UCSF Helen Diller Family Comprehensive Cancer Center

Phase II Study of Pembrolizumab Plus Capecitabine and Bevacizumab in Microsatellite Stable Metastatic Colorectal Cancer

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PROTOCOL SIGNATURE PAGE

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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 in accordance with applicable IRB requirements, Federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.
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 in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), and with local regulatory requirements. In accordance with the FDA Modernization Act, I will ensure the registration of the trial on the www.clinicaltrials.gov website.
5. I agree to maintain adequate and accurate records in accordance with IRB policies, Federal, state and local laws and regulations.

UCSF Principal Investigator / Study Chair

Printed Name

_____ _____

Signature Date

TRIAL SUMMARY

Title	Phase II Study of Pembrolizumab Plus Capecitabine and Bevacizumab in Microsatellite Stable Metastatic Colorectal Cancer
Trial Phase	Phase II
Clinical Indication	Metastatic or locally advanced unresectable microsatellite stable or mismatch repair proficient colorectal cancer with stable disease or progression on fluoropyrimidine-based therapy
Trial Type	Interventional
Type of control	No treatment control
Route of administration	Intravenous (IV) pembrolizumab & bevacizumab; oral capecitabine (PO)
Trial Blinding	Unblinded open-label
Treatment Groups	Single arm study: Pembrolizumab (MK-3475) 200 mg IV every 3 weeks (Q3W) capecitabine 1000 mg/m2 PO BID on days 1-14 Q3W and bevacizumab 7.5 mg/kg IV Q3W
Number of trial subjects	Approximately 44-56 subjects will be enrolled
Estimated enrollment period	Q3 2017 – Q1 2020
Estimated duration of trial	54 months: from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	24 months
Estimated average length of treatment per patient	8 cycles (24 weeks)

LIST OF ABBREVIATIONS

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical (Classification System)
AUC	Area under the curve
BUN	Blood urea nitrogen
CBC	Complete blood cell (count)
CR	Complete response
CRC	Clinical Research Coordinator
CRC	Colorectal cancer
CRF	Case report form
CSF	Cerebral spinal fluid
CT	Computerized tomography
CTCEA	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTMS	Clinical Trial Management System
DCR	Disease control rate
DFS	Disease-free survival
DLT	Dose limiting toxicity
DOR	Duration of response
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECI	Events of clinical interest
ECOG	Eastern Cooperative Oncology Group
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBeAg	Hepatitis B “e” antigen
HBV	Hepatitis B virus
HCT	Hematocrit
HCV	Hepatitis C virus
HDFCCC	Helen Diller Family Comprehensive Cancer Center
HGB	Hemoglobin
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
IND	Investigational new drug application
IP	Investigational product
IRB	Institutional Review Board
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
IV	Intravenous
LDH	Lactate dehydrogenase
LFT	Liver function test
MedDRA	Medical Dictionary for Regulatory Activities

MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NHL	Non-Hodgkin's Lymphoma
ORR	Overall Response Rate
OS	Overall Survival
PFS	Progression Free Survival
PD	Disease Progression
PK	Pharmacokinetics
PO	Per OS (by mouth, orally)
PR	Partial Response
PRC	Protocol Review Committee (UCSF)
QOL	Quality of Life
RBC	Red Blood Cell (count)
SAE	Serious Adverse Event
SD	Stable Disease
SD	Standard Deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
ULN	Upper Limit of Normal
VEGF	Vascular Endothelial Growth Factor
WBC	White Blood Cell (count)

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1 TRIAL DESIGN

1.1 Trial Design

This is a single-arm, open-label; single-site trial of pembrolizumab, capecitabine, and bevacizumab in previously treated subjects who have locally advanced unresectable or metastatic (Stage IV) microsatellite stable (MSS) colorectal carcinoma (CRC) who experienced stable disease or progression on fluoropyrimidine-based therapy, either 5-fluorouracil (5-FU) or capecitabine. Subjects who have withdrawn from standard treatment due to unacceptable toxicity from an agent other than 5-FU, capecitabine, or bevacizumab or warranting discontinuation of that treatment and precluding retreatment with the same agent before progression of disease will also be eligible. Regimens given with adjuvant intent will be counted as treatment for metastatic disease if the patient's disease had progressed within 6 months following treatment. Subjects with MSS or mismatch repair proficient (pMMR) CRC are eligible to enroll. Subjects will be required to have at least one measurable lesion by Response Evaluation Criteria in Solid Tumors (RECIST 1.1) for response assessment, and have been previously treated with approved standard therapies, which must include a fluoropyrimidine with or without bevacizumab. Subjects enrolled in the phase II must have a lesion that is safely accessible for biopsy.

Initially, a safety lead-in will be conducted because pembrolizumab has not been previously administered with both capecitabine and bevacizumab. Phase II doses for pembrolizumab plus capecitabine and pembrolizumab plus bevacizumab are available; capecitabine plus bevacizumab is a standard of care regimen for metastatic colorectal cancer. The adverse event profiles of pembrolizumab, capecitabine, and bevacizumab do not appear to interact, thus the three agents are anticipated to be tolerable when administered together at standard dose levels. In the safety lead-in, 3 subjects will be treated with full-dose pembrolizumab (200 mg IV q21 days), bevacizumab (7.5 mg/kg IV q21 days), and capecitabine (1000 mg/m2 PO BID on days 1-14) for 1 cycle (3 weeks) prior to enrolling additional patients. If 0-1 patients experience an unexpected dose-limiting toxicity (DLT), 3 additional patients will be enrolled, treated at full dose, and followed for 3 weeks before enrolling additional patients. If two or more of the first 6 patients experience a DLT, then the capecitabine dose will be reduced.

The safety lead-in will determine the recommended phase II dose (RP2D)/maximum tolerated dose (MTD) of capecitabine administered with pembrolizumab and bevacizumab.

Approximately 44-56 subjects will be allocated in this study to receive pembrolizumab with capecitabine and bevacizumab. Patients in the safety lead-in cohort treated at MTD will be included in the phase II study. Following the safety lead-in, all subjects enrolled in the phase II study prior to the interim analysis will undergo a tumor biopsy prior to the start of treatment. Patients with an evaluable pre-treatment biopsy, and in whom repeat biopsy is feasible and not associated with excessively high procedural risk, will undergo a second biopsy at mid-cycle 1 (day 10-14). In order to avoid bleeding complications from the biopsy, cycle 1 will be administered without bevacizumab. After interim analysis, if the total number of biopsies already performed is <46, additional pre-treatment (but not on-treatment) biopsies will be required in post interim analysis patients until the total number of tumor biopsies performed reaches 46. Post interim analysis, bevacizumab will be administered starting at cycle 1.

The primary objective of this trial is to determine the overall response rate (ORR) of pembrolizumab given with capecitabine and bevacizumab versus the appropriate historical controls among patients with metastatic CRC and stable (SD) or progressive disease (PD) on prior fluoropyrimidine-based therapy with or without bevacizumab. Secondary objectives include safety and tolerability, duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS). Beginning with screening, all imaging assessments will be evaluated using RECIST 1.1 for determining eligibility and assessment of response. On study imaging assessments will be performed every 9 weeks (Q9W), calculated from the first dose and independent of treatment delays. RECIST 1.1 will be used by the site for treatment decisions until first radiologic evidence of PD. Following the first evidence of radiologic PD, treatment decisions may be made by the adaption of RECIST 1.1 as described in Section 11.5, termed immune-related RECIST (irRECIST) to accommodate for the tumor response patterns seen with pembrolizumab treatment (e.g., tumor flare). For a clinically stable subject with first radiologic evidence of PD, it is at the discretion of the site investigator to continue treating the subject with pembrolizumab, capecitabine, and bevacizumab, until PD is confirmed at least 4 weeks from the date of the first tumor imaging suggesting PD. If radiologic PD is confirmed by the subsequent tumor imaging the subject should be discontinued from treatment unless, in the opinion of the investigator, the subject is achieving a clinically meaningful benefit; an exception to continue treatment may be considered following consultation with the Principal Investigator.

Subjects will continue to be treated with pembrolizumab, capecitabine, and bevacizumab until progressive disease, unacceptable toxicity, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, administrative reasons, or until the subject has received 35 trial treatments (approx. 2 years) with pembrolizumab. Subjects who discontinue treatment for reasons other than progressive disease will have post-treatment follow-up visits for disease status until disease progression, initiation of a non-study cancer treatment, withdrawal of consent, or loss of subject to follow-up. All subjects will be followed for survival until death, withdrawal of consent, or the end of the study, whichever comes first.

Subjects who attain a confirmed complete response (assessed by the site) by 2 tumor imaging assessments at least 4 weeks apart, and who have received at least 8 treatments (approximately 6 months) with pembrolizumab, may discontinue treatment at the discretion of the investigator after receiving at least 2 treatments beyond the initial determination of a CR.

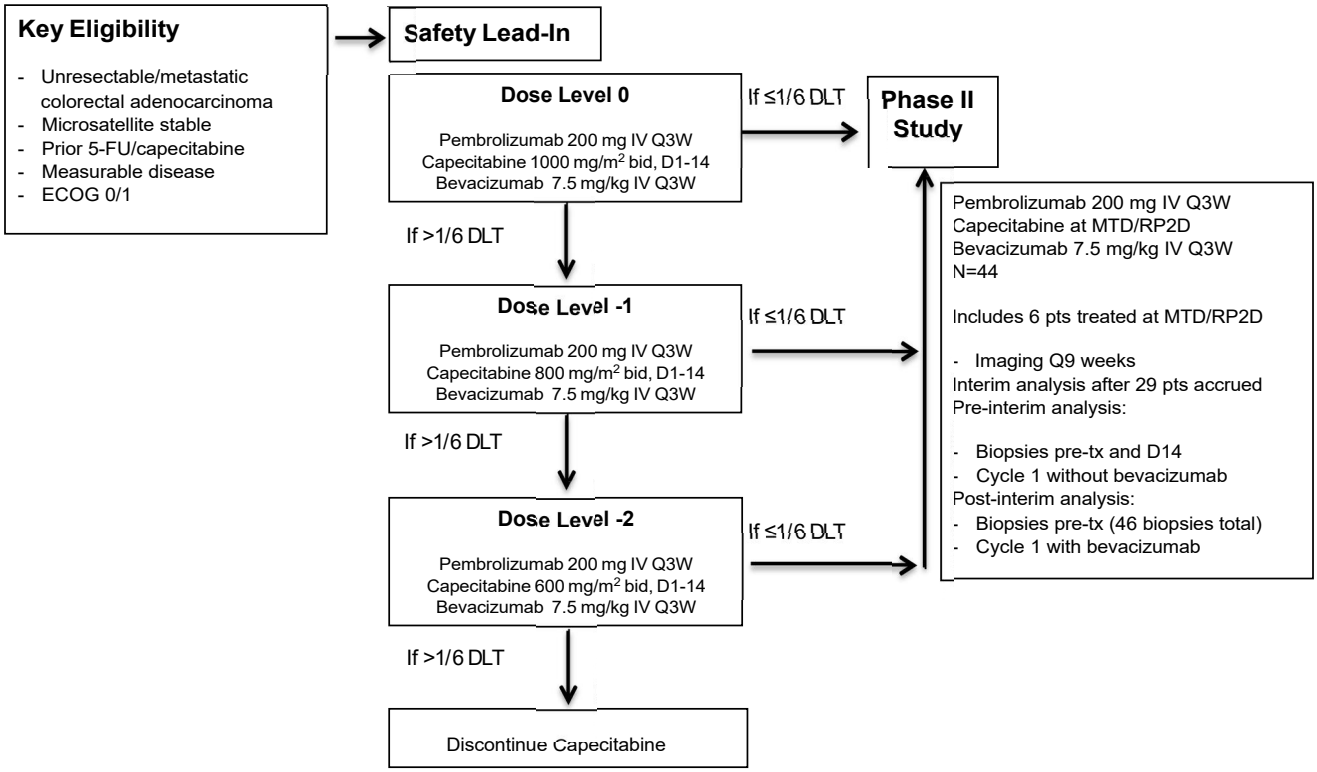
Adverse events (AE) will be monitored throughout the trial and graded in severity according to the guidelines outlined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (Section 7.2.4). After the end of treatment, each subject will be followed for 30 days for AE monitoring. Serious adverse events (SAEs) and events of clinical interest (ECIs) will be collected for 90 days after the end of treatment or 30 days after last dose of trial treatment if the subject initiates new anticancer therapy, whichever is earlier.

There is one interim analysis planned in this study after 29 patients have been accrued at the MTD/RP2D. If there are 1 or fewer responses in these 29 patients, the study will be stopped. Otherwise, 15 additional patients will be accrued. See Section 8.2 for details about the timing and purpose of the interim analysis. Enrollment will not be paused when interim analysis is conducted. Results will be reviewed by study team.

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

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart – Section 6.1. Details of each procedure are provided in Section 7.0– Trial Procedures.

1.2 Trial Diagram



2 OBJECTIVE(S) & HYPOTHESIS(ES)

2.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective of the safety lead-in cohort:** To determine the RP2D/MTD of capecitabine when administered with pembrolizumab and bevacizumab.

(2) **Objective of the phase II expansion cohort**: to evaluate the overall response rate (ORR) to pembrolizumab plus capecitabine and bevacizumab (complete or partial response rate per RECIST 1.1) in subjects with metastatic or locally advanced unresectable MSS/pMMR CRC that is stable or progressing on 5FU-based therapy.

Hypothesis: The ORR based on RECIST 1.1 in subjects with locally advanced unresectable or metastatic MSS/pMMR CRC is at least 15%.

2.2 Secondary Objectives & Hypotheses (phase II expansion cohort)

In subjects with metastatic or locally advanced unresectable MSS/pMMR CRC treated with pembrolizumab, capecitabine, and bevacizumab:

(1) To determine the safety and tolerability of pembrolizumab in combination with capecitabine and bevacizumab.

(2) To evaluate ORR per irRECIST.

(3) To evaluate duration of response (DOR), disease control rate (DCR), and progression-free survival (PFS) per RECIST 1.1 and irRECIST and overall survival (OS).

2.3 Exploratory Objectives

(1) Correlation of outcomes to line of therapy; stable disease or progression on a prior regimen containing infusional 5-FU or capecitabine; prior exposure to bevacizumab; primary tumor location; and on-study administration of bevacizumab starting in cycle 1 or cycle 2

(2) To explore baseline immune profiles via PD-L1, and multiplex IHC (immunohistochemistry) for identification of potentially predictive biomarkers in patients with metastatic or locally advanced, unresectable CRC treated with pembrolizumab-based combination therapy.

(3) To characterize the change in the populations of tumor-infiltrating immune cells (TIICs) by IHC induced by pembrolizumab-based combination therapy in paired pre- and on-treatment tumor biopsies from patients with metastatic or locally advanced, unresectable MSS/pMMR CRC.

Hypothesis: We hypothesize that combination of chemotherapy plus immunotherapy will induce increased populations of TIICs within CRC patient samples and will be associated with objective responses.

(4) To determine the change in T cell repertoire via next-generation sequencing (NGS) within blood and tumor biopsy samples induced by pembrolizumab-based combination therapy in patients with metastatic or locally advanced, unresectable MSS/pMMR CRC.

(5) To establish human immune system (HIS) patient-derived xenograft (PDX) models from pre-treatment biopsies to a) analyze change in immune cell profiles HIS PDX models using the same techniques as described for corresponding patients, above and b) correlate response to pembrolizumab-containing therapy in patients and HIS PDX

3 BACKGROUND & RATIONALE

3.1 Background on Indication

3.1.1 Colorectal Cancer

Colorectal cancer (CRC) is a major global public health problem. Approximately 1 in 20 Americans will be diagnosed with CRC in their lifetime. Metastatic CRC is the second leading cause of cancer death in the U.S., with over 50,000 deaths attributed to this disease each year. The 5-year survival rate is only 13% for patients with distant metastases[1]. Chemotherapy is the mainstay of treatment for patients with metastatic CRC. The backbone of therapy for nearly 40 years has been the fluoropyrimidine, 5-fluorouracil (5-FU).

Capecitabine, the orally administered pro-drug of 5-FU is now also an FDA approved therapy. The most broadly used FDA approved biologic agent is bevacizumab, an antibody that binds vascular endothelial growth factor (VEGF), thereby preventing the interaction of VEGF and its receptors and inhibiting angiogenesis. With the addition of biologics to chemotherapy, the median overall survival of patients with metastatic CRC has increased to about 2.5 years [2,3]. Nonetheless, there remains a significant unmet need for new agents which may both extend survival and maintain quality of life among patients receiving long-term therapy. The need is particularly great for the 96% of patients with MSS/pMMR metastatic CRC, whose cancers do not respond to pembrolizumab monotherapy [4]. As detailed below, there is evidence of immune-stimulatory effects induced by both capecitabine and bevacizumab, which we hypothesize will promote tumor response following the addition of pembrolizumab in MSS/pMMR metastatic CRC.

3.2 Background on Compounds

3.2.1 Pembrolizumab

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

3.2.1.1 Pharmaceutical and Therapeutic Background on Pembrolizumab

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

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig

Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM), and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ, and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T- cell responses is similar to but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs, and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non- hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. KeytrudaTM (pembrolizumab) has recently been approved in the United States for the treatment of patients with unresectable or metastatic melanoma, first- and second-line non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma, and relapsed/refractory Hodgkin's disease.

3.2.1.2 Preclinical and Clinical Trial Data

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

Clinical Trials Testing Pembrolizumab in Colorectal Cancer

Immune checkpoint inhibitors such as pembrolizumab have shown robust single-agent antitumor activity in the ~4% of patients with metastatic CRCs harboring microsatellite instability (MSI-high) or mismatch repair deficiency (dMMR). Preliminary reporting indicated an (immune-related) objective response rate of 40% (4 of 10 patients). On the other hand, 0% (0 of 18 patients) with MSS or pMMR metastatic CRCs achieved an objective response (NCT01876511)[4]. As a result, additional studies are underway for patients with metastatic CRC

and MSI-high or dMMR to test pembrolizumab monotherapy in the previously-treated with chemotherapy setting (KEYNOTE-164; NCT02460198)[5] or pembrolizumab vs. standard chemotherapy in the first-line setting (KEYNOTE-177; NCT02563002)[6]. Pembrolizumab has been added to the 2017 National Comprehensive Cancer Network guidelines for treatment of dMMR/MSI-high metastatic CRC.

Identification of new strategies to augment immune-related responses in the broader population of metastatic CRC patients, without dMMR or MSI-high tumors, is essential[7]. A recent Phase 1b study of the anti-PD-L1 antibody, atezolizumab, plus the MEK inhibitor, cobimetinib, found an overall response rate (ORR) of 17% (4 PR) in 23 patients with metastatic CRC (NCT01988896)[8]. Because neither atezolizumab nor cobimetinib-alone would be expected to induce responses in patients with MSS CRC, this study represents proof-of-concept that combining immunotherapy with other therapies can induce responses. Preclinical data suggest that pembrolizumab may combine effectively with an approved regimen for metastatic CRC, capecitabine plus bevacizumab *(NCCN Guidelines V.2.2016).* As discussed below, the combinations of pembrolizumab plus capecitabine and pembrolizumab plus bevacizumab have already been evaluated in other disease settings; phase II doses are available, and no unexpected toxicities have been observed. Like pembrolizumab, capecitabine plus bevacizumab is a regimen with a 3-week cycle, so if effective, pembrolizumab in combination with capecitabine and bevacizumab would be a convenient regimen for patients that would avoid additional infusion center visits.

3.2.2 Capecitabine

Capecitabine is classified as an antineoplastic agent, antimetabolite (pyrimidine analog). Capecitabine is an oral pro-drug of 5-FU: it undergoes hydrolysis in the liver and tissues to the active moiety, 5-FU. In turn, 5-FU is a fluorinated pyrimidine antimetabolite that inhibits thymidylate synthetase, blocking the methylation of deoxyuridylic acid to thymidylic acid, which interferes with DNA, and to a lesser degree, RNA synthesis. 5-FU appears to act specifically at the G1 and S phases of the cell cycle.

Capecitabine is available as 150 and 500 mg tablets and should be taken orally with water within 30 minutes of meals to improve absorption. Capecitabine is commercially available and FDA approved for patients with metastatic CRC in contexts where fluoropyrimidine therapy is indicated, based on non-inferiority of capecitabine to 5-FU and leucovorin (5-FU/LV) in the adjuvant setting. Refer to the package insert for more detailed information on capecitabine.

3.2.3 Bevacizumab

Bevacizumab is a humanized IgG1 monoclonal antibody (MAb) that binds all biologically active isoforms of human VEGF (or VEGF-A) with high affinity (kd = 1.1 nM). The antibody consists of a human IgG1 framework and the antigen-binding complementarity-determining regions from the murine anti-VEGF MAb A.4.6.1.16-18. Bevacizumab is commercially available, and FDA approved for patients with metastatic CRC, including in combination with 5-FU and following progression on a prior bevacizumab-containing regimen. Refer to the package insert for more detailed information on bevacizumab.

3.2.4 Capecitabine Plus Bevacizumab in Colorectal Cancer

Capecitabine entered the National Comprehensive Cancer Network (NCCN) colon cancer guidelines via a study showing at least equivalent disease control as compared to IV 5FU/leucovorin *(NCCN Guidelines V.2.2016)*[9]. Bevacizumab plus fluoropyrimidine-based regimens has been the subject of several prospective and observational studies[10-16]. Combined analysis of three independent multicenter randomized trials of patients with previously untreated metastatic CRC compared efficacy of the 5-FU/leucovorin (LV) or Irinotecan/5-FU/LV (IFL) regimens (control) vs. 5-FU/LV plus bevacizumab. Addition of bevacizumab was found to improve response rate in the first-line setting (34.1% v 24.5%; P .019), together with improved median PFS and OS[10-12]. Response rates were similar with or without the addition of bevacizumab to first-line oxaliplatin-based chemotherapy regimens (5-FU/leucovorin or capecitabine plus oxaliplatin), although PFS was significantly improved with addition of bevacizumab[13]. Among patients previously treated with a fluoropyrimidine plus irinotecan, ORR for FOLFOX4+bevacizumab, FOLFOX4, or bevacizumab alone were 22.7%, 8.6%, and 3.3%, respectively (P < .0001 for FOLFOX4 with bevacizumab v FOLFOX4 comparison)[14]. The Bevacizumab Regimens: Investigation of Treatment Effects and Safety (BRiTE) study and the subsequent ML18147 trial found that continuing bevacizumab beyond first progression is associated with improved overall survival in metastatic CRC[15,17]. Among patients with advanced CRC that had progressed after irinotecan- and oxaliplatin-based chemotherapy, the response rate to bevacizumab plus 5-FU/LV was 1%[16].

Capecitabine plus bevacizumab became a standard of care regimen following the European Bevacizumab Expanded Access Trial (BEAT), showing safety and improved survival with addition of bevacizumab to first-line FOLFOX, XELOX, FOLFIRI, and fluoropyrimidines *(NCCN Guidelines V.2.2016)*[18] showing that the efficacy and safety of bevacizumab in routine clinical was similar to that in prospective randomized clinical trials. In the Avastin in the Elderly with Xeloda (AVEX), patients 70 years or older with previously untreated, unresectable metastatic CRC who were not candidates for oxaliplatin or irinotecan-based regimens, were randomized to receive capecitabine (1000 mg/m2 twice daily on days 1-14 of a 21-day cycle) or capecitabine plus bevacizumab (7.5 mg/kg every 21 days), with tumor assessments every 9 weeks. The combination of capecitabine plus bevacizumab was well-tolerated and resulted in significantly longer progression-free survival. Of note, the ORR in this first-line setting was 19% in the capecitabine plus bevacizumab group vs. 10% in patients with capecitabine monotherapy (p=0·04)[19].

Capecitabine plus bevacizumab is also used as a maintenance strategy after 5FU-based induction therapy[20]. Maintenance capecitabine plus bevacizumab resulted in a longer time to second progression and global quality of life was reportedly not compromised by maintenance therapy, although 23% of patients developed hand-foot syndrome. Subsequent fluoropyrimidine plus bevacizumab or bevacizumab alone maintenance studies have also found increased time to progression as compared to no treatment[21,22]. As above, the NCCN recommended dosing of capecitabine and bevacizumab in colorectal cancer is capecitabine 850-1250 mg/m2 PO twice daily on days 1-14 of a 21-day cycle, and bevacizumab 7.5 mg/kg every 21 days *(NCCN Guidelines V.2.2016).*

3.2.5 Trials of Pembrolizumab in Combination with Capecitabine

Pembrolizumab plus capecitabine is being studied in a number of cancers including rectal cancer with radiation (NCT02586610), breast cancer (NCT02734290), and gastric or gastroesophageal junction (GEJ) adenocarcinomas (KEYNOTE-059, NCT02335411; and KEYNOTE-062, NCT02494583)[23,24]. No dose-reduction was required in determination of the RP2D of capecitabine in combination with pembrolizumab. The dose of capecitabine used in the phase II and phase III gastric and GEJ studies, in combination with pembrolizumab (200 mg IV, every 3 weeks) is 1000 mg/m2 twice daily on days 1-14 of each 3-week cycle. This capecitabine dose is consistent with the recommended dose of capecitabine in combination with bevacizumab for patients with metastatic colorectal cancer (850-1250 mg/m2 twice daily on days 1-14 of each 3-week cycle).

3.2.6 Trials of Pembrolizumab in Combination with Bevacizumab

Pembrolizumab plus bevacizumab is being tested in other cancers including renal cell carcinoma (NCT01633970; NCT02348008)[25,26], glioblastoma (NCT02337491)[27], melanoma, and non-small cell lung cancer (NCT02681549). The combination of pembrolizumab and bevacizumab has been well-tolerated, without unexpected side-effects or dose-limiting toxicities. The RP2D dose of bevacizumab in combination with pembrolizumab (200 mg IV every 3 weeks) is 15 mg/kg every 3 weeks (renal cell carcinoma) or 10 mg/kg every 2 weeks (glioma). Both of these bevacizumab doses exceed the recommended dose of bevacizumab in combination with capecitabine for patients with metastatic colorectal cancer: 7.5 mg/kg every 3 weeks. Combination of the anti-PD- L1 antibody, atezolizumab, with bevacizumab was found to be safe in patients with MSI-high metastatic CRC[28]. In untreated metastatic renal cell carcinoma, atezolizumab plus bevacizumab resulted in higher PFS and ORR compared to atezolizumab alone or sunitinib[29].

3.3 Rationale

3.3.1 Rationale for the Trial and Selected Subject Population

Metastatic CRC is the second leading cause of cancer death in the U.S., accounting for over 50,000 deaths each year. Approximately 96% of patients with metastatic CRC have MSS/pMMR disease and are in need of new therapies with manageable side-effects which can produce durable treatment responses, as has been observed with pembrolizumab monotherapy in patients with dMMR CRC1. First and second-line standard of care regimens for metastatic CRC are FOLFOX and FOLFIRI with or without a biologic agent (bevacizumab or, if RAS wild-type, an EGFR- targeted antibody). Patients may be treated to disease progression with FOLFOX and FOLFIRI or, due to toxicities, patients may be treated to disease stabilization and then switched to a maintenance regimen, commonly capecitabine plus bevacizumab. Recently FDA-approved third-line therapies are regorafenib and TAS-102. Regorafenib was approved based on a median OS of 6.4 months compared to 5 months with placebo and is associated with a median PFS of 2 months and ORR of 1% 30. TAS-102 was approved based on a median OS of 7.1 months, vs. 5.3 months with placebo; with a median PFS of 2 months and OOR of 1.6%[31].

As above, capecitabine plus bevacizumab is a standard of care regimen for patients with metastatic or locally advanced, unresectable CRC, typically administered after disease

stabilization on a 5FU-based regimen. The RR for capecitabine plus bevacizumab in this maintenance setting, or following progression on a 5FU-based regimen, is estimated to be 4% or less[14,16].

Pembrolizumab alone is not anticipated to produce responses in patients with MSS/pMMR metastatic CRC1. Due to immune-stimulatory effects induced by both capecitabine and bevacizumab, we hypothesize that addition of pembrolizumab will effectively promote tumor shrinkage. An ORR of 15% is targeted as a clinically meaningful benefit following disease stabilization or progression on 5-FU-based therapy and is comparable to the ORR of 17% reported with atezolizumab plus cobimetinib in a similar patient population[8]. Subjects with MSS or pMMR metastatic or locally advanced, unresectable CRC will be included in this study.

3.3.2 Rationale for Pembrolizumab in Combination with Capecitabine

In preclinical models, 5FU depletes myeloid-derived suppressor cells (immature myeloid cells with intratumoral systemic and immunosuppressive functions) and has immunostimulatory effects[32-34]. Direct immune-stimulatory effects are attributed to increased levels of tumor-associated macrophages, reprogrammed toward an immune-stimulatory phenotype, and increased tumor infiltration by regulatory T cells[35]. A related nucleoside analog, gemcitabine (not used in CRC), also increases antigenicity by stimulating the expression of MHC class I molecules by tumor cells[36]. Gemcitabine upregulated immune-specific genes and improved anti-tumor activity of pembrolizumab in mouse models[37].

3.3.3 Rationale for Pembrolizumab in Combination with Bevacizumab

Growing data demonstrate that VEGF contributes significantly to the immunosuppressive ability of tumors[38-40]. Specifically, VEGF can inhibit dendritic cell maturation and antigen presentation, induce apoptosis of CD8+ T cells, enhance Treg activity, and diminish T cells infiltration into tumor deposits [40-45,46]. Preclinical and emerging clinical data suggest that anti-VEGF therapies may enhance effectiveness of immunotherapy [25,40-44,47-53]. The rationale underlying the combination of immunotherapy approaches with anti-angiogenic agents is based on the ability of VEGF inhibition to diminish immunosuppressive features of tumors [39-44,51-53], and enhance the anti-tumor activity of immunotherapies[48,50-53]. Moreover, preclinical strategies to normalize tumor vasculature, including administration of anti-VEGF therapy, can shift tumor-associated macrophages from immune-inhibitory M2-like phenotype toward an immune-stimulatory M1-phenotype, increase tumor-infiltrating CD8+ T cells and enhance survival following whole tumor cell vaccination[49]. A recently published phase I study found that administration of bevacizumab with ipilimumab, an inhibitor of the CTLA-4 immune checkpoint, led to improved overall survival and evidence of increased immune cell trafficking into tumor deposits in patients with metastatic melanoma[47].

3.3.4 Rationale for Combining Pembrolizumab with Capecitabine and Bevacizumab in Colorectal Cancer

Approximately 95% of individuals with metastatic CRC have MSS/pMMR tumors, which are unlikely to respond to pembrolizumab monotherapy[4]. New therapies to improve survival and maintain quality of life for this sizeable patient population are urgently needed[7]. As discussed above, capecitabine plus bevacizumab is an approved regimen for metastatic CRC. There is

preclinical rationale for combining pembrolizumab with capecitabine and pembrolizumab with bevacizumab; phase II doses for each doublet are available. Due to non-overlapping toxicities, triplet therapy with pembrolizumab, capecitabine, and bevacizumab is expected to be well-tolerated. Patients with MSS/pMMR tumors and stable disease or progression on 5-FU-based therapies are not expected to achieve tumor response with pembrolizumab monotherapy[4] or with capecitabine plus bevacizumab. Tumor responses with triplet therapy (pembrolizumab plus capecitabine and bevacizumab) would thus represent a significant advance, as would increased duration of disease control. Like pembrolizumab, capecitabine plus bevacizumab is administered on a 3-week cycle, making this a convenient regimen for patients.

3.3.5 Rationale for Dose Selection/Regimen/Modification for Pembrolizumab

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

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

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

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

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

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

3.3.6 Rationale for Capecitabine and Bevacizumab Doses in Combination with Pembrolizumab

The recommended dosing of capecitabine in combination with bevacizumab for metastatic CRC is capecitabine 850-1250 mg/m2 PO twice daily on days 1-14 of a 21-day cycle *(NCCN Guidelines V.2.2016).* The RPD2 dose of capecitabine in combination with pembrolizumab in gastric and GEJ tumors (with cisplatin) is 1000 mg/m2 PO twice daily on days 1-14 of a 21-day cycle. Therefore, 1000 mg/m2 PO twice daily on days 1-14 of a 21-day cycle will be the starting dose of capecitabine in combination with pembrolizumab and capecitabine. Capecitabine dose reduction recommendations are provided in the event that DLTs are observed in the safety lead-in.

Bevacizumab is FDA approved in metastatic CRC for dosing at 7.5 mg/kg every 3 weeks in combination with fluoropyrimidine-based chemotherapy, including in patients who have progressed on a first-line bevacizumab-containing regimen. The standard CRC dose is lower than the RP2D of bevacizumab in combination with pembrolizumab, 15 mg/kg every 3 weeks in renal cell carcinoma, so a dose of 7.5 mg/kg will be administered in combination with pembrolizumab and bevacizumab. There is no role for bevacizumab dose reduction, however, criteria for holding or discontinuing bevacizumab are provided.

3.3.6 Rationale for Endpoints

3.3.6.1 Efficacy Endpoints

3.3.6.1.1 Primary Endpoint

The primary efficacy objective of this study is to evaluate the anti-tumor activity of pembrolizumab in combination with capecitabine and bevacizumab in subjects with locally

advanced unresectable or metastatic (Stage IV) CRC. Overall response rate (ORR) will be used as the primary endpoint per RECIST 1.1.

3.3.6.1.2 Secondary Endpoints

The secondary efficacy objectives of this study are to evaluate the endpoints ORR per irRECIST and DOR, DCR, PFS per RECIST 1.1 and irRECIST, and OS in subjects with locally advanced unresectable or metastatic (Stage IV) CRC.

3.3.6.2 Safety Endpoints

An important secondary objective of this study is to characterize the safety and tolerability of pembrolizumab when administered with capecitabine and bevacizumab among subjects with locally advanced unresectable or metastatic (Stage IV) CRC. The safety analysis will be based on subjects who experience toxicities as defined by CTCAE 4.0 criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received pembrolizumab with capecitabine and bevacizumab, including serious adverse events (SAEs) and events of clinical interest (ECIs).

Safety will be assessed by reported adverse experiences using CTCAE, Version 4.0. The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs will be analyzed including but not limited to all AEs, SAEs, and fatal AEs. Furthermore, specific immune-related adverse events (irAEs) will be collected and designated as immune-related events of clinical interest (ECIs) as described in Section 7.2.3.2.

3.3.6.3 Correlative Studies Background

Correlative science to inform optimal use of pembrolizumab with capecitabine and bevacizumab in the patients with metastatic or locally advanced unresectable CRC and to identify candidate biomarkers of response, resistance or toxicity, is an integral part of this study. Correlative research will be performed on archival tumor samples (when available), paired baseline and on-treatment (prior to cycle 2) tumor biopsies, as well as serial blood samples (baseline, on-treatment, and at progression or treatment discontinuation). Goals of the correlative research include baseline profiling of PD-L1 and other potentially predictive biomarkers via IHC; characterization of change tumor-infiltrating immune cells via IHC following treatment with pembrolizumab plus chemotherapy; characterization of treatment-associated changes in T cell repertoire via NGS, and establishment of human immune system patient-derived xenografts.

After study initiation, molecular correlates of response to atezolizumab alone or in combination with bevacizumab in renal cell carcinoma was published in *Nature Medicine*[29]. It was observed that myeloid inflammatory gene expression signatures were strongly associated with PFS: patients with $Teff^{High}$/$Myeloid^{High}$ tumors experienced significantly longer PFS if they received atezolizumab plus bevacizumab as compared atezolizumab or sunitinib alone. This offers a mechanistic explanation for how blocking VEGF may overcome resistance to immune checkpoint blockade. We hypothesize that high expression of myeloid inflammation-associated genes may contribute to resistance to pembrolizumab monotherapy in MSS/pMMR CRC, and that administration of bevacizumab in Cycle 1 of combination therapy with pembrolizumab +

capecitabine may be essential to overcome resistance to checkpoint inhibitor immunotherapy. In order to explore the hypothesis that efficacy may depend on the schedule of bevacizumab, blood-based biomarkers, and clinical outcomes in patients who do or do not receive bevacizumab in Cycle 1 will be compared.

3.3.6.4 Future Biomedical Research

The investigators will conduct Future Biomedical Research on specimens collected for future biomedical research during this clinical trial. This research may include flow cytometry, genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma), characterization of circulating cell-free DNA, and/or the measurement of other analytes. Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research 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 and/or to ensure that subjects receive the correct dose of the correct drug at the correct time.

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

- DNA for future research.
- Leftover tumor for future research
- Leftover DNA and RNA from Correlative Studies
- Leftover plasma and serum from Biomarker Studies
- Leftover PBMC from whole blood from correlative studies

3.3.6.4.1 Withdrawal from Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from a responsible party of the biorepository to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

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

4 METHODOLOGY

4.1 Entry Criteria

4.1.1 Diagnosis/Condition for Entry into the Trial

Locally advanced unresectable or metastatic (stage IV) colorectal adenocarcinoma.

4.1.2 Subject Inclusion Criteria

1. Have histologically confirmed, locally advanced unresectable or metastatic (stage IV) colorectal adenocarcinoma
2. Have locally confirmed MSS or pMMR CRC. MSS is defined as 0-1 allelic shifts among 3- 5 tumor microsatellite loci using a PCR-based assay. pMMR is defined as presence of protein expression of 4 MMR enzymes (MLH1, MSH2, MSH6, and PMS2) by immunohistochemistry.
3. Have stable disease or progression on a prior regimen containing infusional 5-FU or capecitabine according to the interpretation of the treating provider
4. Be willing and able to provide written informed consent/assent for the trial.
5. Be 18 years of age on day of signing informed consent.
6. Have measurable disease based on RECIST 1.1.
7. Be willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion (Phase II expansion cohort only). Newly-obtained is defined as a specimen obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1. Subjects for whom newly-obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived specimen only upon agreement from the Sponsor.
8. Have a performance status of 0 or 1 on the ECOG Performance Scale.
9. Demonstrate adequate organ function as defined in **Table 1**, all screening labs should be performed within 10 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels >1.5 X institutional ULN
Hepatic	
Serum total bilirubin[b]	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases

System	Laboratory Value
Albumin	≥2.5 g/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard. [b]Patients with Gilbert's disease may be included if their direct bilirubin is ≤ 1.5 X ULN.	

10. Female subjects of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
11. Female subjects of childbearing potential (Section 4.7.2 Contraception) must be willing to use an adequate method of contraception as outlined in Section 4.7.2 – Contraception, for the course of the study through 120 days after the last dose of study medication.
12. Male subjects of childbearing potential (Section 4.7.2) must agree to use an adequate method of contraception as outlined in Section 4.7.2 Contraception, starting with the first dose of study therapy through 120 days after the last dose of study therapy.

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

4.1.3 Subject Exclusion Criteria

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

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.
2. Has a known diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
3. Has a known history of active TB (Bacillus Tuberculosis).
4. Known hypersensitivity to pembrolizumab or any of its excipients.

5. Known hypersensitivity/intolerance to capecitabine, infusional 5-fluorouracil, or bevacizumab.

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

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

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

    - Note: If subject received major surgery, they must have recovered adequately, in the opinion of the treating provider, from the toxicity and/or complications from the intervention prior to starting therapy.

8. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

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

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

11. Has known history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or current pneumonitis/interstitial lung disease.

12. Has an active infection at the time of cycle 1 day 1 requiring systemic therapy.

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

14. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial in the opinion of the treating provider.

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

16. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

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

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

19. Requires therapeutic anticoagulation with warfarin at baseline.

    Patients must be off warfarin or warfarin-derivative anti-coagulants for at least 7 days prior to starting study drug, however, therapeutic or prophylactic therapy with low-molecular weight heparin is allowed.

20. Has history of known coagulopathy that increases risk of bleeding or a known history of clinically significant hemorrhage within 12 months of start of study drug.

21. Known bleeding risk including serious hemorrhage or hemoptysis within the last 3 months; major surgery within the past 8 weeks or minor surgery within the past 4 weeks.

22. Has known gastrointestinal bleeding or any other hemorrhage/bleeding event CTCAE Grade > 3 within 6 months of start of study drug.

23. Has greater than 1+ proteinuria on a urine dipstick or equivalent routine laboratory analysis will require further testing with a urine protein to creatinine ratio (UPCR). UPCR must be calculated as follows: UPCR = protein concentration (mg/dL)/creatinine (mg/dL). If the UPCR ≥ 1, then the patient will not be eligible for study entry. However, if urinalysis or equivalent routine laboratory analysis shows no protein, then UPCR testing is not required. Patients with 1+ proteinuria are eligible even if UPCR is >/=1.

24. Has a known history of non-healing wounds or ulcers, or bone re-fractures within 3 months of fracture.

25. Has a history of arterial thromboembolism within 12 months of start of study drug.

26. Has inadequately controlled hypertension (defined as systolic blood pressure greater than 150 mm Hg or diastolic blood pressure greater than 95 mm Hg). The use of antihypertensive medications to control blood pressure is permitted. Retesting is permitted.

27. Has a known history of hypertensive crisis or hypertensive encephalopathy within 6 months prior to planned start of study drug.

28. Has had known clinically significant cardiovascular disease within 12 months of planned start of study drug, including myocardial infarction, unstable angina, grade 2 or greater peripheral vascular disease, cerebrovascular accident, transient ischemic attack,

congestive heart failure, or arrhythmias not controlled by outpatient medication, percutaneous transluminal coronary angioplasty/stent.

29. Has a known history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to planned start of study drug.
30. Known reversible posterior leukoencephalopathy syndrome (RPLS).
31. Difficulty swallowing, malabsorption, known active partial or complete bowel obstruction, or other chronic gastrointestinal diseases or conditions that may hamper compliance and/or absorption of capecitabine.
32. Has received a live vaccine or live-attenuated vaccine within 30 days prior to the first dose of study drug. Administration of killed vaccines is allowed.

4.2 Trial Treatments

4.2.1 Dose Selection

This is a single-center, single-arm, open-label, phase II trial of pembrolizumab in combination with capecitabine and bevacizumab in subjects with locally advanced, unresectable, or metastatic MSS/pMMR CRC. An initial safety lead-in will be performed to define the maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) of capecitabine when administered with pembrolizumab and bevacizumab. The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background and Rationale.

Of note, the adverse event profiles of pembrolizumab, capecitabine, and bevacizumab do not appear to interact, thus the three agents are anticipated to be tolerable when co-administered. The dose of pembrolizumab administered during the safety lead-in will not exceed the established phase II dose when administered as monotherapy. The doses of capecitabine and bevacizumab administered during the safety lead-in will not exceed the standard of care doses, in combination, for CRC, or the RP2D of each drug in combination with pembrolizumab. The safety lead-in also incorporates a de-escalation of capecitabine dosing if unexpected dose-limiting toxicity is observed.

The RP2D/MTD of capecitabine administered with pembrolizumab and bevacizumab will be incorporated into the phase II portion of this study. In the unlikely event that the safety lead-in phase of this study is unable to define an adequately safe dose of capecitabine administered with pembrolizumab and bevacizumab, a phase II study of pembrolizumab with bevacizumab or capecitabine will be performed.

Each treatment cycle will be 3 weeks. The drug doses, frequency, route of administration, and regimen are outlined in **Table 2**.

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3-week cycle	Experimental
Bevacizumab	7.5 mg/kg	Q3W	IV infusion	Day 1 of each 3-week cycle	Standard of care
Capecitabine	1000 mg/m^2 or MTD from safety run-in	BID	PO tablets	Day 1-14 of each 3-week cycle	Standard of care

Trial treatment should begin on the day of registration, within 28 days of signing consent. For the phase II cohort prior to interim analysis only, IV infusion of bevacizumab will begin on Day 1 of Cycle 2.

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

4.2.1.1 Safety Run-in Schedule to Establish the MTD of Capecitabine in Combination with Pembrolizumab and Bevacizumab

The established safety data for pembrolizumab, capecitabine, and bevacizumab, when administered separately, do not appear to overlap indicating that the three agents are expected to be tolerable when co-administered at established dose levels. However, since there is no safety data available for the combination of capecitabine administered with pembrolizumab and bevacizumab, the first 6 patients will be considered as safety lead-in and observed in groups of 3 for DLTs for an evaluation period of 21 days (see DLT definitions in Section 5.2.1.2 and 5.2.1.3) as follows:

- If at Dose Level 0, ≤1 of the first 3 patients develop DLT, 3 more patients will be enrolled to Dose Level 0.
- If at Dose Level 0, >1 of the first 3 patients or >1 of the first 6 patients develops DLT, cohort enrollment will be stopped immediately and re-started from the beginning with 3+3 patients enrolled at a dosing interval of 3 weeks (Dose Level -1).
- If at Dose Level -1, >1 of the first 3 patients or >1 of 6 patients develops DLT, cohort enrollment will be stopped immediately and re-started from the beginning with 3+3 patients enrolled at a dosing interval of 3 weeks (Dose Level -2).
- If at Dose level -2, >1 of the first 6 patients develops DLT, the safety lead-in will be discontinued.
- If the safety lead-in is discontinued due to capecitabine toxicity, a phase II study of pembrolizumab plus bevacizumab will be performed.

The safety lead-in will determine the RP2D/MTD of capecitabine when administered with pembrolizumab and bevacizumab. Capecitabine will be initially administered at 1000 mg/m2 PO BID on days 1-14 of every 3-week cycle with pembrolizumab at 200 mg IV and bevacizumab 7.5 mg/kg IV every three weeks. Dose modification guidelines for capecitabine drug-related adverse events are provided in **Table 6**. A subject who experiences a DLT considered at least possibly related to capecitabine may remain in the trial and continue receiving

capecitabine at a lower dose (plus pembrolizumab and bevacizumab) if the investigator deems potential benefits outweigh the risks. If more than 2 DLTs considered at least possibly related to capecitabine are observed amongst the six first subjects, a de-escalation of capecitabine will begin at the dose levels listed in **Table 3**.

Table 3. Dosing of Capecitabine During the Safety Lead-in

Dose level	Dose of Capecitabine	Minimum Number of Patients
0	1000 mg/m^2 PO BID	6
-1	800 mg/m^2 PO BID	6
-2	600 mg/m^2 PO BID	6

The dose levels of pembrolizumab and bevacizumab are fixed at levels listed in Table 2 and will not be modified. Criteria for holding or permanently discontinuing pembrolizumab or bevacizumab are provided in Table 5 and Table 7.

4.2.1.2 Definition of Dose-limiting Toxicity

Dose-limiting toxicity (DLT) will be defined as clinically-significant toxicities which are at least possibly treatment-related and meet the criteria listed below:

Hematologic toxicities

- Grade 4 absolute neutropenia lasting >7 days
- Grade ≥3 febrile neutropenia (ANC <1000 and T≥38.5°C)
- Grade 4 thrombocytopenia
- Grade 3 thrombocytopenia lasting >7 days, requiring dose modifications during Cycle 1, requiring platelet transfusion, or associated with clinically significant bleeding (defined as bleeding requiring hospitalization, transfusion, or an invasive procedure such as endoscopy).
- Grade 4 anemia
- Grade 3 anemia requiring transfusion

Other treatment-related toxicities:

- Any treatment-related death
- Any dose reduction required during Cycle 1 due to potential treatment-related toxicity
- Any other treatment-related toxicity that results in >7 consecutive days of missed capecitabine doses or a dosing delay lasting >7 consecutive days during cycle 1
- Any treatment delay of > 21 consecutive days during cycle 1 due to toxicity that fails to resolve to baseline or grade ≤1
- Any drug-related grade ≥3 non-hematologic toxicity despite optimal supportive care (toxicity grade should be determined after optimal supportive care has been provided, when appropriate) except the following:

- Grade ≥3 nausea, vomiting, or diarrhea lasting ≤72 hr in the absence of maximal medical therapy
- Alopecia
- Grade 3 hypertension that recovers to grade ≤2 within 7 days of adjustment or addition of oral blood pressure medication(s)
- Grade 3 fatigue, asthenia, anorexia, fever, or constipation that resolves to grade ≤2 within 72 hr
- Grade 3 infusion-related reaction resolving within 6 hours with medical management
- Asymptomatic changes in laboratory values (including electrolytes abnormalities that respond to medical intervention or are clinically insignificant; elevation of amylase/lipase with recovery to grade ≤ 2 within 7 days; elevation of alkaline phosphatase)
- Grade 3 immune-related adverse events (such as endocrinopathies, dermatitis, colitis, or pneumonitis) known to be associated with pembrolizumab that improve to grade ≤ 1 within 21 days of supportive management (Table 5)

4.2.1.3 Dose Modifications

Safety Run-In and the Phase II Study

In the event that capecitabine or bevacizumab is discontinued, the subject may still be eligible for continued treatment with pembrolizumab plus bevacizumab or pembrolizumab plus capecitabine, respectively. If both capecitabine and bevacizumab are discontinued, or if pembrolizumab is discontinued, the subject will come off study. Subjects who do not complete the first on-treatment imaging assessment may be replaced.

Refer to **Table 5**, **Table 6,** and **Table 7** for dose modification guidelines for adverse events for pembrolizumab, capecitabine, and bevacizumab respectively. If a subject experiences several toxicities and there are conflicting recommendations, follow the most conservative dose adjustment recommended (dose modification appropriate to the most severe toxicity).

Reduction or withholding of one agent and not the other agent is appropriate if, in the opinion of the Investigator, the toxicity is clearly related to one of the study treatment.

If, in the opinion of the Investigator, the toxicity is related to the combination of two agents, capecitabine may be reduced, or both treatments may be interrupted or discontinued according to recommended dose modifications. If the toxicity is related to the combination of three agents, capecitabine may be reduced, or all three agents held according to the recommended dose modifications. Exceptional circumstances to following the dose modification tables below may be considered after consultation with the Sponsor.

If a toxicity is not otherwise specified, investigators should refer to the label or local standard of care for dose adjustments. At the Investigator's discretion, dose modification according to **Table 4** is allowed for intolerable Grade 2-3 toxicities that are not specified in the tables below. These dose modification decisions must be documented in the subject records.

The Common Terminology Criteria for Adverse Events version 4.0 (CTCAE 4.0) must be used to grade the severity of adverse events.

If appropriate, the Investigator may attribute each toxicity event to pembrolizumab, capecitabine, or bevacizumab alone and use stepwise capecitabine dose modifications according to **Table 4**.

Pembrolizumab and bevacizumab dose reductions are not permitted. Pembrolizumab or bevacizumab treatment may be interrupted or discontinued due to toxicity.

Table 4. Dose Modifications for Capecitabine, Pembrolizumab, and Bevacizumab

Drug	Starting Dose	Dose Level -1	Dose Level -2	Dose Level -3
Capecitabine	1000 mg/m^2 BID	800 mg/m^2 BID	600 mg/m^2 BID	Discontinue
Pembrolizumab	200 mg fixed-dose	Dose reductions are not permitted	Dose reductions are not permitted	Dose reductions are not permitted
Bevacizumab	7.5 mg/kg	Dose reductions are not permitted	Dose reductions are not permitted	Dose reductions are not permitted

Dose Modifications for Pembrolizumab

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per **Table 5** below.

Table 1 Dose Modification and toxicity management for immune-related AEs associated with pembrolizumab and combination therapy

AEs associated with pembrolizumab exposure, including coadministration with additional compounds, may represent an immunologic aetiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab/combination 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/combination treatment, 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/combination treatment are provided in **Table 1**.

Attribution of Toxicity:

When study interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event [to the combination, to capecitabine or bevacizumab alone or to pembrolizumab alone, for adverse events listed in **Table 1**, both interventions must be held according to the criteria in Table 1 Dose Modification and toxicity management for immune-related AEs associated with pembrolizumab and combination therapy.

Holding Study Interventions:

When study interventions are administered in combination, if the AE is considered immune-related, both interventions should be held according to recommended dose modifications.

Restarting Study Interventions:

Participants may not have any dose modifications (no change in dose or schedule) of pembrolizumab in this study, as described in **Table 1**

- If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from all study interventions.
- If the toxicities do resolve and conditions are aligned with what is defined in **Table 1**, the combination of capecitabine, bevacizumab and pembrolizumab may be restarted at the discretion of the investigator. In these cases where the toxicity is attributed to the combination or to capecitabine, pembrolizumab and bevacizumab alone, re-initiation of pembrolizumab as a monotherapy may be considered at the principal investigator's discretion .

Table 1 Dose Modification and toxicity management for immune-related AEs associated with pembrolizumab and combination therapy

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	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		
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		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
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 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]		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
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: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 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	Persistent Grade 2	Withhold	• Based on severity of AE	• Ensure adequate evaluation to confirm

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
irAEs	Grade 3	Withhold or discontinue based on the event [e]	administer corticosteroids	etiology or exclude other causes
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

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 to5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

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

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

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

[e] Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs (eg vasculitis and sclerosing cholangitis).

Dose Modifications for Capecitabine

If the starting dose of capecitabine is 1000 mg/m2, subjects may have up to 2 capecitabine dose level reductions throughout the course of the study, as described in **Table 4**. If further toxicity occurs or the criteria for resuming treatment are not met, capecitabine treatment may be discontinued. If a dose level reduction for toxicity occurs with capecitabine, the dose may not be re-escalated. Dose modifications are always based on the previous cycle.

Any toxicity associated or possibly associated with capecitabine treatment should be managed according to standard medical practice. Patients who require capecitabine hold, dose reduction, or discontinuation are permitted to continue to receive study treatment with pembrolizumab in combination with bevacizumab.

Table 6. Dose Modification Guidelines for Capecitabine Drug-related Adverse Events

Toxicity	Hold Capecitabine Treatment for Grade	Timing for Restarting Capecitabine Treatment	Dose for Restarting Capecitabine Treatment	Discontinue Capecitabine Treatment
Hematologic				
Neutropenia	3[a]	Neutrophil count resolves to >1,000/mm3	No Reduction *consider G-CSF	Toxicity does not resolve within 12 weeks of last dose, or >2 Dose Level reductions exceeded
	4[a]	Neutrophil count resolves to >1,000/mm3	Reduction by 1 DL *consider G-CSF	Toxicity does not resolve within 12 weeks of last dose, or >2 Dose Level reductions exceeded
Febrile Neutropenia	3[a]	Toxicity resolves to Grade 0-1	Reduction by 1 DL	Toxicity does not resolve within 12 weeks of last dose, or >2 Dose Level reductions exceeded
	4[a]	NA	**Discontinue**	**Permanently discontinue capecitabine**
Thrombocytopenia	3-4[a]	Platelet count resolves to >75,000 mm3	Reduction by 1 DL	Toxicity does not resolve within 12 weeks of last dose, or >2 Dose Level reductions exceeded
Non-hematologic				
Diarrhea, Mucositis, or Hand-foot	2-3	Toxicity resolves to Grade 0-1	Reduction by 1 DL	Toxicity does not resolve within 12 weeks of last dose,

Toxicity	Hold Capecitabine Treatment for Grade	Timing for Restarting Capecitabine Treatment	Dose for Restarting Capecitabine Treatment	Discontinue Capecitabine Treatment
Syndrome				or >2 Dose Level reductions exceeded
	4	NA	**Discontinue**	**Permanently discontinue capecitabine**
All other Non-Hematologic Toxicities[b]	3-4[a]	Toxicity resolves to Grade 0-1	Reduction by 1 DL	Toxicity does not resolve within 12 weeks of last dose, or >2 Dose Level reductions exceeded
Laboratory adverse events.	4	NA	Reduction by 1 DL	Toxicity does not resolve within 12 weeks of last dose, or >2 Dose Level reductions exceeded

[a] Permanent discontinuation should be considered for any severe or life-threatening event.

[b] Subjects with intolerable or persistent Grade 2 drug-related AE may hold at physician discretion. Permanently discontinue from agent for persistent Grade 2 adverse reactions for which treatment has been held and did not recover to Grade 0-1 within 12 weeks of the last dose.

Dose Modifications for Bevacizumab

There are no recommended dose reductions of bevacizumab. Guidelines for bevacizumab dose management due to adverse events considered at least possibly related to bevacizumab are summarized in **Table 7**. If adverse events occur that require holding bevacizumab, the dose will remain the same once treatment resumes. Patients who require bevacizumab hold or discontinuation are permitted to continue to receive study treatment with pembrolizumab in combination with capecitabine.

Any toxicity associated or possibly associated with bevacizumab treatment should be managed according to standard medical practice. Bevacizumab has a terminal half-life of 2 to 3 weeks; therefore, its discontinuation results in slow elimination over several months. There is no available antidote for bevacizumab. Subjects should be assessed clinically for toxicity prior to, during, and after each infusion. If unmanageable toxicity occurs because of bevacizumab at any time during the study, treatment with bevacizumab should be discontinued.

Adverse events requiring delays or permanent discontinuation of bevacizumab are listed in **Table 7**.

Table 7. Dose Modification Guidelines for Bevacizumab Drug-related Adverse Events

Toxicity/Event	Grade	Action to be taken
Hypertension	1-2	No dose modifications
	3	If not controlled to ≤159/99 mmHg with medication, **discontinue** bevacizumab
	4 (including RPLS - confirmed by MRI, or hypertensive encephalopathy)	**Discontinue bevacizumab**
Hemorrhage	1-2	No dose modification for grade 1 non-CNS events
	Grade ≥ 1 New CNS hemorrhage	**Discontinue bevacizumab**
	Grade > 1 non- CNS hemorrhage	**Discontinue bevacizumab**
Venous Thrombosis	**1-2**	No dose modification for grade 1/2 events
	3-4 Asymptomatic	Hold study drug treatment. If the planned duration of full-dose anticoagulation is 2 weeks, study drug should be held until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is >2 weeks, study drug may be resumed during the period of full-dose anticoagulation if the following criteria is met: The participant must be therapeutically anticoagulated with an approved anticoagulant agent (no oral coumadin derivatives) according to standard prescribing guidelines.
	4 Symptomatic	**Discontinue bevacizumab**
Arterial Thromboembolic event:	**Any grade**	**Discontinue bevacizumab**
Angina, Myocardial Infarction, Transient Ischemic Attack, Cerebrovascular Accident, any other arterial TBE event.		
CHF (LVSD)	**1-2**	No dose modification
	3	**Hold** bevacizumab until resolution to Gr 1
	4	**Discontinue bevacizumab**
Proteinuria	**1-2**	No dose modification

Toxicity/Event	Grade	Action to be taken
	3	**Hold** bevacizumab until resolution to ≤Gr 2. If UA results with ≥2 g/dL protein, collect 24-hour urine protein. Resume treatment when 24-hour urine protein is <2 g/dL
	4 (nephrotic syndrome)	**Discontinue bevacizumab**
GI Perforation	**Any event**	Discontinue bevacizumab
Bowel Obstruction	**1**	Continue patient for partial obstruction NOT requiring medical intervention
	2	Hold bevacizumab for partial obstruction requiring medical intervention. Patient may restart upon complete resolution
	3-4	Hold bevacizumab for complete obstruction. Patient may restart upon complete resolution. If surgery is necessary, patient may restart bevacizumab after full recovery from surgery, and at investigator's discretion.
Wound dehiscence[a] requiring medical or surgical therapy		**Discontinue bevacizumab**
Infusion Related Reaction	**1-2** **3-4**	Slow infusion. **Discontinue bevacizumab**
Other Unspecified Bev-related AES	**3** **4**	Hold bevacizumab until recovery to ≤Grade 1 **Discontinue bevacizumab**
[a]Bevacizumab will be temporarily suspended at least 4 weeks prior to elective surgery.		

4.2.2 Timing of Dose Administration

All trial treatments will be administered in the order presented below. All study treatments are anticipated to be administered on an outpatient basis; however, inpatient administration is permitted.

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.1). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

Safety lead-in:

Study treatment with pembrolizumab must be administered on Day 1 Cycle 1, followed by bevacizumab and capecitabine.

Phase II:

Cycle 1 Day 1:

Study treatment with pembrolizumab must be administered on Day 1 Cycle 1, followed by capecitabine. Prior to the interim analysis, bevacizumab will not be administered in Cycle 1. Post interim analysis, study treatment with pembrolizumab must be administered on Day 1 Cycle 1, followed by bevacizumab and capecitabine.

Cycle 2 Onwards:

Study treatment with pembrolizumab, followed by bevacizumab and capecitabine may be administered up to 3 days before or after the scheduled Day 1 of each cycle for administrative reasons.

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study treatment (e.g., elective surgery, unrelated medical events, subject vacation, and/or holidays). Subjects may restart study treatment as soon as clinically appropriate at the Investigator's discretion, and not exceeding 3 weeks from the interrupted dosing. Discussion with the Sponsor should occur if the Investigator determines a subject cannot restart study medication within 3 weeks. The reason for interruption should be documented in the subject's study record.

Pembrolizumab

Pembrolizumab 200 mg will be administered as a 30-minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible.

However, given the variability of infusion pumps from site to site, a window of -5 minutes and

+10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min). The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution. Pembrolizumab will be provided to patients enrolled in this study by Merck Pharmaceuticals.

Capecitabine

Administration of capecitabine should begin on Day 1 of each 3-week cycle following administration of pembrolizumab and bevacizumab, as detailed in Table 8 and the Trial Flow Chart (Section 6.1). Please refer to the product label for additional guidance on administration procedures for commercially available capecitabine. Capecitabine will be

administered orally as a dose of 1000 mg/m2 twice daily from Day 1 to Day 14 of each treatment cycle, for a total of 28 doses over 14 days. On Day 1 of Cycle 1, the subjects will begin oral dosing with their evening meal. If the morning dose of capecitabine is missed on Day 1, patients are allowed to make up this missed dose on Day 15 to complete 28 doses.

The capecitabine dose will be based on the subject's actual body weight, and the dose will be recalculated if there is a weight change of >10% from baseline. Capecitabine is supplied commercially and is available in 500 and 150 mg tablets. Either tablet may be prescribed per UCSF standard of care, treating provider's judgment and to optimize patient management. The

daily dose will be adjusted to the nearest full tablet strength. If the nearest total daily dose is an odd number of tablets, do not split. Instead, dose one additional tablet in the morning or evening to achieve required average BID dose. Capecitabine is swallowed with water within 30 minutes after a meal.

Bevacizumab

Bevacizumab infusion will begin no sooner than 1 hour after completion of pembrolizumab infusion for the first cycle of combined therapy. Thereafter bevacizumab may begin upon completion of pembrolizumab. The bevacizumab dose (7.5 mg/kg) will be based on the subject's actual body weight, and the dose will be recalculated if there is a weight change of >10% from baseline. Bevacizumab will be administered as a 90-minute (+/-15 minutes) infusion for the first treatment; 60 minute (+/-10 minutes) infusion for the second treatment; and 30 minute (+/-10 minutes) infusion for subsequent cycles. The infusion rates may be adjusted based on tolerability and may be decreased in the setting of infusion-related reactions.

Table 8. Dose Schedule and Administration of Capecitabine, Pembrolizumab, and Bevacizumab

	Cycle 1			**Cycle ≥2**		
	Week 1	Week 2	Week 3	Week 1	Week 2	Week 3
Capecitabine						
Schedule	Daily[a]	Daily	Rest	Daily	Daily	Rest
Dose	1000 mg/m^2 BID PO	1000 mg/m^2 BID PO		1000 mg/m^2 BID PO	1000 mg/^{m2} BID PO	
Administration	With water within 30 mins after a meal	With water within 30 mins after a meal		With water within 30 mins after a meal	With water within 30 mins after a meal	
Pembrolizumab						
Schedule	Day 1	NA	NA	Day 1	NA	NA
Dose	200 mg			200 mg		
Administration	Infusion: 30 min (-5/+10 min)			Infusion: 30 minutes (-5 min/+10 min)		
Bevacizumab						
Schedule	Day 1[b]	NA	NA	Day 1[c]		
Dose	7.5 mg/kg			7.5 mg/kg		
Administration	Infusion:90 min (+/-15 min)[b]			Infusion: 90 min (+/- 15 min) if first		

	Cycle 1			Cycle ≥2		
	Week 1	Week 2	Week 3	Week 1	Week 2	Week 3
				infusion, 60 min (+/-10 min) if second, 30 min (+/-10 min) subsequent cycles as tolerated.		
Comment	Start 1 hr after completion pembrolizumab infusion			Start 1 hr after completion of pembrolizumab infusion, if first combined treatment with pembrolizumab		

[a] First dose of the capecitabine on Day 1 Cycle 1 begins after evening meal

[b] Day1 Cycle 1 infusion of bevacizumab for safety run-in cohort and for the phase II expansion cohort.

[c] First bevacizumab infusion for phase II cohort prior to interim analysis is Day 1 Cycle 2.

4.2.3 Trial Blinding/Masking

This is an open-label trial; therefore, the Sponsor, investigator, and subject will know the treatment administered.

4.3 Randomization or Treatment Allocation

This is a single-arm non-randomized trial.

4.4 Stratification

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

4.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

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

4.5.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded 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. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

4.5.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology, or as a premedication for iodinated contrast if not amenable to MRI imaging instead of contrast CT. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

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:

- Oral coumadin-derivative anticoagulants such as warfarin are prohibited

In addition:

- Monitor phenytoin levels, as the phenytoin dose may need to be reduced with taken concomitantly with capecitabine.
- Exercise caution if CYP2C9 substrates are co-administered with capecitabine.

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

4.6 Rescue Medications & Supportive Care

4.6.1 Supportive Care Guidelines for Pembrolizumab

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

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 5.2.1.3 for dose modification.

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

- **Pneumonitis:**
  - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
  - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
  - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
- **Diarrhea/Colitis:**
  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and bowel perforation (such as peritoneal signs and ileus).
  - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and

electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.

- For **Grade 2 diarrhea/colitis,** administer oral corticosteroids.
- For **Grade 3 or 4 diarrhea/colitis,** treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
  - For **T1DM or Grade 3-4** Hyperglycemia
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
- **Hypophysitis:**
  - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- **Hyperthyroidism or Hypothyroidism:**

  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
  - **Grade 2** hyperthyroidism events (and Grade 2-4 hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.

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

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

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

- **Management of Infusion Reactions:** Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

  Table 9 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 9. Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids);	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to:	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with:

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
prophylactic medications indicated for ≤ 24 hrs	• IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of antipyretic).
<u>Grades 3 or 4</u> **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)	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDS • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids	No subsequent dosing.

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 4: Life-threatening; pressor or ventilatory support indicated	• Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

Supportive Care Guidelines for Capecitabine and Bevacizumab

Please refer to the product label or local standards of care for additional supportive measures for capecitabine and bevacizumab.

4.7 Diet/Activity/Other Considerations

4.7.1 Diet

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

4.7.2 Contraception

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

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

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

(1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormone 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 (one of the following is acceptable):

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

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

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

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

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

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

4.7.3 Use in Pregnancy

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

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and Merck and followed as described above and in Section 7.2.2

4.7.4 Use in Nursing Women

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

4.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.5.1 – Other Procedures.

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

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

  Note: For unconfirmed radiographic disease progression, please see Appendix 11.5.

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section 7.1.2.7.

- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study medication, whichever is later.

  Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab after 24 months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 7.1.5.1.

- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.6.4 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.2.3.1). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

4.8.1 Discontinuation of Study Therapy after CR

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

4.9 Subject Replacement Strategy

Subjects who do not complete the first on-treatment imaging assessment may be replaced.

4.10 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

5 TRIAL PROCEDURES

5.1 Trial Procedures

The Study Flow Charts (Section 5.1) summarize the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at additional or unscheduled time points if deemed clinically necessary by the investigator.

In some cases, the evaluations or testing may be potentially sensitive in nature (e.g., HIV, HBV, or HCV results), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

5.1 Study Calendar

Trial Period:	**Screening Phase**	**Treatment Cycles**								**End of Treatment**	**Post-treatment**		
Treatment Cycle/Title:	**Screening (Visit 1)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8 to 35**	**Discontinuation**	**Safety Follow-up**	**Follow Up Visits**	**Survival Follow-Up**[a]
										At Time of Discontinuation	**30 Days from Last Dose**	**Every 9 Weeks Post-discontinuation**	**Every 9 Weeks**
Scheduling Window (Days)	**-28 to 0**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 7**	**± 7**	**± 7**
Administrative Procedures													
Informed Consent	X												
Inclusion/Exclusion Criteria	X												
Subject Identification Card (Optional)	X												
Demographics and Medical History	X												
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X		
Clinical Procedures/Assessments													
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	
Full Physical Examination	X									X			
Directed Physical Examination		X	X	X	X	X	X	X	X				
Height, Weight, and Vital Signs (T,P,RR,BP)[b]	X	X	X	X	X	X	X	X	X	X			
12-Lead Electrocardiogram	X												
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X			
Post-study Anticancer Therapy Status											X	X	X

Trial Period:	**Screening Phase**	**Treatment Cycles**								**End of Treatment**	**Post-treatment**		
Treatment Cycle/Title:	**Screening (Visit 1)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8 to 35**	**Discontinuation**	**Safety Follow-up**	**Follow Up Visits**	**Survival Follow-Up[a]**
										At Time of Discontinuation	**30 Days from Last Dose**	**Every 9 Weeks Post-discontinuation**	**Every 9 Weeks**
Scheduling Window (Days)	**-28 to 0**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 7**	**± 7**	**± 7**
Survival Status													X
Pembrolizumab Administration		X	X	X	X	X	X	X	X				
Bevacizumab Administration, Ph II pre-interim analysis			X	X	X	X	X	X	X				
Bevacizumab-Safety Run-in and PhII post interim analysis		X	X	X	X	X	X	X	X				
Capecitabine		28 doses each cycle over 14 days											
Laboratory Assessments[i]													
Pregnancy Test - Urine or Serum \-hCG	X[c]		X	X	X	X	X	X	X	X	X		
PT/INR and aPTT[e]	X[d]												
CBC with Differential[e]	X[d]		X	X	X	X	X	X	X	X	X		
Chemistry Panel[e]	X[d]		X	X	X	X	X	X	X	X	X		
Urinalysis[e]	X[d]	X	X	X	X	X	X	X	X[e]	X	X		
T3, FT4, and TSH[e]	X[d]		X		X		X		X[e]	X	X		
Serum Tumor Markers[f]	X[d]	X	X	X	X	X	X	X	X	X			
Tumor Tissue Collection													

Trial Period:	**Screening Phase**	**Treatment Cycles**								**End of Treatment**	**Post-treatment**		
Treatment Cycle/Title:	**Screening (Visit 1)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8 to 35**	**Discontinuation**	**Safety Follow-up**	**Follow Up Visits**	**Survival Follow-Up[a]**
										At Time of Discontinuation	**30 Days from Last Dose**	**Every 9 Weeks Post-discontinuation**	**Every 9 Weeks**
Scheduling Window (Days)	**-28 to 0**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 7**	**± 7**	**± 7**
Archival Tumor Tissue	X												
Biopsy-Fresh Tissue[g] **(PhII cohort only)**	X		X										
Research blood - Heparin[h]	X	X	X	X						X			
Research blood- PAXgene[h]	X		X	X						X			
Efficacy Measurements													
Tumor Imaging[k]	X[J]	X[k]								X[l]		X	

a) Subjects that experience site assessed PD or start a new anti-cancer therapy should be followed Q9W to assess for survival status.
b) Height will be measured at Visit 1 only.
c) For women of reproductive potential, a serum or urine pregnancy test should be performed within 72 hours prior to each dose of trial treatment and 30 days post last dose of study treatment.
d) Laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment.
e) After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. Thyroid function tests to be performed every other cycle. CBC with differential, chemistry, and urinalysis to be performed prior to every cycle.
f) Serum tumor markers (CEA) should be collected at screening (baseline) and every Cycle until treatment discontinuation.
g) **Phase II cohort, pre-interim analysis cohort ONLY**: CT or US-guided core needle biopsy of a metastatic site will be performed during the screening phase for immune biomarker analysis. An H&E will be performed at a UCSF core facility within 1 week of the pre-treatment biopsy to confirm presence of tumor cells. A second biopsy will be taken on-treatment, prior to cycle 2 in patients where the pre-treatment biopsy contained tumor cells and in whom repeat biopsy is feasible and not associated with excessively risk procedural risk. **Phase II cohort, post interim analysis:** If the total number of biopsies performed is <46, additional pre-treatment (but not on-treatment) biopsies will be required in post interim analysis patients until the total number of tumor biopsies performed reaches 46.
h) PAXgene blood draw volume is 10 ml. Heparin (green top) blood draw volume is 40 ml during screening, 60 ml on C1D1, and C2D1; 40 ml on C3D1 and End of Treatment.
i) Blood will be collected from patients prior to treatment initiation during the screening phase; every 3 weeks on study therapy, including the time of disease progression.
j) Screening tumor imaging will be performed within 28 days prior start of treatment.
k) The first on-study imaging time point will be performed at 9 weeks (63 days ± 7 days) calculated from the date of the first dose of study drugs and will continue to be performed Q9W (63 days ± 7 days), or earlier if clinically indicated.
l) In subjects who discontinue study therapy without confirmed PD by the site per irRECIST, tumor imaging should be performed at the time of treatment discontinuation (± 4 weeks). If previous tumor imaging was obtained within 4 weeks prior to the date of discontinuation, then additional tumor imaging at treatment discontinuation is not required.

5.1.1 Administrative Procedures

5.1.1.1 Informed Consent

The treating investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

5.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

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

The initial informed consent form, any subsequent revised written informed consent form, and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations, and Sponsor requirements. The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject.

5.1.1.2 Inclusion/Exclusion Criteria

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

5.1.1.3 Medical History

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

5.1.1.4 Prior and Concomitant Medications Review

5.1.1.4.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days

before starting the trial. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

5.1.1.4.2 Concomitant Medications

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

5.1.1.5 Disease Details and Treatments

5.1.1.5.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

5.1.1.5.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation, and surgeries.

5.1.1.5.3 Subsequent Anti-Cancer Therapy Status

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

5.1.1.6 Assignment of Screening Number

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

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit. Specific details on the screening visit requirements (screening/rescreening) are provided in Section 6.0.

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

Interruptions from the protocol-specified treatment plan for greater than 12 weeks between pembrolizumab doses require consultation with the Sponsor-Investigator and written documentation of the decision on subject management.

Administration of trial medication will be witnessed by the investigator and/or trial staff while the subject is in the treatment center.

5.1.2 Clinical Procedures/Assessments

5.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 11.2). Toxicities will be characterized

in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

All AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs); see the separate ECI guidance document in the administrative binder regarding the identification, evaluation, and management of potential irAEs.

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

5.1.2.2 Full Physical Exam

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

5.1.2.3 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

5.1.2.4 Vital Signs

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

5.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix 11.2) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

5.1.2.6 Tumor Imaging and Assessment of Disease

Tumor imaging should be performed by computed tomography (CT) (preferred). MRI or magnetic resonance imaging should only be used when CT is contraindicated or for imaging in the brain, but the same imaging technique should be used in a subject throughout the trial. CT imaging is the more commonly used modality and is preferred for the majority of subjects. An MRI can be utilized if clinically appropriate. Imaging should include the chest, abdomen, and pelvis at baseline and all subsequent follow-up time points. Imaging of the abdomen and pelvis should be IV-contrast enhanced.

5.1.2.6.1 Baseline Tumor Imaging

Initial tumor imaging at screening must be performed within 28 days prior to the date of the first cycle. 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 are

acceptable for use as initial tumor imaging if they are of diagnostic quality, include all anatomy as described in the SIM, and performed within 28 days prior to the date of allocation.

5.1.2.6.2 Tumor Imaging During Trial

The first on study imaging assessment should be performed at 9 weeks (63 ±7 days from the date of allocation). Subsequent tumor imaging should be performed Q9W (63 days ±7 days) or more frequently if clinically indicated until PD. Imaging should not be delayed for delays in cycle starts or extension of pembrolizumab cycle intervals. Per RECIST 1.1, partial or complete response should be confirmed by a repeat tumor imaging assessment not less than 4 weeks from the date the response was first documented. The tumor imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled tumor imaging (i.e. 9 weeks later), whichever is clinically indicated. Subjects will then return to regular scheduled imaging Q9W, starting with the next scheduled imaging time point. Subjects who obtain a confirmation imaging assessment do not need to undergo scheduled tumor imaging if it is < 4 weeks later and may wait until the next scheduled imaging time point.

Per irRECIST (Appendix 11.5), if radiologic imaging identifies PD, tumor assessment should be repeated on 4.2.3.1.2.1), and the subject remains on treatment while awaiting radiologic confirmation of progression. Subjects who obtain confirmation tumor imaging do not need to undergo scheduled tumor imaging if it is < 4 weeks later and may wait until the next scheduled imaging time point if clinically stable. Imaging should continue to be performed until disease progression by RECIST 1.1 (unless the investigator chooses to manage the patient by irRECIST which would then be irPD), the start of new anti-cancer treatment, withdrawal of consent, death, or notification by the Sponsor-Investigator, whichever occurs first. Disease progression may be confirmed at least 4 weeks after the first tumor imaging indicating PD disease in clinically stable subjects.

If the subject is clinically stable as per Appendix 11.5, it is the discretion of the PI to continue to treat and image the subject at least 4 weeks after the first tumor imaging indicating PD by RECIST

1.1 by the site. irRECIST would then be followed by the study site to determine if the follow-up tumor imaging confirms PD (irPD). Subjects who have unconfirmed PD may continue on treatment and follow the regular imaging schedule intervals until subsequent PD (irPD) is confirmed by the site per irRECIST provided they have met the conditions detailed in Appendix 11.5.

5.1.2.6.3 End of Treatment and Follow-up Tumor Imaging

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

In subjects who discontinue trial treatment without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging using the same

imaging schedule of Q9W to monitor disease status until the start of new anticancer treatment, disease progression, death, or the end of the study, whichever occurs first.

5.1.2.7 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be applied as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (e.g., discontinuation of study therapy).

During the follow-up period, imaging will be repeated every Q9W (63 ±7 days) until PD. See the Trial Flow Charts - Section 6.0 and Section 7.1.6.4 for information about the Follow-up Visits.

5.1.2.8 Immune-related RECIST (irRECIST)

As noted above, if the site has identified PD by RECIST 1.1, subject management can shift to irRECIST if clinically stable. The study site may elect to continue treatment, repeat ≥ 4 weeks later, and assess tumor response or confirmed progression per irRECIST (see Appendix 11.5 and **Table 10** below).

Table 10. Imaging and Treatment after First Radiologic Evidence of PD

	Clinically Stable		Clinically Unstable	
	Tumor Imaging	**Treatment**	**Tumor Imaging**	**Treatment**
1st radiologic evidence of PD	Repeat tumor imaging at > 4 weeks at site to confirm PD	May continue study treatment at the local site investigator's discretion while awaiting confirmatory tumor imaging by site	Repeat tumor imaging at > 4 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat tumor imaging confirms PD	No additional tumor imaging required*	Discontinue treatment*	No additional tumor imaging required	N/A
Repeat tumor imaging shows SD, PR, or CR	Continue regularly scheduled tumor imaging assessments	Continue study treatment at the local site investigator's discretion	Continue regularly scheduled tumor imaging assessments	May restart study treatment if condition has improved and/or clinically stable per local site investigator's discretion

In determining whether or not the tumor burden has increased or decreased, local study site investigators should consider all target lesions as well as non-target lesions as per irRECIST. Subjects that are deemed clinically unstable are not required to have repeat tumor imaging for confirmation.

For a **clinically stable** subject with first radiologic evidence of PD (i.e., unconfirmed progression of disease), it is at the discretion of the site investigator to continue treating the subject with the assigned treatment per protocol until progression of disease is confirmed at least 28 days from the date of the tumor imaging first suggesting PD. If radiologic progression is confirmed by subsequent tumor imaging (irPD) then the subject will be discontinued from trial treatment. If radiologic progression is not confirmed, then the subject should resume or continue trial treatment and have their next tumor imaging according to the protocol schedule of Q9W (63 days ± 7 days).

*__NOTE:__ If a subject has confirmed radiographic progression (i.e. 2 tumor imaging assessments at least 4 weeks apart demonstrating PD per irRECIST), but the subject is achieving a clinically meaningful benefit, an exception to continue treatment may be considered following consultation with the Sponsor-Investigator. If treatment is continued beyond confirmed radiographic progression, tumor imaging assessments should continue to be performed Q9W.

NOTE: In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging Q9W (63 days ± 7 days), until; the start of new anticancer treatment, disease progression, death, or the end of the study, whichever occurs first.

irRECIST data will be collected in the clinical database.

5.1.3 Tumor Tissue Collection and Correlative Studies Blood Sampling

Many collateral research opportunities exist with this study. Correlative science will be performed in collaboration with Dr. Larry Fong and UCSF Cancer Immunotherapy Lab (UCSF CIL).

5.1.3.1 Tumor Tissue collection

Archival tumor samples. Where available, an archival tumor formalin-fixed paraffin-embedded (FFPE) tissue block will be collected.

Pre-treatment and on-treatment biopsies (phase II portion only). Pre-interim analysis: during the screening phase, core needle biopsy of a metastatic site will be performed for immune biomarker analysis. An H&E stain will be performed at a UCSF core facility to confirm presence of tumor cells. A second biopsy will be taken on-treatment, prior to cycle 2, in patients where the pre-treatment biopsy contained tumor cells and in whom repeat biopsy is feasible and not associated with excessively high procedural risks. Post interim analysis: If the total number of biopsies already performed is <46, additional pre-treatment (but not on-treatment) biopsies will be required in sequential post interim analysis patients until the total number of tumor biopsies performed reaches 46.

5.1.3.2 Blood collections for Correlative Studies.

Blood will be collected from patients prior to treatment initiation during the screening phase (baseline); prior to cycle 1, prior to cycle 2, prior to cycle 3 and at the time of disease progression or treatment discontinuation.

5.1.3.3 Future Biomedical Research Sample Collection

The following specimens are to be obtained as part of Future Biomedical Research (FBR) from subjects who sign the FBR component of the consent:

- Leftover archival or newly obtained tumor tissue
- Leftover blood
- Leftover RNA, DNA, or other derivatives of the above collections

5.1.4 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. Laboratory Safety Evaluations (Hematology, Chemistry, and Urinalysis) and laboratory tests for hematology, chemistry, urinalysis, and others are specified in **Table 11.**

Table 11. Laboratory Tests

Hematology	**Chemistry**	**Urinalysis**	**Other**
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Total triiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡ *(CO2 or bicarbonate)*	Urine pregnancy test †	Free thyroxine (T4)
Absolute Lymphocyte Count			Thyroid-stimulating hormone (TSH)
	Uric Acid		PK - Blood for correlative studies
	Calcium		Carcinoembryonic antigen (CEA)
	Chloride		
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		
	Creatinine		

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

Laboratory tests for screening should be performed within 10 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

5.1.5 Other Procedures

5.1.5.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in **Section 5.8.1 – Discontinuation of Study Therapy after CR**. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.6.4) and then proceed to the Follow-Up Period of the study (described in Section 7.1.6.4.1).

Withdrawal from Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Investigator will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

5.1.6 Visit Requirements

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

5.1.6.1 Screening

5.1.6.1.1 Screening Period

Approximately 28 days prior to treatment allocation, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.0. Screening procedures may be repeated.

Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose of trial treatment except for the following:

- Laboratory tests are to be performed within 10 days prior to the first dose of trial treatment.

- For women of reproductive potential, a serum pregnancy test will be performed within 72 hours prior to the first dose of trial treatment. A urine test may be considered if serum test is not appropriate.

Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments performed during the initial screening period are acceptable in lieu of repeat screening tests if performed within the specified time frame and the inclusion/exclusion criteria are met. Subjects who are rescreened will retain their original screening number.

5.1.6.2 Treatment Period

Visit requirements are outlined in the Trial Flow Chart (Section 6.0). Specific procedure-related details are provided above in the Trial Procedures (Section 7.0)

5.1.6.3 Post-Treatment Visits

5.1.6.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new antineoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

5.1.6.4 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 9 weeks (63 ± 7 days) by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, or end of the study. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

5.1.6.4.1 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 9 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.2 Assessing and Recording Adverse Events

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

and/or intensity) of a preexisting condition that is temporally associated with the use of pembrolizumab, is also an adverse event.

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

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

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

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

From the time of treatment allocation/randomization through 30 days following last dose of trial treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

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

5.2.1 Definition of an Overdose for this Protocol and Reporting of Overdose to the Sponsor-Investigator and Merck

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor-Investigator and within 2 working days hours to Merck Global Safety [redacted]

5.2.2 Reporting of Pregnancy and Lactation to the Sponsor-Investigator and Merck

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

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

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

Such events must be reported within 24 hours to the Sponsor-Investigator and within 2 working days to Merck Global Safety [redacted]

5.2.3 Immediate Reporting of Adverse Events to the Sponsor-Investigator and Merck

5.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of pembrolizumab that:

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

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.

- Is a new cancer (that is not a condition of the study);

- Is associated with an overdose.

Refer to **Table 12** for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until registration for treatment, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.2.3.1 for additional details) that occurs to any subject must be reported within 24 hours to the Sponsor-Investigator and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

For the time period beginning at registration for treatment through 90 days following cessation of treatment, or 30 days following last dose of trial treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.2.5 for additional details), whether or not related to pembrolizumab, must be reported within 24 hours to the Sponsor-Investigator and within 2 working days to Merck Global Safety.

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

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

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

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

5.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 24 hours to the Sponsor-Investigator and within 2 working days to Merck Global Safety [redacted]

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor-Investigator and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified

intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

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

Events of clinical interest for this trial include:

1. An overdose of pembrolizumab, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor-Investigator, that is not associated with clinical symptoms or abnormal laboratory results.
2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.* However, patients with Gilbert's disease with a direct bilirubin of $\leq$ 1.5 X ULN will not be considered an ECI.

   *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.

5.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to Merck as described in Section 7.2.3 - Immediate Reporting of Adverse Events to the Sponsor-Investigator and Merck, unless there is evidence suggesting a causal relationship between the drug and the event. Any such event will be submitted to the Sponsor-Investigator within 24 hours and to Merck Global Safety within 2 working days either by electronic or paper media.

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

The Sponsor-Investigator will monitor aggregated efficacy endpoint events and safety data to ensure the safety of the subjects in the trial. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to Merck Global Safety as an SAE within 2 working days of determination that the event is not progression of the cancer under study

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

5.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which

changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

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

Table 12. Evaluating Adverse Events for Pembrolizumab

An investigator who is a qualified physician, will evaluate all adverse events as to:		
V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life-threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of pembrolizumab that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of pembrolizumab and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis); or	
An investigator who is a qualified physician, will evaluate all adverse events as to:		
Is a new **cancer** (that is not a condition of the study) (although not serious per ICH definition, is reportable to the Sponsor-Investigator within 24 hours and to Merck within 2 working days to meet certain local requirements); **or**		
Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours to the Sponsor-Investigator and to Merck within 2 working days.		
Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).		
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units.	
Action taken	Did the adverse event cause pembrolizumab to be discontinued?	
Relationship to Pembrolizumab	Did pembrolizumab cause the adverse event? The determination of the likelihood that Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information.	

	The following components are to be used to assess the relationship between pembrolizumab and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely pembrolizumab caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to pembrolizumab such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of pembrolizumab? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.
The following components are to be used to assess the relationship between the test drug and the AE:		
An investigator who is a qualified physician, will evaluate all adverse events as to:		
Relationship to Pembrolizumab **(continued)**	**De-challenge**	Was pembrolizumab discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the product; or (3) the trial is a single-dose drug trial); or (4) Product(s) is/are only used one time.)
	Re-challenge	Was the subject re-exposed to pembrolizumab in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY PEMBROLIZUMAB, OR IF REEXPOSURE TO PEMBROLIZUMAB POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR-INVESTIGATOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding pembrolizumab or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		

Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of pembrolizumab relationship).**
An investigator who is a qualified physician will evaluate all adverse events as to:	
Yes, there is a reasonable possibility of pembrolizumab relationship.	There is evidence of exposure to pembrolizumab. The temporal sequence of the AE onset relative to the administration of pembrolizumab is reasonable. The AE is more likely explained by pembrolizumab than by another cause.
No, there is not a reasonable possibility of pembrolizumab relationship	Subject did not receive the pembrolizumab OR temporal sequence of the AE onset relative to administration of pembrolizumab is not reasonable OR the AE is more likely explained by another cause than the pembrolizumab. (Also entered for a subject with overdose without an associated AE.)

5.2.5 Sponsor-Investigator Responsibility for Reporting Adverse Events

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

6 STATISTICAL ANALYSIS PLAN

6.1 Statistical Analysis Plan Summary

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E- 9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. No separate Statistical Analysis Plan (SAP) for the primary, secondary, and exploratory endpoints will be issued for this study.

6.2 Statistical Analysis Plan

Key elements of the statistical analysis plan are summarized in **Table 13**. The comprehensive plan is provided in Sections 8.2 through 8.5.7

Table 13. Key Elements of the Statistical Analysis Plan

Study Design Overview	A phase II study of pembrolizumab plus capecitabine and bevacizumab in metastatic or locally advanced unresectable microsatellite stable colorectal cancer.
Treatment Assignment	This is an open-label study.
Analysis Populations	All Subjects as Treated (ASaT)
Primary Endpoint(s)	ORR based on RECIST 1.1
Statistical Methods for Key Efficacy Analyses	The primary hypothesis will be evaluated by testing for RECIST 1.1 ORR greater than 15% using Exact method based on binomial distribution. [95% CI for ORR will be calculated using Exact method based on binomial distribution.]
Statistical Methods for Key Safety Analyses	Count and percentage of AE will be provided.
Interim Analyses	There is one interim analysis planned in this study which will be performed after the first 29 patients accrued in the expansion cohort. If there are 1 or fewer responses in these 29 patients, the study will be stopped. Otherwise, 15 additional patients will be accrued.
Multiplicity	The overall type I error is controlled at 5% (one-sided) by Simon's two-stage design.
Sample Size and Power	In the initial safety lead-in phase, minimum of 6 patients and a maximum of 18 patients are required. For expansion cohort: Simon's two-stage design (Simon, 1989) will be used. The null hypothesis that the true response rate is 4% will be tested against a one-sided alternative. In the first stage, 29 patients will be accrued (the patients in the safety lead-in cohort at MTD will be included in the expansion cohort). If there are 1 or fewer responses in these 29 patients, the study will be stopped. Otherwise, 15 additional patients will be accrued for a total of 44. The null hypothesis will be rejected if 5 or more responses are observed in 44 patients. This design yields a type I error rate of 0.0295 and power of 80% when the true response rate is 15%.

	In this study, approximately total 44-56 subjects (the patients in the safety lead in cohort at MTD will be included in the expansion cohort) with locally advanced unresectable or metastatic CRC will be enrolled.

Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the study affiliated biostatistician at UCSF.

This trial is being conducted as an open-label study, i.e., subjects, investigators, and sponsor-investigator personnel will be aware of subject treatment assignments after each subject is enrolled and treatment is assigned.

The Clinical Biostatistics department will generate the allocation schedule.

A DLT evaluation of the first 6 patients will be conducted to confirm the safety of administering pembrolizumab at 200 mg (flat dosing) every three weeks with capecitabine and bevacizumab and follows the principles of standard 3+3 dose escalation studies, i.e., if ≤1 of 3 patients develops DLT, expand to 6, and if >1 of 3 or >1 of 6 patients develop DLT, de-escalate to the next lower dose level. Criteria to define DLT are described in Section 5.1.1. The highest dose level associated with ≤1 of 6 patients developing a DLT will define the maximum tolerated dose (MTD) or recommended phase 2 dose level (RP2D) and will not exceed dose level zero (pembrolizumab 200 mg (flat dosing) and bevacizumab 7.5 mg/kg administered once every 3 weeks; capecitabine 1000 mg/m2 bid administered on days 1-14). This process may require up to 3 dose level evaluations and up to 18 patients (Section 5.1). The MTD/RP2D will be used for the subsequent phase II portion of this study. If at capecitabine 600 mg/m2 bid (minus 2 dose level), >1 patient develops DLT, further accrual to the safety lead-in will discontinue and the subsequent phase II portion of this study will be replaced with a phase II study evaluating pembrolizumab with either capecitabine or bevacizumab (doublet rather than triplet therapy) as outlined in Section 13.2.3.3. Because adverse event profiles of pembrolizumab, capecitabine, and bevacizumab are non- overlapping, however, this combination of agents is expected to be well tolerated when administered at standard dose levels; thus the safety lead-in is expected to likely only require the six patients treated at the initial dose level.

6.3 Analysis Endpoints

6.3.1 Efficacy Endpoints

6.3.1.1 Primary Efficacy Endpoint Overall response rate (ORR) - RECIST 1.1

Overall response rate is defined as the proportion of the subjects in the analysis population who have a complete response (CR) or partial response (PR).

6.3.1.2 Secondary Efficacy Endpoints

Disease Control Rate (DCR) - RECIST 1.1 and irRECIST

Disease control rate (DCR) is defined as the percentage of subjects who have achieved confirmed CR or PR or have demonstrated SD for at least 24 weeks prior to any evidence of progression.

Duration of Response (DOR) - RECIST 1.1 and irRECIST

For subjects who demonstrate CR or PR, duration of response is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.

Progression-free Survival (PFS) - RECIST 1.1 and irRECIST

PFS is defined as the time from first day of study treatment to the first documented disease progression or death due to any cause, whichever occurs first.

Overall survival (OS)

OS is defined as the time from first day of study treatment to death due to any cause. Subjects without documented death at the time of the final analysis will be censored at the date of the last follow-up.

6.3.1.3 Safety Endpoints

The primary safety objective of this trial is to characterize the safety and tolerability of pembrolizumab in combination with capecitabine and bevacizumab in subjects with metastatic CRC. The primary safety analysis will be based on subjects who experienced toxicities as defined by CTCAE, Version 4.0 criteria (Appendix 12.6). The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes.

Furthermore, specific immune-related adverse events (irAEs) will be collected and designated as immune-related events of clinical interest (ECIs) as described in Section 7.2.3.2.

6.4 Analysis Populations

6.4.1 Efficacy Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of ORR, DCR, PFS, and OS.

The ASaT population consists of all subjects who received at least one dose of study treatment. The analysis population for DOR consists of responders.

Details on the approach to handling missing data are provided in Section 8.5 Statistical Methods.

6.4.2 Safety Analysis Populations

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

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

Details on the approach to handling missing data for safety analyses are provided in Section 8.5 Statistical Methods.

6.5 Statistical Methods

6.5.1 Statistical Methods for Efficacy Analyses

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

For the primary efficacy endpoint of ORR, the point estimate and 95% confidence interval, will be provided using exact binomial method proposed by Clopper and Pearson (1934)[54]. Subjects in the primary analysis population (ASaT) without ORR data will be counted as non-responders.

For DCR, the point estimate, 95% confidence interval will be provided using exact binomial method proposed by Clopper and Pearson (1934)[54]. Subjects in the analysis population (ASaT) with missing DCR are considered as disease not under control.

For DOR, Kaplan-Meier (KM) curves and median estimates from the KM curves will be provided as appropriate.

Censoring rules for DOR are summarized in **Table 14**.

Table 14. Censoring Rules for DOR

Situation	Date of Progression of Censoring	Outcome
Neither progression nor death, no new anti-cancer therapy initiated	Last adequate disease assessment	Censor (nonevent)
Neither progression nor death, new anti-cancer therapy initiated	Last adequate disease assessment before new anti-cancer therapy initiated	Censor (non-event)
Death or progression after ≥ 2 consecutive missed adequate disease assessments	Last adequate disease assessment prior to ≥ 2 missed adequate disease assessments	Censor (non-event)
Death or progression after ≤ 1 missed adequate disease assessments	PD or death	End of response (Event)
Subjects are considered to have an ongoing response if censored, alive, have not progressed, have not started a new anti-cancer therapy, and have not been determined to be lost to follow-up.		

For PFS and OS endpoints, Kaplan-Meier (KM) curves and median estimates from the KM curves will be provided as appropriate.

The efficacy analysis is summarized in **Table 15**.

Table 15. Analysis Strategy for Efficacy Variables

Endpoint/Variable‡ (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoint and Hypothesis			
ORR • RECIST 1.1 • Hypotheses: ORR per RECIST 1.1 is greater than assumed historical control (4%).	Exact method based on binomial distribution	ASaT	Subjects with missing data are considered non- responders
Secondary Endpoints			
DCR • RECIST 1.1	Exact method based on binomial distribution	ASaT	Subjects with missing data are considered as disease not under control
DOR • RECIST 1.1	Summary statistics using Kaplan-Meier method	All responders	Non-responders are excluded from analysis
PFS • RECIST 1.1	Summary statistics using Kaplan-Meier method	ASaT	Censored at last assessment
OS	Summary statistics using Kaplan-Meier method	ASaT	Censored at last known alive date

6.5.2 Statistical Methods for Safety Analyses

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

6.5.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

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

6.5.4 Analysis of Immunocorrelative Data

Wilcoxon rank-sum test will be used to assess whether there is a relationship between any of the immune cell subsets and objective response and with long/short-term survivors. Cox-proportional hazard models will be applied to assess if there is relationship between any of the immune cell subsets and DOR, PFS, and OS, respectively. 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 response), and between subjects who have progression at 18 weeks vs. those who have not progressed in each arm. Additional analyses of immunocorrelative data are detailed in Appendices 11.6 and 11.7.

6.5.5 Interim Analyses
There is one interim analysis planned in this study which will be performed after the first 29 patients are accrued in the expansion cohort. If there are 1 or fewer responses in these 29 patients, the study will be stopped. Otherwise, 15 additional patients will be accrued.

6.5.6 Multiplicity
The overall type I error is controlled at 5% (one-sided) by Simon's two-stage design.

6.5.7 Sample Size and Power Calculations
In the initial safety lead-in phase, minimum of 6 patients and a maximum of 18 patients are required.

For expansion cohort: Simon's two-stage design (Simon, 1989) will be used. The null hypothesis that the true response rate is 4% will be tested against a one-sided alternative. In the first stage, 29 patients will be accrued (the patients in the safety lead-in cohort at MTD will be included in the expansion cohort). If there are 1 or fewer responses in these 29 patients, the study will be stopped. Otherwise, 15 additional patients will be accrued for a total of 44. The null hypothesis will be rejected if 5 or more responses are observed in 44 patients. This design yields a type I error rate of 0.0295 and power of 80% when the true response rate is 15%.

In this study, approximately total 44-56 subjects (the patients in the safety lead-in cohort at MTD will be included in the expansion cohort) with locally advanced unresectable or metastatic CRC will be enrolled.

6.6 Subgroup Analyses and Effect of Baseline Factors
The estimate of the treatment effect for the primary endpoint will be estimated and plotted within each category of the following classification variables:

- Age category (≤65 vs. >65 years)
- Sex (female vs. male)
- Race (white vs. non-white)
- Prior exposure to bevacizumab
- Stable disease or progression with prior exposure to 5FU or capecitabine
- Primary tumor location (right vs. left colon or rectum)

The consistency of the treatment effect will be assessed descriptively via summary statistics by category for the classification variables listed above.

6.6.1 Compliance (Medication Adherence)
Drug accountability data for pembrolizumab, capecitabine, and bevacizumab will be collected during the study. Capecitabine accountability will be assessed based on the patient's drug diary, which the study team will provide to the patient before each cycle. The drug diary will include the number of tablets and the strength of each tablet taken on each day of every cycle. Any missed doses or deviations from expected dosing will be documented in the form of a note-to-file or detailed in the office note from the next visit. Any deviation from protocol-directed administration will be reported.

Patients should take 28 doses of capecitabine over 14 days per cycle. If patients miss their morning dose on Day 1, they are allowed to make up this missed dose on Day 15 to complete 28 doses.

Patients in the safety lead-in cohort need to take >75% of prescribed capecitabine tables to be considered "evaluable" during Cycle 1 for DLT determination.

6.6.2 Extent of Exposure

Extent of Exposure for a subject is defined as number of cycles in which the subject receives the study medication infusion. Summary statistics will be provided on Extent of Exposure for ASaT population.

7 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

7.1 Pembrolizumab

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

Clinical Supplies will be provided by Merck as summarized in **Table 16**.

Table 16. Product Description

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

7.1.1 Packaging and Labeling Information

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

7.1.2 Clinical Supplies Disclosure

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

7.1.3 Storage and Handling Requirements

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

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

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

7.1.4 Returns and Reconciliation

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

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

7.2 Bevacizumab

7.2.1 Form

Bevacizumab is a clear to slightly opalescent, colorless to pale brown, sterile liquid concentrate for solution for intravenous (IV) infusion. Vials contain bevacizumab with phosphate, trehalose, polysorbate 20, and sterile water for injection (SWFI), USP. Vials contain no preservative and are suitable for single use only. This agent is commercially available and manufactured by Genentech.

7.2.2 Storage and Stability

According to guidelines specified in the package insert.

7.2.3 Preparation

According to guidelines specified in the package insert.

7.2.4 Administration

Bevacizumab is to be administered according to institutional standards.

The dose of bevacizumab is 7.5 mg/kg IV on Day 1 of each three-week cycle. A window of + 3/- 1 day for bevacizumab dosing is acceptable but bevacizumab doses must be at least 10 days apart.

7.2.5 Accountability

The investigator or designated study personnel are responsible for maintaining accurate dispensing records of bevacizumab which are to include start time of infusion, stop time of infusion, total volume.

7.3 Capecitabine

7.3.1 Form

Capecitabine supplied as biconvex, oblong film-coated tablets for oral administration. Each light peach-colored tablet contains 150 mg of capecitabine, and each peach-colored tablet contains 500 mg of capecitabine. This agent is commercially available and manufactured by Genentech.

7.3.2 Storage and Stability

According to guidelines specified in the package insert.

7.3.3 Preparation

According to guidelines specified in the package insert.

7.3.4 Administration

Capecitabine tablets should be swallowed whole with water within 30 minutes after a meal. Do not crush or cut capecitabine tablets. Capecitabine dose is calculated according to body surface

area. The dose of capecitabine is 1000 mg/m2 PO on Day 1-14 of each three-week cycle. A window of

+ 3/- 1 day for capecitabine dosing each cycle is acceptable. Do not make up missed doses within a cycle.

7.3.5 Accountability

Capecitabine accountability will be assessed based off of the patient's drug diary, which the study team will provide to the patient before each cycle. The drug diary will include the number of tablets and the strength of each tablet taken on each day of the cycle. Any missed doses or deviations from expected dosing will be documented in the form of a note-to-file signed by the clinician or detailed in the office note from the next visit.

8 ADMINISTRATIVE AND REGULATORY DETAILS

8.1 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 Principal Investigator (PI) will have written and dated approval from the UCSF IRB 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 Investigator has received a letter from FDA stating that the study is exempt from IND requirements.

All investigators 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.

8.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the UCSF IRB (Institutional Review Board). Prior to obtaining IRB approval, the protocol must be approved by the Helen Diller Family Comprehensive Cancer Center GI Oncology 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.

8.3 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the IRB-approved informed consent form prior to participation in any study specific procedure. The participant 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.

8.4 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 Investigator and approved by PRC and the IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to IRB approval. In this circumstance, however, the Investigator must then notify the IRB in writing within five (5) working days after implementation.

8.5 Handling and Documentation of Clinical Supplies

The UCSF PI 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 patients to whom study drug has been dispensed by patient number and initials will be included. The UCSF PI or Pharmacy designee 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 patients. Furthermore, the PI will not allow the investigational drug to be used in any manner other than that specified in this protocol.

8.6 Case Report Forms (CRFs)

The PI and/or qualified designees will prepare and maintain adequate and accurate participant 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 (see Section 6.0), using single data entry with a secure access account. The Clinical Research Coordinator (CRC) will complete the CRFs as soon as possible upon completion of the study visit; the Investigator 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 patient's medical records maintained by UCSF personnel. All source documentation should be kept in separate research folders for each patient.

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

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

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, the Trial Statistician, and the Protocol Project Manager.

8.7 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 11.1 Data and Safety Monitoring Plan for a Safety Lead-In and Phase 2 Institutional Study, for additional information.

8.8 Record Keeping and Record Retention

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

The Principal Investigator 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 including, for example, progress notes of the physician, 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, Study Chair-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient 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 study shall retain records for a period of 2 years following the date 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.

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APPENDIX A: Data and Safety Monitoring Plan: Institutional (Single Site) Phase II Trial with Safety Lead-In Phase

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 trials. A summary of DSMC activities for this trial 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 trials with a safety lead-in are designated with a high-risk assessment during the safety lead-in phase and a moderate risk assessment for the remainder of the trial. 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). Additionally, the assigned DSMC Monitor/Auditor will review no more than a total of 10 participant charts through five cycles of treatment 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. An abbreviated regulatory review (i.e., reviewing protocol and consent versions, SAEs, PVs, DOA logs, 1572 forms, etc.) will occur at each participant monitoring review; however, a full regulatory review will occur on a biennially basis by the DSMC for regulatory compliance.

Auditing of all enrolled participants in these trials will be complete after 20% of enrolled participants have been audited through five cycles of treatment. However, regulatory reviews of the trial, safety reviews (i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV)

reviews), and audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.

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]
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John McAdams (DSMC Director)
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San Francisco, CA 94143

APPENDIX B: ECOG Performance Status

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

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

APPENDIX C: Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

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

APPENDIX D: Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

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

* As published in the European Journal of Cancer:

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

APPENDIX E: Response Evaluation by Immune-related RECISE (irRECIST)

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen with treatment of pembrolizumab. Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. RECIST may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Immune-related RECIST (irRECIST) is RECIST 1.1 adapted as described below to account for the unique tumor response seen with immunotherapeutics. Following site identification of PD, irRECIST will be used by site investigators to assess tumor response and progression and make treatment decisions.

- If radiologic imaging by the site identifies PD by RECIST 1.1, subject management and tumor assessment will shift to irRECIST. Imaging should be repeated ≥4 weeks later in order to confirm PD with the option of continuing treatment per below while awaiting radiologic confirmation of progression.
- If repeat imaging shows < 20% tumor burden compared to nadir, stable or improved previous new lesion (if identified as cause for initial PD), and stable/improved non -target disease (if identified as cause for initial PD), PD is not confirmed. Treatment may continue and subsequently follow regular imaging schedule.
- If repeat imaging confirms PD (irPD) due to any of the scenarios listed below, subjects will be discontinued from study therapy (exception noted in Section 7.1.4.1.5.1). In determining whether or not the tumor burden has increased or decreased, site study team should consider all target lesions as well as non-target lesions.

Scenarios where PD is confirmed at repeat imaging:

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

In subjects who have initial evidence of radiological PD by the site, it is at the discretion of the site investigator whether to continue a subject on study treatment until repeat imaging is obtained (irRECIST subject management). This clinical judgment decision should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive study treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of symptoms and signs indicating clinically significant progression of disease, including worsening of laboratory values
- No decline in ECOG performance status
- Absence of rapid progression of disease

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

When feasible, subjects should not be discontinued until progression is confirmed. This allowance to continue treatment despite initial radiologic progression takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, but with subsequent disease response. Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation of PD.

APPENDIX F: Immunocorrelative Biomarker Specimen Guidance
Background and Overview

Blood and tumor specimens will be processed and banked for use in immunocorrelative research including but not limited to that described below.

Characterization and quantification of tumor-infiltrating immune cells and other potentially predictive biomarkers: Baseline tumor and on-treatment immune profile will be assessed by quantifying the number of infiltrating T cells subsets, including cytotoxic CD8+, helper CD4+FOXP3-, and regulatory CD4+FOXP3+ T cells. The proportion of activated T cells (e.g. PD1+ and Ki67+) will also be analyzed, as will myeloid-derived suppressor cells (e.g. M2 CD68/Arg-1, M1 CD68/iNOS).

T cell receptor (TCR) sequencing (blood and tumor biopsy): TCR sequencing can also be used to track immunotherapy induced changes in T cell repertoire and T cell clonotypes in the blood and tumor tissue. T cells see antigen through their TCR, which is comprised of two subunits, α and β. Each is generated by a variable diversity joining (VDJ) recombination event resulting in a broad range of T cell clones with different specificities. The β subunit has greater clonal diversity. Next- generation sequencing (NGS) of the T cell receptor β chain (TCRβ) has been used to define the diversity and frequency of T cell clones in the blood and tumor tissue of cancer patients after immunotherapy treatment and has been shown to associate with clinical response and OS (Vanneman, Nat. Rev. Cancer 2012; Robert, NEJM 2011). Fong, et al. performed TCR next- generation sequencing (NGS) on serial blood (PBMC) samples and prostatectomy samples from sipuleucel-T treated patients (Fong, JNCI 2014). Changes in TCR sequence frequency and diversity showed that sipuleucel-T treatment narrows the TCR repertoire in the blood while increasing the TCR diversity in prostate tissue. The increase in common TCR sequences (clonotypes) between tumor and blood supports the notion of treatment-induced T cell migration into prostate tissue.

CTLA-4 blockade also induces global remodeling of the T cell repertoire (Cha Sci Transl Med, 2014). Anti-CTLA-4 administration promotes active turnover in the T cell repertoire, which increases with sequential treatments and leads to increased repertoire diversity. These changes occurred both in naïve and non-naïve T cells, the latter of which includes the antigen-experienced, effector T cell population. Interestingly, maintenance of pre-existing, high-frequency clonotypes (greater than 1 in 1000) is associated with clinical response and improved overall survival following ipilimumab. Importantly, recent data suggest that immune repertoire diversity following immune checkpoint blockade can be detrimental as well as beneficial (Oh, Procl AACR 2016). Patients with immune related adverse events also demonstrate a more diverse T cell repertoire with an increase in T cell clonotypes, and greater degree of change in clonal frequencies of CD8+ T cells.

Using established techniques (UCSF CIL), NGS will be used to quantify the T cell immune response induced by pembrolizumab. TCR clonotypes will be characterized at baseline (blood and pre- treatment tumor biopsy), as will changes in the T cell immune response over time

(blood; on-treatment biopsy). The data may inform optimal use of therapies in the patient population under study and identify candidate biomarkers of response, resistance or toxicity.

Characterization of peripheral immune cell subsets (blood): Circulating immune cells may be assessed by multiparameter flow cytometry on peripheral blood samples. T cell activation status may be characterized.

Specimen Collection Procedures

Archival Tumor

A minimum of 1 formalin-fixed paraffin-embedded (FFPE) archival tumor tissue block (preferred) or a minimum of 15 FFPE unstained sections from most recent pre-registration biopsy/surgery are to be collected, if available, together with the corresponding pathology report, within 60 days of registration.

Specimens will be transported to the UCSF CIL for storage and processing.

Slides should be shipped in a plastic slide holder/slide box. Place a small wad of padding in top of the container in order to avoid slides breaking during shipping and handling process.

UCSF Cancer Immunotherapy Lab (CIL)

[redacted]

Fresh Tumor Biopsies

All patients in the Phase II portion of the study prior to the interim analysis will undergo a mandatory core needle biopsy of a metastatic tumor prior to cycle 1 day 1, as well as prior to cycle 2, day 1 (pre-treatment and on-treatment biopsies).

Six 18-gauge cores, 1 cm depth (or equivalent) should be obtained at each time point with the prioritization below. A fine needle aspirate is not acceptable.

If it is not feasible to use an 18-gauge needle, a 20-gauge needle may be used with sponsor-investigator approval, in which case all six cores should be processed as FFPE.

Core #	Processing Method
1	FFPE
2	Flash Frozen
3	FFPE
4-6	Fresh

FFPE and flash frozen cores should be processed per UCSF Biospecimen Resources (BIOS) standard operating procedures. Fresh Cores for UCSF CIL should be placed on a sterile gauze, wet with DPBS, placed in sterile container(s) appropriately labeled with patient and sample information, placed on ice, and delivered directly to the Fong lab (UCSF CIL) within 4 hours of tissue acquisition. All patient identifiers will be blacked out or scratched off before disposal of the container.

An H&E stained FFPE section of the pre-treatment biopsy and will be reviewed by a pathologist for tumor content. If no tumor cells are identified on the H&E, an on-treatment biopsy will not be performed (the pre-treatment biopsy will also not be repeated). The total number of biopsies performed will be tallied at the time of interim analysis. If the total number of biopsies is <46, additional pre-treatment (but not on-treatment) biopsies will be required in post interim analysis patients until the total number of tumor biopsies performed reaches 46.

Research Blood Collection

All patients will have green top (heparin-treated) and PAXgene tubes of blood specimens collected following the schedule below.

Time point	**# of green top tubes** (heparin treated). Up to:	**# of PAXgene tube**
Screening (Day -28 to -1)	4 (40 mL)	1 (10 mL)
Day 1 of cycle 1	6 (60mL total)	0
Day 1 of cycle 2	6 (60mL total)	1 (10 mL)
Day 1 of cycle 3	4 (40mL total)	1 (10 mL)
Progression or treatment discontinuation	4 (40mL total)	1 (10 mL)

These specimens will be transported at room temperature to UCSF CIL within 12 hours of blood collection.

The study CRC will notify appropriate personnel in the UCSF CIL of anticipated tissue and blood arrival with at least 24-hour notice.