first dose of study drug(s). Concomitant medications administered after 90 days following the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.3.5.

6.4.2 Prohibited Medications

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

- Antineoplastic systemic chemotherapy or biological therapy not specified in this protocol
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed 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. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with Merck.
- Rifaximin or lactulose to control encephalopathy
- Strong inhibitors of CYP3A4/5 (e.g. ketoconazole, grapefruit or grapefruit juice)

- Strong/moderate inducers of CYP3A4/5 (e.g. rifampin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifapentin, phenobarbital, St. John's wort, bosentan, efavirenz, etravirine, modafinil, nafcillin)*

- * Subjects enrolled on Arm A (pembrolizumab monotherapy), who may require the use of any CYP3A4/5 inducer, may be permitted to do so for clinical management of symptoms as determined by the Investigator. These medications are prohibited in Arm B (pembrolizumab + axinitib).

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

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

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

6.5 Dietary Restrictions

There are no dietary restrictions on this study. Subject should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

6.6 Pregnancy and Contraception

6.6.1 Contraception

Pembrolizumab and/or axitinib may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab and/or axitinib 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) Has a congenital or acquired condition that prevents childbearing.

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

(1) Practice abstinence† from heterosexual activity;

OR

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

Acceptable methods of contraception are‡:

Single method (1 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 2 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 IRBs/ERCs. 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 medications 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.

6.6.2 Use in Pregnancy

If a subject inadvertently becomes pregnant while on study treatment, the subject will be immediately discontinued from study treatment. 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 Merck without delay and within 24 hours if the outcome is a SAE (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to Merck. If a male subject impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to Merck and followed as described in Section 7.8.

6.6.3 Use in Nursing Women

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

6.6.4 Pregnancy tests

All women who are being considered for participation in the trial, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy within 72 hours of each cycle of trial treatment and 30 days post treatment. If a urine test is positive or not evaluable, a serum test will be required. Subjects must be excluded/discontinued from the study in the event of a positive or borderline-positive test result.

6.7 Clinical Criteria for Early Trial Termination

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

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

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

6.8 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the

trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in the laboratory manual.

Refer to the Trial Flow Chart - Section 6.2 for the schedule of laboratory assessments.

6.8.1 Laboratory Safety Evaluations (Hematology, Chemistry, Urinalysis, and Others)

Laboratory tests for hematology, chemistry, urinalysis and others are specified here in Table 8.

Table 8 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase (ALP)	Glucose	PT (INR)
Platelet count	Alanine aminotransferase (ALT)	Protein	aPTT
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Total triiodothyronine (T3)
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal results are noted)*	Free tyroxine (T4)
Absolute Neutrophil Count	Carbon Dioxide *(CO_2 or biocarbonate)*	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
Absolute Lymphocyte Count	Uric Acid		Blood for correlative studies
	Calcium		
	Chloride		
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		

Hematology	Chemistry	Urinalysis	Other
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		
† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.			

Laboratory tests for screening should be performed within 10 days prior to treatment. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to dose of trial treatment. Unresolved abnormal laboratory values that are drug-related AEs should be followed until resolution. Laboratory tests do not need to be repeated after the end of treatment if laboratory results are within normal range.

7 Reporting and Documentation of Results

7.1 Evaluation of Efficacy: Antitumor Effect - Solid Tumors

Subject eligibility will be determined using local assessment (Investigator assessment) based on RECIST 1.1. RECIST 1.1 will also be used by the investigator as the primary measure for assessment of tumor response, date of PD, and as a basis for all protocol guidelines related to disease status (e.g., discontinuation of study treatment).

Only those subjects who have measurable disease present at baseline have received at least 1 treatment with pembrolizumab-based therapy, and have had their disease re-evaluated, will be considered evaluable for response. Subjects who exhibit objective disease progression prior to the end of Cycle 1 will also be considered evaluable.

While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred tumor imaging technique in this study. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. Images (including via other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons, but which demonstrate radiologic progression, should also be reviewed by the Investigator. MRI is the strongly preferred modality for imaging the brain. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a subject throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging.

Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

If the Investigator identifies radiographic progression per RECIST 1.1, treatment should continue until PD has been verified.

RECIST guideline version 1.1 is 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.

7.1.1 Initial Tumor Imaging

Initial tumor imaging at Screening must be performed within 28 days prior to the date of allocation. The site study team must review screening images to confirm the subject has measurable disease per RECIST 1.1.

Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if it is of diagnostic quality and performed within 28 days prior to the date of allocation and can be assessed by the investigator.

If brain imaging is performed to document the stability of existing metastases, MRI should be used if possible. If MRI is medically contraindicated, CT with contrast is an acceptable alternative.

7.1.2 Tumor Imaging During the Study

The schedule of on-trial imaging is outlined in Section 6.1 and Table 6.2. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression, the start of new anticancer treatment, withdrawal from study, death, or end of study, whichever occurs first. All supplemental imaging must be reviewed by the investigator.

7.1.3 Response Evaluation Following Surgery

Following CN/MET, little to no residual tumor may be present. Progressive disease is defined as the growth of the primary tumor or appearance of any new tumors following CN/MET as assessed by the Investigator per RECIST 1.1.

Objective response (PR and CR) should be confirmed in subjects with residual disease following CN/MET by a repeat imaging assessment. The imaging for confirmation of response may be performed no earlier than 4 weeks after the first indication of a response is observed. Subjects will then return to the regular imaging schedule, starting with the next scheduled imaging time point. Subjects who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

First evidence of PD by RECIST 1.1 should be confirmed by repeat imaging assessment at 4-8 weeks in clinically stable subjects. Clinically stable subjects may continue study treatment until the repeat imaging assessment to confirm PD. In clinically unstable subjects, per the investigator's assessment, neither repeat imaging assessment nor continuation of study treatment may be feasible or in the best interest of the subject.

See section 7.1.6 for further details regarding RECIST 1.1 response criteria.

7.1.4 Disease Parameters

Measurable disease

Measurable disease is defined as lesions (or tumors) that can be accurately measured in at least 1 dimension (longest diameter [LD] to be recorded) with a minimum size of 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm), and/or 10 mm caliper measurement by clinical exam (when superficial).

All tumor measurements will be recorded in millimeters or decimal fractions of centimeters. Previously irradiated lesions are considered non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

Target lesions

All measurable lesions up to a maximum of 10 lesions total (and a maximum of 5 lesions per organ) representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions will be selected on the basis of their size (lesions with the LD) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the LD for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target lesions

All other lesions (or sites of disease), including any measurable lesions over and above the 10 target lesions, should be identified as non-target lesions and should also be recorded at baseline. It is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”). Bone lesions may be measurable if ≥1 cm on MRI. Measurements of these lesions are not required, but the presence or absence of each will be noted throughout follow-up.

Non-measurable disease

Non-measurable disease is all other lesions (or sites of disease), including small lesions (LD <20 mm with conventional techniques or <10 mm using spiral CT scan). Leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques are all non-measurable.

7.1.5 Methods for Evaluation of Measurable Disease

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

The same method of assessment and the same technique will be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

7.1.6 Response Criteria

Evaluation of Target Lesions

Complete Response

Disappearance of all target lesions determined by 2 separate observations conducted not less than 4 weeks apart. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (the sum may not be "0" if there are target nodes). There can be no appearance of new lesions.

Partial Response

At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum of the LD. There can be no appearance of new lesions.

Progressive Disease

At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum of the LD recorded since the treatment started and minimum 5 mm increase over the nadir, or the appearance of 1 or more new lesions.

Stable Disease

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of the LD since the treatment started.

Evaluation of Non-Target Lesions

Complete Response

Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Incomplete Response/Stable Disease

Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease

Appearance of 1 or more new lesions and/or unequivocal progression of existing non-target lesions.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until PD/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). The subject's best response assignment will depend on the achievement of both measurement and confirmation criteria (Table 9).

Table 9 Response Criteria

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires
CR	CR	No	CR	>4 weeks confirmation
CR	Non-CR/ Non-PD	No	PR	>4 weeks confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once >4 weeks from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

Abbreviations: CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.
* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression

7.2 Evaluation of Safety

Analyses will be performed for all patients having received at least 1 dose of study drug. Safety parameters commonly used for evaluating investigational systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/ SAEs, and changes in vital signs and laboratory values. Investigators who are qualified physicians will assess adverse events as defined by NCI CTCAE, Version 5.0 (http://ctep.cancer.gov/reporting/ctc.html). Any AE that changes NCI CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.

All AEs regardless of NCI CTCAE grade must also be evaluated for seriousness.

7.3 Definitions of Adverse Events

7.3.1 Adverse Event

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

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's 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 trial is not considered an AE.

7.3.2 Adverse reaction

An adverse reaction is defined as any AE caused by the use of a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

7.3.3 Suspected Adverse Reaction

A suspected adverse reaction is defined as any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, "reasonable possibility" indicates that there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

7.3.3.1 Unexpected

An AE or suspected adverse reaction is considered *unexpected* if it is not listed in the IB or package insert(s), or is not listed at the specificity or severity that has been observed, or, if an IB is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

"Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

AEs that would be anticipated to occur as part of the disease process are considered *unexpected* for the purposes of reporting because they would not be listed in the IB. For example, a certain number of non-acute deaths in a cancer trial would be anticipated as an outcome of the underlying disease, but such deaths would generally not be listed as a suspected adverse reaction in the IB.

Some AEs are listed in the IB as occurring with the same class of drugs, or as anticipated from the pharmacological properties of the drug, even though they have not been observed with the drug under investigation. Such events would be considered *unexpected* until they have been

observed with the drug under investigation. For example, although angioedema is anticipated to occur in some subjects exposed to drugs in the angiotensin-converting enzyme (ACE) inhibitor class and angioedema would be described in the investigator brochure as a class effect, the first case of angioedema observed with the drug under investigation should be considered *unexpected* for reporting purposes.

7.3.3.2 Serious

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

- Death;
- Life-threatening (i.e., results in an immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Permanent or significant disability/incapacity;
- Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above;
- Event occurring in a gene therapy study;
- Event that changes the risk/benefit ratio of a study;
- Any other event the Principal Investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution

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

Note: In addition to the above criteria, AEs meeting either of the below criteria, although not serious per International Council for Harmonisation (ICH) definition, are reportable to 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.

Additionally, if an Investigator who is a qualified physician considers an SAE to be related to Merck's product, and the SAE 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 Merck clinical team. All subjects with SAEs must be followed up for outcome.

7.3.3.3 Life-threatening

An AE or suspected adverse reaction is considered *life-threatening* if, in the view of either the investigator or Merck, its occurrence places the subject or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

7.3.4 Definition of an Overdose

For this trial, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater (≥5 times the indicated dose). An overdose of other study treatment will be defined as the administration of a dose that exceeds the dose described in the protocol.

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

7.3.5 Events of Clinical Interest

Selected non-serious and SAE are also known as ECIs and must be reported to Merck.

For the time period beginning when the ICF is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any patient must be reported within 24 hours to the Merck clinical team if it causes the patient 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 through 30 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to Merck's product, must be reported within 24 hours to the Merck clinical team, either by electronic media or paper.

Events of clinical interest for this trial include:

1. An overdose of Merck's product, as defined in Section 7.3.4, 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 3 × ULN and an elevated total bilirubin lab value that is greater than or equal to 2 × ULN and, at the same time, an ALP lab value that is less than 2 × ULN, 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. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

7.4 Recording of an Adverse Event

Refer to the Data Safety Monitoring Plan, located in Appendix 2.

7.5 Follow-up of Adverse Events

All AEs will be followed with appropriate medical management until resolved. Subjects removed from study for unacceptable AEs will be followed until resolution or stabilization of the AE. For selected AEs for which administration of the investigational drug was stopped, a re-challenge of the subject with the investigational drug may be conducted if considered both safe and ethical by the Investigator.

7.6 Adverse Events Monitoring

Refer to the Data Safety Monitoring Plan, located in Appendix 2.

7.7 Expedited Reporting

Reporting to the Data and Safety Monitoring Committee

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s) or to a study procedure, the Investigator or his/her designee must notify the DSMC Chair (or qualified alternate) within 1 business day of knowledge of the event. The contact may be made via phone or e-mail.

Reporting to UCSF Institutional Review Board

The UCSF PI must report events to the UCSF IRB according to institutional guidelines.

UCSF IRB website for guidance in reporting adverse events: https://irb.ucsf.edu/adverse-event

Expedited Reporting to the Food and Drug Administration

If the study is being conducted under an IND, the Sponsor (or the Sponsor-Investigator) is responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting in accordance with federal regulations (21 CFR §312.32).

The Sponsor (or Sponsor-Investigator) must report in an IND safety report any suspected adverse reaction that is both serious and unexpected. The Sponsor needs to ensure that the event meets all three definitions:

- **Suspected adverse reaction**
- **Unexpected**
- **Serious**

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The timeline for submitting an IND safety report to FDA is no later than **15 calendar days** after the Investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)).

Any unexpected fatal or life-threatening suspected adverse reaction will be reported to FDA no later than **7 calendar days** after the Investigator's initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IND safety report will be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

Reporting to Merck

See section 7.8.

7.8 Reporting Events to Merck

All AEs, SAEs and other reportable safety events that occur after the ICF is signed but before treatment allocation must be reported by the investigator if the subject is receiving placebo run-in or other run-in treatment, if the event causes the subject to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of treatment allocation through 30 days following cessation of study treatment must be reported by the investigator.
- All AEs meeting serious criteria, from the time of treatment allocation/randomization through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of treatment allocation/randomization through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the subject initiates new anticancer therapy, must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to the Merck clinical team if the event is considered to be drug related.

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Merck clinical team.

All initial and follow-up AEs, SAEs and other reportable safety events will be recorded and reported to the Merck clinical team or designee within the timeframes as indicated in Table 10.

Table 10 Reporting Time Periods and Timeframes for Adverse Events and Other Reportable Safety Events

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation	Reporting Time Period: Randomization/ Allocation through Protocol-Specified Follow-up Period	Reporting Time Period: After the Protocol Specified Follow-up Period	Timeframe to Report Event and Follow-up Information to Merck[a]:
Serious Adverse Event (SAE)	Report if: - due to protocol-specified intervention - causes exclusion - subject is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome.)	Within 24 hours of learning of event
Non-Serious Adverse Event (NSAE)	Report if: - due to protocol-specified intervention - causes exclusion - subject is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 days of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - Potential DILI - Require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (Do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 days of learning of event

Type of Event	**Reporting Time Period:** **Consent to Randomization/ Allocation**	**Reporting Time Period:** **Randomization/ Allocation through Protocol-Specified Follow-up Period**	**Reporting Time Period:** **After the Protocol Specified Follow-up Period**	**Timeframe to Report Event and Follow-up Information to Merck[a]:**
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 days of learning of event
Pregnancy/Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
a. SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-661-6229.				

7.8.1 Reporting of Pregnancy and Lactation

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a subject (spontaneously reported to the investigator or their designee) that occurs during the trial is reportable to the Merck clinical team.

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 Merck clinical team by either electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.8.2 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to the Merck clinical team. See Table 10 for events that are reportable to Merck.

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

The investigator will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the patients in the trial. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to Merck as an SAE within 24 hours of determination that the event is not progression of the cancer under study.

8 Statistical Considerations and Evaluation of Results

8.1 Study Endpoints

Primary endpoint: The proportion of subjects with ≥2-fold increase in the number of TIICs between baseline and CN/MET specimens.

Secondary endpoints:

- The clinical efficacy of preoperative pembrolizumab-based therapy in subjects with advanced RCC will be assessed by ORR, defined as CR or PR by RECIST 1.1 criteria.
- The clinical efficacy of:
    - Continued pembrolizumab-based therapy will be assessed as follows:
        - In subjects who achieve CR or PR/SD followed by R0 resection: proportion of subjects who remain disease-free at the end of the 1 year continued treatment period (1-year DFS rate), and at 1 year following the end of the continued treatment period (2-year DFS rate), and the median DFS.
        - In subjects who achieve PR/SD with residual disease following CN/MET: proportion of subjects who remain progression-free at the end of the 1 year continued treatment period (1-year PFS rate) and at 1 year following the end of the continued treatment period (2-year PFS rate), and the median PFS.
- Safety will be assessed and reported using NCI CTCAE version 5.0.
    - Surgical complications using Clavien-Dindo classification (Appendix 3)

Exploratory endpoints

- The relationship between clinical efficacy (by above measures) and changes in TIICs (by above measures) will be explored.
- Clinical efficacy: pathologic response rate, R0 resection rate
- The changes in frequency and numbers of circulating T cells will be assessed by flow cytometry.
- Comprehensive assessment will be performed to explore the tumor microenvironment, including for PD-L1 status. Transcriptional profiling of tumor microenvironment

constituents (including T cell subsets, tumor, and stroma) in pre- and post-treatment specimens will be analyzed .

- Changes in the T cell repertoire will be explored via high resolution TCR sequencing, in both blood and tumor specimens.

- Molecular profiling of pre- and post-treatment tumor and normal tissue will be performed to explore biomarkers of response. Neoepitope burden will be assessed.

- Wilcoxon rank-sum test will be used to assess whether there is a relationship between any of the immune cell subsets and objective radiographic response as well as pathologic response. Cox-proportional hazard models will be applied to assess if there is relationship between any of the immune cell subsets and PFS. Parallel analysis will be performed for PD-L1 expression. Wilcoxon rank-sum test will also be used to assess whether the T cell receptor clonality diversity index is different between responders vs. non-responders (defined by objective radiographic response or pathologic response), and between subjects who have progression within 1-year vs. those whose disease has not progressed. Additional analyses of immunocorrelative data are detailed in the procedures manual.

8.1.1 Study Design

This is an open-labeled phase II study, in which eligible subjects with treatment-naïve, advanced RCC will be treated with perioperative pembrolizumab-based therapy prior to and after CN/MET. After safety lead in for each cohort, group sequential design will be applied for each combination cohort.

8.1.2 Randomization

This is a non-randomized study. Cohorts will be accrued concurrently.

8.1.3 Stratification Factors

There are no planned stratification factors.

8.2 Determination of Sample Size and Accrual Rate

8.2.1 Sample Size and Power Estimate

For the primary objective, there will be a binary classification. A subject will be considered to have a “positive response” if there is a ≥2-fold increase (from pre- to post-treatment) in the number of TIICs, and a “negative response” if there is <2-fold increase.

For Cohort A, with 12 subjects, if the true response rate is 30%, the 90% confidence interval of the response rate is (8%, 52%).

For each of the combination cohorts (cohorts B and C), the expanded part will be accrued based on group sequential design. In the first stage, 12 subjects (including the 6 subjects in safety lead-in) will be accrued at the dose level decided at safety lead in. If there are one or fewer responses in these 12 subjects, the study will be stopped due to futility, and if there are 5 or more responses,

the study will be stopped due to efficacy (one-sided alpha spending =0.0004). The final decision to terminate the cohort or continue accruing after these first 12 subjects will be based on discussion amongst members of the Joint Steering Committee, which is comprised of representatives for both Merck and the Sponsor. If accrual to the cohort is continued, additional subjects will be accrued for up to 36 evaluable subjects (or up to 30 if no dose reductions occur).

The null hypothesis of a 10% response rate will be rejected if 6 or more responses are observed in 30 subjects. This design yields a one-side type I error rate of 0.05 and power of 82.3% when the true response rate is 30%. Additionally, the first 6 subjects will be considered the "safety lead-in" for each cohort. If there are ≥2 DLTs in these first 6 subjects, then dose reduction will proceed as described in Section 5.1 and an additional 6 subjects will be accrued. The 6 subjects accrued as the safety lead-in are evaluable. Therefore, a minimum of 4, and a maximum of 36 subjects will be accrued to each pembrolizumab-based combination cohort.

8.2.2 Replacement Policy

A replacement subject may be enrolled if deemed appropriate by the Sponsor-Investigator. Up to 2 subjects may be replaced if they are not evaluable for the primary outcome.

8.2.3 Accrual estimates

Based on current estimates of the number of eligible subjects, we estimate approximately 2 subjects to accrue per month, and anticipate completing accrual to the first cohort within 12 months.

8.3 Interim Analyses and Stopping Rules

Each cohort will be stopped early for lack of safety, if the safety lead-in portion cannot be completed as outlined in the Study Design (Section 3).

The planned interim analysis for both futility and efficacy will be included based on group sequential design for the combination cohorts. 12 subjects (including the 6 subjects in safety lead-in) will be accrued at the dose level decided at safety lead-in. If there are one or fewer responses in these 12 subjects, the study will be stopped due to futility, and if there are 5 or more responses, the study will be stopped due to efficacy (one-sided alpha spending =0.0004). The final decision to terminate the cohort or continue accruing after these first 12 subjects will be based on discussion amongst members of the Joint Steering Committee, which is comprised of representatives for both Merck and the Sponsor.

8.4 Analyses Plans

8.4.1 Analysis Population

- The analysis population for the primary outcome will be all subjects with pre- and post-pembrolizumab treatment tumor specimens that are evaluable for TIICs.
- The All Subjects as Treated (APaT) population will be used for the analysis of the secondary endpoints of clinical efficacy (ORR) and safety/toxicity outcomes. The APaT population consists of all subjects who received at least 1 dose of pembrolizumab-based therapy. At least 1 laboratory or vital sign measurement obtained subsequent to at least 1

dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

- Subjects who undergo CN and/or MET will be evaluable for the exploratory clinical efficacy endpoints: pathologic response rate and R0 resection rate
- Additionally, subjects who receive continued pembrolizumab-based therapy will be evaluable for additional exploratory clinical endpoints (DFS/PFS at 1 and 2 years, median DFS and PFS)

8.4.2 Primary Analysis (or Analysis of Primary Endpoints)

TIICs will be analyzed in pre- and post-pembrolizumab-based treatment tumor specimens. The proportion of subjects with a ≥2-fold increase (from pre- to post-treatment) in the number of TIICs will be calculated.

8.4.3 Secondary Analysis (or Analysis of Secondary Endpoints)

The study will use descriptive statistics to report on the ORR (by RECIST 1.1) following preoperative therapy; DFS/PFS rate at 1-year and 2-years following CN/MET; safety/toxicity of preoperative pembrolizumab-based therapy by NCI CTCAE. Median DFS/PFS following CN/MET will reported using the Kaplan-Meier estimate.

8.5 Evaluation of Safety

Analyses will be performed for all subjects having received at least 1 dose of pembrolizumab-based therapy. The study will use the NCI CTCAE v5.0.

9 Study Management

9.1 Pre-study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4), consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the PI will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects.

The clinical investigation will not begin until either FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed or the FDA has determined that the study is exempt from IND requirements.

The PI must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

9.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of subject-facing materials related to the study (e.g. advertisements used to recruit subjects) will be reviewed and approved by the UCSF IRB. Prior to obtaining IRB approval, the protocol must be approved by the Helen Diller Family Comprehensive Cancer Center Site Committee and by the Protocol Review Committee (PRC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

9.3 Informed Consent

All subjects must be provided a consent form describing the study with sufficient information for each subject to make an informed decision regarding their participation. Subjects must sign the IRB -approved informed consent form prior to participation in any study specific procedure. The subject must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

9.4 Changes in the Protocol

Once the protocol has been approved by the UCSF IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the PI and approved by PRC and the IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to subjects, an amendment may be implemented prior to IRB approval. In this circumstance, however, the PI must then notify the IRB according to institutional requirements.

9.5 Handling and Documentation of Clinical Supplies

The UCSF PI and each participating site will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs. The date, quantity and batch or code number of the drug, and the identification of subjects to whom study drug has been dispensed by subject number and initials will be included. The sponsor-investigator will maintain written records of any disposition of the study drug.

The PI shall not make the investigational drug available to any individuals other than to qualified study subjects. Furthermore, the PI will not allow the investigational drug to be used in any manner other than that specified in this protocol.

The PI will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs at the site. The date, quantity and batch or code number of the drug, and the identification of subjects to whom the investigational product has been dispensed by subject number and initials will be included.

The PI shall not make the investigational drug available to any individuals other than to qualified study subjects. Furthermore, the PI will not allow the investigational product to be used in any manner other than that specified in this protocol.

9.6 Protection of Privacy

Subjects will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will become part of the subject's medical records, and each subject will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

9.7 Case Report Forms (CRFs)

The PI and/or designee will prepare and maintain adequate and accurate subject case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. Study personnel will complete the CRFs; the PI will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the subject's medical records maintained by study personnel. All source documentation should be kept in separate research files for each subject.

In accordance with federal regulations, the PI is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The PI will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

The PI will be responsible for ensuring the accurate capture of study data. At study completion, when the CRFs have been declared to be complete and accurate, the database will be locked. Any changes to the data entered into the CRFs after that time can only be made by joint written agreement among the PI and the trial statistician.

All source documentation and CTMS data will be available for review/monitoring by the UCSF DSMC and regulatory agencies.

9.8 Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center DSMC will be the monitoring entity for this study. The UCSF DSMC will monitor the study in accordance with the NCI-approved Data and Safety Monitoring Plan (DSMP). The DSMC will routinely review all adverse events and suspected adverse reactions considered "serious." The DSMC will audit study-related activities to ensure that the study is conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). Significant results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as applicable. See Appendix 2 - Data and Safety Monitoring Plan.

9.9 Record Keeping and Record Retention

The PI is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The PI is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records such as the physician's progress notes, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed subject consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

In accordance with FDA regulations, the investigator shall retain records for a period of 2 years following the date on which a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

10 References

1. Siegel, R.L., K.D. Miller, and A. Jemal, *Cancer statistics, 2016.* CA Cancer J Clin, 2016. **66**(1): p. 7-30.

2. Motzer, R.J., et al., *Sunitinib versus interferon alfa in metastatic renal-cell carcinoma.* N Engl J Med, 2007. **356**(2): p. 115-24.

3. Sternberg, C.N., et al., *Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial.* J Clin Oncol, 2010. **28**(6): p. 1061-8.

4. Motzer, R.J., L. McCann, and K. Deen, *Pazopanib versus sunitinib in renal cancer.* N Engl J Med, 2013. **369**(20): p. 1970.

5. Heng, D.Y., et al., *Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study.* J Clin Oncol, 2009. **27**(34): p. 5794-9.

6. Fyfe, G., et al., *Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy.* J Clin Oncol, 1995. **13**(3): p. 688-96.

7. Motzer, R.J., et al., *Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma.* N Engl J Med, 2015. **373**(19): p. 1803-13.

8. Motzer, R., et al., *IMMotion151: A Randomized Phase III Study of Atezolizumab Plus Bevacizumab vs Sunitinib in Untreated Metastatic Renal Cell Carcinoma (mRCC).* J Clin Oncol, 2018. **36**: p. (suppl 6S; abstr 578).

9. Disis, M.L., *Immune regulation of cancer.* J Clin Oncol, 2010. **28**(29): p. 4531-8.

10. Dudley, M.E., et al., *Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma.* J Clin Oncol, 2005. **23**(10): p. 2346-57.

11. Hunder, N.N., et al., *Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1.* N Engl J Med, 2008. **358**(25): p. 2698-703.

12. Greenwald, R.J., G.J. Freeman, and A.H. Sharpe, *The B7 family revisited.* Annu Rev Immunol, 2005. **23**: p. 515-48.

13. Okazaki, T., et al., *PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine.* Proc Natl Acad Sci U S A, 2001. **98**(24): p. 13866-71.

14. Zhang, X., et al., *Structural and functional analysis of the costimulatory receptor programmed death-1.* Immunity, 2004. **20**(3): p. 337-47.

15. Chemnitz, J.M., et al., *SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation.* J Immunol, 2004. **173**(2): p. 945-54.

16. Sheppard, K.A., et al., *PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta.* FEBS Lett, 2004. **574**(1-3): p. 37-41.

17. Riley, J.L., *PD-1 signaling in primary T cells.* Immunol Rev, 2009. **229**(1): p. 114-25.

18. Parry, R.V., et al., *CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms.* Mol Cell Biol, 2005. **25**(21): p. 9543-53.

19. Francisco, L.M., P.T. Sage, and A.H. Sharpe, *The PD-1 pathway in tolerance and autoimmunity.* Immunol Rev, 2010. **236**: p. 219-42.

20. Sonpavde, G., T.E. Hutson, and B.I. Rini, *Axitinib for renal cell carcinoma.* Expert Opin Investig Drugs, 2008. **17**(5): p. 741-8.

21. Rini, B.I., et al., *Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial.* Lancet, 2011. **378**(9807): p. 1931-9.

22. Rini, B.I., et al., *Axitinib with or without dose titration for first-line metastatic renal-cell carcinoma: a randomised double-blind phase 2 trial.* Lancet Oncol, 2013. **14**(12): p. 1233-42.

23. Flanigan, R.C., et al., *Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer.* N Engl J Med, 2001. **345**(23): p. 1655-9.

24. Mickisch, G.H., et al., *Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial.* Lancet, 2001. **358**(9286): p. 966-70.

25. Heng, D.Y., et al., *Cytoreductive nephrectomy in patients with synchronous metastases from renal cell carcinoma: results from the International Metastatic Renal Cell Carcinoma Database Consortium.* Eur Urol, 2014. **66**(4): p. 704-10.

26. Lee, S.E., et al., *Metastatectomy prior to immunochemotherapy for metastatic renal cell carcinoma.* Urol Int, 2006. **76**(3): p. 256-63.

27. Karam, J.A., et al., *Metastasectomy after targeted therapy in patients with advanced renal cell carcinoma.* J Urol, 2011. **185**(2): p. 439-44.

28. Alt, A.L., et al., *Survival after complete surgical resection of multiple metastases from renal cell carcinoma.* Cancer, 2011. **117**(13): p. 2873-82.

29. Dabestani, S., et al., *Local treatments for metastases of renal cell carcinoma: a systematic review.* Lancet Oncol, 2014. **15**(12): p. e549-61.

30. Daliani, D.D., et al., *Prospective assessment of systemic therapy followed by surgical removal of metastases in selected patients with renal cell carcinoma.* BJU Int, 2009. **104**(4): p. 456-60.

31. Naito, S., et al., *Prognostic factors of patients with metastatic renal cell carcinoma with removed metastases: a multicenter study of 556 patients.* Urology, 2013. **82**(4): p. 846-51.

32. Zaid, H.B., et al., *Outcomes Following Complete Surgical Metastasectomy for Patients with Metastatic Renal Cell Carcinoma: A Systematic Review and Meta-Analysis.* J Urol, 2017. **197**(1): p. 44-49.

33. Rini, B.I., et al., *The effect of sunitinib on primary renal cell carcinoma and facilitation of subsequent surgery.* J Urol, 2012. **187**(5): p. 1548-54.

34. Rini, B.I., et al., *A Phase II Study of Pazopanib in Patients with Localized Renal Cell Carcinoma to Optimize Preservation of Renal Parenchyma.* J Urol, 2015. **194**(2): p. 297-303.

35. Powles, T., et al., *The outcome of patients treated with sunitinib prior to planned nephrectomy in metastatic clear cell renal cancer.* Eur Urol, 2011. **60**(3): p. 448-54.

36. Powles, T., et al., *Safety and Efficacy of Pazopanib Therapy Prior to Planned Nephrectomy in Metastatic Clear Cell Renal Cancer.* JAMA Oncol, 2016. **2**(10): p. 1303-1309.

37. Lala, M., et al., *A six-weekly (Q6W) dosing schedule for pembrolizumab based on an exposure-response (E-R) evaluation using modeling and simulation.* Journal of Clinical Oncology, 2018. **36**(15_suppl): p. 3062-3062.

38. McDermott, D.F., et al., *A phase II study of atezolizumab (atezo) with or without bevacizumab (bev) versus sunitinib (sun) in untreated metastatic renal cell carcinoma (mRCC) patients (pts).* Journal of Clinical Oncology, 2017. **35**(6_suppl): p. 431-431.

11 Appendices

Appendix 1: Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity Fully active, able to carry on all pre-disease performance without restriction	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
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)	80	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self, unable to carry on normal activity or to do active 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	60	Requires occasional assistance, but is able to care for most of his/her needs
		50	Requires considerable assistance and frequent medical care
3	In bed > 50% of the time Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated Death not imminent
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair	20	Very sick, hospitalization indicated Death not imminent
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

Appendix 2: Data and Safety Monitoring Plan for a Phase 2 or 3 Institutional Study

1. Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for auditing data quality and participant safety for all HDFCCC institutional clinical studies. A summary of DSMC activities for this study includes:

- Review of all participant data in safety lead-in phase
- Approval to enroll past safety lead-in phase by DSMC Chair or Vice Chair
- Semiannual auditing after safety lead-in phase
- Review of serious adverse events
- Minimum of biennial regulatory auditing

2. Monitoring and Reporting Guidelines

Investigators will conduct a continuous review of data and participant safety at monthly site committee meetings where the results of each participant's treatment are discussed and documented in the site committee minutes.

All institutional Phase II studies with a lead-in are designated with a high-risk assessment during the safety lead-in phase and a moderate risk assessment afterwards. During the safety lead-in phase, the DSMC will audit all visits through the first cycle of treatment for all participants enrolled in this phase of the trial.

After the completion of enrollment in the safety lead-in phase, the Principal Investigator will submit a report to the DSMC Chair outlining all AEs, SAEs, and DLTs (as defined in the protocol) with a request to proceed onto the next phase of the study. Within two business days of receipt, the DSMC Chair or designee will review the report and issue written authorization to proceed or a request for more information. The report is then reviewed at the subsequent DSMC meeting.

After DSMC authorization to enroll beyond the safety lead-in phase is granted, study data is audited semiannually, with a random selection of twenty percent of the participants reviewed (or at least three participants if the calculated value is less than three). The DSMC Monitor/Auditor will audit a maximum of 5 cycles of treatment in participants selected for review or until the selected participants discontinue study participation or the trial is closed with the IRB. The assigned DSMC Monitor/Auditor will review no more than 10 total participant charts during the course of auditing this trial. DSMC Monitor/Auditors will send a follow-up report to the study team within 20 business days after the auditing visit is complete for the PI and the study team to resolve all action items from this report within 20 business days. Additionally, a regulatory audit will occur on a biennial basis to review all regulatory documents for the trial.

3. Review and Oversight Requirements

3.1 Adverse Event Monitoring

All Grade 3-5 adverse events (AEs), whether or not considered to be expected or unexpected and whether or not considered to be associated with the investigational

agent(s) or study procedure, will be entered into OnCore®, UCSF's Clinical Trial Management System.

Adverse events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) as developed and revised by the Common Therapy Evaluation Program (CTEP) of the National Cancer Institute. Adverse events are further given an assignment of attribution or relationship to the investigational agent(s) or study procedure. Attribution categories are:

- **Definite** – The adverse event is clearly related to the investigational agent(s) or study procedure.
- **Probable** – The adverse event is likely related to the investigational agent(s) or study procedure.
- **Possible** – The adverse event may be related to the investigational agent(s) or study procedure.
- **Unrelated** – The adverse event is clearly not related to the investigational agent(s) or study procedure.

All Grade 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the UCSF Coordinating Center's Site Committee. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution assignment.

3.2 Serious Adverse Event Reporting

By definition, an adverse event is defined as a serious adverse event (SAE) according to the following criteria:

- Death.
- Life-threatening (i.e. results in an immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Permanent or significant disability/incapacity.
- Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above.
- Event occurring in a gene therapy study.
- Event that changes the risk/benefit ratio of a study.
- Any other event the Principal Investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution.

Serious adverse event reporting will be in accordance with all IRB regulations. For trials conducted under an investigational new drug (IND) application, the SAE will be reported in accordance with Code of Federal Regulation Title 21 Part 312.32 and will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:
https://irb.ucsf.edu/adverse-event

Med Watch forms and information:
www.fda.gov/medwatch/getforms.htm

All serious adverse events are entered into OnCore®, All SAEs are reviewed and monitored by the DSMC on an ongoing basis and discussed at DSMC meetings, which take place every six weeks. The date the SAE was sent to all required reporting agencies will be documented in OnCore®.

If an SAE involves death, and occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s), and is determined to be possibly, probably, or definitely related either to the investigational drug or any research related procedure, then the event must be reported to the DSMC Chair (or Vice Chair) and DSMC Director within one business day.

3.3 Review of Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, the Principal Investigator is responsible for notifying the DSMC via report at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator's Brochure or package insert.

If at any time the Principal Investigator stops enrollment or stops the study due to safety issues, the DSMC Chair (or Vice Chair) and DSMC Director must be notified within one business day.

Data and Safety Monitoring Committee Contacts:

Katie Kelley, MD (DSMC Chair)
[redacted]
UCSF HDFCCC
San Francisco, CA 94158

John McAdams (DSMC Director)
[redacted]
UCSF HDFCCC
San Francisco, CA 94143

Appendix 3: The Clavien-Dindo Classification of Surgical Complications

Full Scale			Contracted Form	
Grades	**Definition**		**Grades**	**Definition**
Grade I:	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.		**Grade I:**	Same as for Full Scale
Grade II:	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.		**Grade II:**	Same as for Full Scale
Grade III:	Requiring surgical, endoscopic or radiological intervention		**Grade III:**	Grades IIIa & IIIb
Grade III-a:	intervention not under general anesthesia			
Grade III-b:	intervention under general anesthesia			
Grade IV:	Life-threatening complication (including CNS complications)‡ requiring IC/ICU-management		**Grade IV:**	Grades IVa & IVb
Grade IV-a:	single organ dysfunction (including dialysis)			

Grade IV-b:	multi organ dysfunction			
Grade V:	Death of a subject		**Grade V:**	Same as for Full Scale
Suffix 'd':	If the subjects suffers from a complication at the time of discharge, the suffix "d" (for 'disability') is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.			