TITLE: A phase II clinical trial evaluating the combination of lenvatinib plus pembrolizumab in patients with immune checkpoint inhibitor naïve metastatic uveal melanoma.

IND EXEMPT

Principal Investigator:
Matthew Taylor, MD
Co-director, Providence Melanoma Program
Providence Cancer Institute
4805 NE Glisan St., Portland, Oregon 97123
Phone: 503-215-6614
Fax: 503-215-6841
Email: Matthew.Taylor@providence.org

Site(s):
Providence Cancer Institute, Providence Portland Medical Center

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1.0 TRIAL SUMMARY

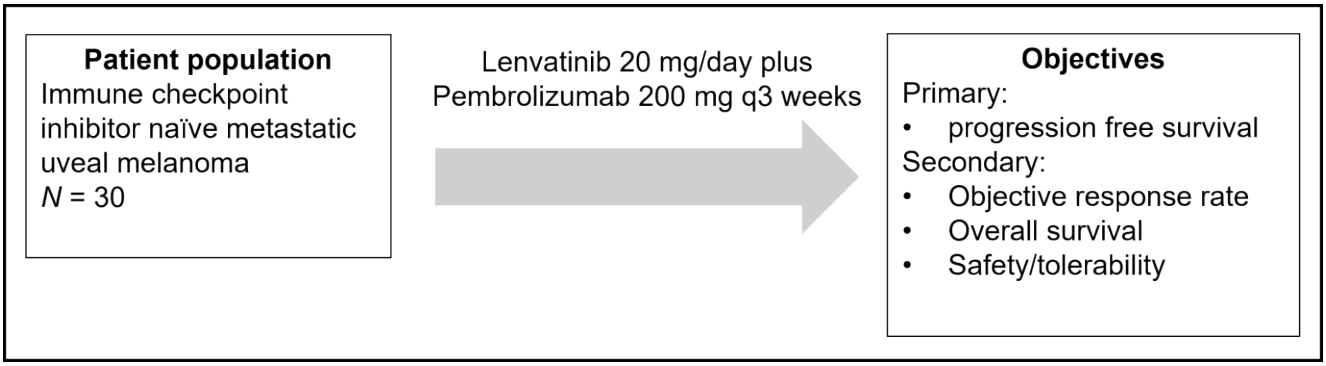
Abbreviated Title	Lenvatinib plus pembrolizumab in patients with immune checkpoint inhibitor naïve metastatic uveal melanoma
Trial Phase	Phase II
Clinical Indication	Treatment of participants with immune checkpoint inhibitor naïve metastatic uveal melanoma
Trial Type	Interventional
Type of control	n/a
Route of administration	Oral and IV
Treatment Groups	Single arm: Lenvatinib 20 mg daily plus pembrolizumab 200 mg IV every 3 weeks.
Number of trial participants	30
Estimated enrollment period	20 months
Estimated duration of trial	48 months (FPFV to LPLV)
Duration of Participation	Subjects will participate in the clinical trial from the time of signing the ICF until the final protocol specified contact. Subjects who discontinue treatment for reasons other than disease progression or treatment related toxicity will have post-treatment follow-up until documented radiographic evidence of disease progression (per iRECIST), initiation of a subsequent anti-cancer therapy, death, pregnancy, withdrawal of consent, lost to follow up or the end of the clinical trial.
Estimated average length of treatment per patient	6 months

2.0 TRIAL DESIGN

2.1 Trial Design

This is a phase II, single arm, single institution clinical trial. Adults (age≥18 years-old) with immune checkpoint inhibitor naïve metastatic uveal melanoma will be evaluated for eligibility. Eligible participants will be treated with the combination of Lenvatinib 20 mg daily + pembrolizumab 200 mg IV every 3 weeks for a maximum of 2 years.

2.2 Trial Schema



2.3 Schedule of Activities

Table 1 Study Schedule of Activities

Study Period:	Screening		Intervention (21-Day Cycles)										End of Treatment	Post treatment Visits			Notes
Visit Number/Title:	1/Screening		C1			C2		C3	C4	C5	C6 to C35	≥ C36		Safety Follow-up	Efficacy Follow-up	Survival FU	
Cycle Day			1	8	15	1	15	1	1	1	1	1					
Scheduling Window (days)	-42 to –1	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	At time of treatment discontinuation	Approx. 30d after last dose (± 7d)	Q6W (Y1) or Q9W (Y2+) (± 7d)	Q12W[a] (± 14d)	
Administrative Procedures																	
Informed Consent	X																
Inclusion/Exclusion Criteria		X															
Demographics and Medical History		X															Includes smoking and tobacco use.
Prior Treatment		X															
Prior/Concomitant Medication Review		X	X	X	X	X	X	X	X	X	X	X	X	X			
Subsequent Antineoplastic Therapy Status													X	X	X	X	
Survival Status			←									→				X	Participants may be contacted for survival status at any time during the course of the study.

Study Period:	Screening		Intervention (21-Day Cycles)										End of Treatment	Post treatment Visits			Notes
Visit Number/Title:	1/Screening		C1			C2		C3	C4	C5	C6 to C35	≥ C36		Safety Follow-up	Efficacy Follow-up	Survival FU	
Cycle Day			1	8	15	1	15	1	1	1	1	1					
Scheduling Window (days)	-42 to –1	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	At time of treatment discontinuation	Approx. 30d after last dose (± 7d)	Q6W (Y1) or Q9W (Y2+) (± 7d)	Q12W[a] (± 14d)	
Study Intervention Administration																	
Lenvatinib Dispensing			X			X		X	X	X	X	X					
Lenvatinib Administration PO QD			←	—	—	—	—	—	—	—	—	→					Taken at home
Lenvatinib container returned						X		X	X	X	X	X					Lenvatinib will be held for 7 days prior to biopsy and will resume 2 days post biopsy.
Pembrolizumab Administration IV Q3W			X			X		X	X	X	X						
Efficacy Procedure																	
Tumor Biopsy Collection		X						X[C]									Fresh tumor biopsy specimens will be collected at Screening and at C3D8 from at least 15 subjects (in no certain order). Archival tissue may be used in place of pre-treatment biopsy.
Tumor Imaging (chest, abdomen, & pelvis) and iRECIST Assessment **Note:** Imaging of the brain required only at screening.		X							X		X	X	X		X		Imaging is performed at Screening, Week 9 and every 9 weeks (± 7 days) during Year 1. After Year 1, imaging is performed every 12 weeks (±7 days). This schedule will be maintained regardless of treatment delays.

Study Period:	Screening		Intervention (21-Day Cycles)										End of Treatment	Post treatment Visits			Notes
Visit Number/Title:	1/Screening		C1			C2		C3	C4	C5	C6 to C35	≥ C36		Safety Follow-up	Efficacy Follow-up	Survival FU	
Cycle Day			1	8	15	1	15	1	1	1	1	1					
Scheduling Window (days)	-42 to -1	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	At time of treatment discontinuation	Approx. 30d after last dose (± 7d)	Q6W (Y1) or Q9W (Y2+) (± 7d)	Q12W[a] (± 14d)	
Safety Procedures																	
AE/SAE Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Report AEs occurring within 30 days after the last dose of study intervention. Report SAEs occurring within 90 days after the last dose of study intervention, or 30 days after the last dose of study intervention if a new anticancer therapy is initiated, whichever is first.
Full Physical Examination		X											X				
Height		X															
Directed Physical Examination			X		X	X	X	X	X	X	X	X		X			
Contact				X													The investigator or medically qualified designee (consistent with local requirements) will assess participants for development of early toxicity. An unscheduled visit can occur before C1D15 if necessary for safety.

Study Period:	Screening		Intervention (21-Day Cycles)										End of Treatment	Post treatment Visits			Notes
Visit Number/Title:	1/Screening		C1			C2		C3	C4	C5	C6 to C35	≥ C36		Safety Follow-up	Efficacy Follow-up	Survival FU	
Cycle Day			1	8	15	1	15	1	1	1	1	1					
Scheduling Window (days)	-42 to -1	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	At time of treatment discontinuation	Approx. 30d after last dose (± 7d)	Q6W (Y1) or Q9W (Y2+) (± 7d)	Q12W[a] (± 14d)	
Vital Signs (resting BP, heart rate, RR, and temp) and weight		X	X		X	X	X	X	X	X	X	X	X	X			The Day 15 visit is mandatory for C1 and C2. During C3 and subsequent cycles, participants may return for the D15 visit if BP monitoring is required.
12-lead ECG with QTcF Determination (Single)		X	X			X					X	X	X	X			Every 4 cycles. ECG at Screening, C1D1, C2D1, D1of every fourth cycle (12 weeks) thereafter (e.g., C6, C10, C14, etc.), EOT, and safety follow-up. For high-risk participants (Section 6.1.2.7), conduct ECG monitoring every cycle. If Lenvatinib is discontinued, ECGs are only required at the EOT and Safety Follow-up visits.

Study Period:	Screening		Intervention (21-Day Cycles)										End of Treatment	Post treatment Visits			Notes
Visit Number/Title:	1/Screening		C1			C2		C3	C4	C5	C6 to C35	≥ C36		Safety Follow-up	Efficacy Follow-up	Survival FU	
Cycle Day			1	8	15	1	15	1	1	1	1	1					
Scheduling Window (days)	-42 to -1	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	At time of treatment discontinuation	Approx. 30d after last dose (± 7d)	Q6W (Y1) or Q9W (Y2+) (± 7d)	Q12W[a] (± 14d)	
MUGA Scan or ECHO		X												X			Additional LVEF assessments may be performed as clinically indicated.
ECOG Performance Status		X*	X			X		X	X	X	X	X	X	X			Performance status obtained on C1D1 may also be used as the screening value to determine eligibility. *Screening ECOG within 7 days before initiation of study intervention. If performed within 7 days prior to day one ECOG does not need to be repeated on Day 1
Laboratory Procedures/Assessments (Local Laboratory)																	
Serum β-hCG Pregnancy Test (WOCBP only)		X				X		X	X	X	X	X	X	X			WOCBP require a negative test. If more than 24 hours have elapsed before the first dose of study intervention, another pregnancy test is required. A serum pregnancy test will be performed per Appendix 2.

Study Period:	Screening		Intervention (21-Day Cycles)										End of Treatment	Post treatment Visits			Notes
Visit Number/Title:	1/Screening		C1			C2		C3	C4	C5	C6 to C35	≥ C36		Safety Follow-up	Efficacy Follow-up	Survival FU	
Cycle Day			1	8	15	1	15	1	1	1	1	1					
Scheduling Window (days)	-42 to -1	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	At time of treatment discontinuation	Approx. 30d after last dose (± 7d)	Q6W (Y1) or Q9W (Y2+) (± 7d)	Q12W[a] (± 14d)	
Serum FSH (WONCBP only)		X															In the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in postmenopausal range is required.
HIV, Hepatitis B, and Hepatitis C		X*															*Required at Screening only if mandated by local health authority
Hematology		X*	X		X	X		X	X	X	X	X	X	X			Labs obtained on C1D1 may also be used as the screening value to determine eligibility. *Perform screening laboratory tests within 7 days before the first dose. If performed within 7 days prior to day one CMP does not need to be repeated on Day 1
Chemistry		X*	X		X	X		X	X	X	X	X	X	X			
Thyroid Function Tests (LDH, Free T4, TSH)		X*	X			X			X		X	X		X			Labs obtained on C1D1 may also be used as the screening value to determine eligibility. *Perform screening laboratory tests within 7 days before first dose, then at C2 and every 2 cycles thereafter (C4, C6, etc.) If performed within 7 days prior to day one thyroid function and LDH does not need to be repeated on Day 1

Study Period:	Screening		Intervention (21-Day Cycles)										End of Treatment	Post treatment Visits			Notes
Visit Number/Title:	1/Screening		C1			C2		C3	C4	C5	C6 to C35	≥ C36		Safety Follow-up	Efficacy Follow-up	Survival FU	
Cycle Day			1	8	15	1	15	1	1	1	1	1					
Scheduling Window (days)	-42 to -1	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	At time of treatment discontinuation	Approx. 30d after last dose (± 7d)	Q6W (Y1) or Q9W (Y2+) (± 7d)	Q12W[a] (± 14d)	
Urine Dipstick Testing		X*	X		X	X	X	X	X	X	X	X	X				After C1, collect samples at C1D15 and C2 D15 and up to 3 days before D1 of each cycle. If lenvatinib is discontinued, urine dipstick testing no longer required. Urine dipstick testing (or urinalysis) obtained and reviewed on C1D1 may also be used as the screening value to determine eligibility. If 24-hour urine collection for quantitative assessment of proteinuria is required, C1D1 is postponed to after proteinuria result available. *Perform screening urinalysis tests within 7 days before the first dose. If performed within 7 days prior to day one urine dipstick does not need to be repeated on Day 1

Study Period:	Screening		Intervention (21-Day Cycles)										End of Treatment	Post treatment Visits			Notes
Visit Number/Title:	1/Screening		C1			C2		C3	C4	C5	C6 to C35	≥ C36		Safety Follow-up	Efficacy Follow-up	Survival FU	
Cycle Day			1	8	15	1	15	1	1	1	1	1					
Scheduling Window (days)	-42 to -1	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	At time of treatment discontinuation	Approx. 30d after last dose (± 7d)	Q6W (Y1) or Q9W (Y2+) (± 7d)	Q12W[a] (± 14d)	
INR or PT and aPTT		X*	X														Labs obtained and reviewed on C1D1 may also be used as the screening value to determine eligibility. Additional testing is to be performed as clinically indicated for participants taking anticoagulants. *Perform screening laboratory tests within 7 days before the first dose. If performed within 7 days prior to day one INR or PT and aPTT does not need to be repeated on Day 1
Biomarkers																	
Blood for Research	X		X[b]			X		X	X	X	X						Collect at screening and pre dose on D1 of Cycles 1-6.
Optional Specimen for Banking	X		X[b]			X		X	X	X	X						Optional blood collection for specimen banking, collect at screening and pre dose on D1 of Cycles 1-6.

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; BP = blood pressure; β-HCG; = β human chorionic gonadotropin; C = cycle; CXDY= Cycle X Day Y; d = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ECHO = echocardiogram; EOT = end of treatment; FSH = follicle-stimulating hormone; FU = follow-up; HIV = human immunodeficiency virus; INR = international normalized ratio; LVEF = left ventricular ejection fraction; MUGA = multigated acquisition; PT = prothrombin time; Q6W = every 6 weeks; Q9W = every 9 weeks; Q12W = every 12 weeks; QTcF = QT interval corrected with Fridericia's formula; RNA= ribonucleic acid; RR = respiratory rate; SAE = serious adverse event; SoA= schedule of activities; T4 = thyroxine; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential; WONCBP = women of nonchildbearing potential.

a. If the poststudy visit occurs less than 14 days after the last dose of study intervention, a subsequent follow-up telephone call should be made at 14 days post the last dose of study intervention to determine of any AEs have occurred since the poststudy clinic visit.

b. Correlative and optional specimen banking samples collected for Screening may be used for C1D1 if the collection is within 3 days prior to C1D1.
c. Collect at C3D8

3.0 OBJECTIVE(S), HYPOTHESIS(ES), AND ENDPOINT(S)

3.1 Primary Objective(s), Hypothesis(es), and Endpoint(s)

(1) **Objective:** To evaluate the effect of lenvatinib + pembrolizumab on progression free survival.

Hypothesis: Treatment with Lenvatinib + pembrolizumab will result in improved progression free survival as compared with previously reported systemic therapies including pembrolizumab monotherapy, ipilimumab + nivolumab and tebentafusp.

Primary Endpoint: Progression free survival, defined as the time from enrollment to the first documented evidence of disease progression or death.

3.2 Secondary Objective(s), Hypothesis(es), and Endpoint(s)

(1) **Objective**: To evaluate the objective response rate resulting from treatment with Lenvatinib + pembrolizumab.

Hypothesis: Treatment with Lenvatinib + pembrolizumab will result in an improved objective response rate as compared with previously reported therapies including pembrolizumab monotherapy, ipilimumab + nivolumab and tebentafusp.

Secondary Endpoint: Objective response rate (complete and partial responses assessed by iRECIST)

(2) **Objective**: To evaluate the effect of treatment with Lenvatinib + pembrolizumab on overall survival.

Hypothesis: Treatment with Lenvatinib + pembrolizumab will result in improved overall survival as compared with previously reported therapies including pembrolizumab monotherapy, ipilimumab + nivolumab and tebentafusp.

Secondary Endpoint: Overall survival, defined as the time from enrollment to death (resulting from any cause).

(3) **Objective**: To evaluate the safety and tolerability of treatment with Lenvatinib + pembrolizumab in patients with metastatic uveal melanoma.

Hypothesis: Treatment with Lenvatinib + pembrolizumab will demonstrate an acceptable toxicity profile in patients with metastatic uveal melanoma.

Secondary Endpoint:

- Adverse events (per CTCAE v5.0)

- Frequency of treatment interruption, dose reduction, and treatment discontinuation due to treatment related adverse events (TRAE).

3.3 Exploratory Objective(s)

(1) **Objective:**

To evaluate correlative biomarkers from tumor and blood specimens in patients treated with Lenvatinib + pembrolizumab.

Hypothesis: Treatment with Lenvatinib + pembrolizumab will result in changes in the tumor infiltrating immune cell profile and tumor gene expression profile.

Secondary Endpoint:

- Multiplex immunohistochemical analysis of tumor biopsy specimens for characterization of the tumor immune profile.

- Gene expression profiling of tumor biopsy specimens by RNAseq.

4.0 BACKGROUND & RATIONALE

4.1 Background

Uveal melanoma

Metastatic uveal melanoma is associated with a very poor prognosis with median survival of 6-12 months [1]. Unfortunately, systemic therapy with immune checkpoint inhibitors has demonstrated inadequate efficacy. In a phase II clinical trial with ipilimumab, no objective responses were observed and the median progression free survival (PFS) was 2.8 months [2]. A small phase II clinical trial (17 patients) evaluated the efficacy of pembrolizumab monotherapy. Two out of the 17 patients had an objective response (11.7%) and median PFS was 3.8 months [3]. Treatment with the combination of ipilimumab + nivolumab was evaluated in a phase II clinical trial that showed an objective response rate (ORR) of 18% with median PFS of 5.5 months and median overall survival of 19.1 months [4]. The results of the phase III clinical trial evaluating the bispecific fusion protein Tebentafusp in patients with metastatic uveal melanoma were reported at the 2021 AACR annual meeting. In this clinical trial, patients were randomly assigned (2:1) to either treatment with tebentafusp or investigator choice of therapy (pembrolizumab, ipilimumab or dacarbazine). The authors reported a median overall survival of almost 22 months for tebentafusp compared with 16 months in the investigator choice arm. Tebentafusp resulted in an ORR of 9% [5]. As such, effective therapies for patients with metastatic uveal melanoma represents a significant unmet clinical need.

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-

L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications because of its mechanism of action to bind the PD-1 receptor on the T cell. For more details on specific indications refer to the Investigator brochure (IB).

Lenvatinib (E7080 or MK-7902) is a potent small molecule inhibitor of multiple kinases including vascular endothelial growth factor receptors (VEGFR) 1-3, fibroblast growth factor receptors (FGFR) 1-4, platelet derived growth factor receptor alpha (PDGFRα), KIT and RET. Several of these kinases are overexpressed by various cancers and contribute to tumor proliferation, invasion, metastasis and immune suppression in the tumor microenvironment [6].

4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector Tcells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley et al., 2005; Hunder et al., 2008].

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 immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald et al., 2005; Okazaki et al., 2001].

The structure of murine PD-1 has been resolved [Zhang et al., 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [Okazaki et al., 2001; Chemnitz et al., 2004; Sheppard et al., 2004; and Riley, 2009]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules

regulate an overlapping set of signaling proteins [Parry et al., 2005; Francisco, 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in metastatic immune checkpoint inhibitor naïve uveal melanoma.

4.1.2 Lenvatinib

VEGF signaling within the tumor microenvironment contributes to tumor proliferation, angiogenesis, and exerts multiple immune suppressive effects which disrupt anti-tumor immunity. Specifically, high levels of VEGF within the tumor microenvironment is associated with increased tumor infiltration of regulatory T cells (Treg). Additionally, VEGF signaling in activated T cells results in increased expression of multiple inhibitory immune receptors including PD-1, CTLA-4, TIM-3 and LAG-3 [18].

Lenvatinib has demonstrated potent antiangiogenic and antiproliferative activity in preclinical models. In a syngeneic mouse tumor model, treatment with Lenvatinib resulted in increased tumor infiltration of activated CD8+ T cells (expressing granzyme B and IFN-γ) and plasmacytoid dendritic cells and decreased the number of tumor associated macrophages (TAM) [19]. Lenvatinib has also resulted in decreased tumor infiltration of Tregs in patients with advanced renal cell carcinoma [20].

4.1.3 Lenvatinib + Pembrolizumab

Multiple factors contribute to tumor immune evasion which include impaired T cell priming and activation by antigen presenting cells, impaired T cell trafficking into tumors, exhaustion of tumor-specific T cells, immunosuppressive cytokines (TGFβ, IL-10, etc.), and others [21]. Due to the immunosuppressive roles of VEGF and PD-1 signaling in tumors, pre-clinical testing was done to evaluate the effect of Lenvatinib + pembrolizumab in syngeneic mouse tumor models. Using the CT26 CRC and Hepa1-6 HCC mouse tumor models, Lenvatinib + pembrolizumab resulted in improved anti-tumor activity than either agent alone [22]. Based on the mechanistic rationale and encouraging pre-clinical data, the Study 111/Keynote-146 was designed to evaluate the safety, tolerability and efficacy of the combination of Lenvatinib + pembrolizumab in patients with advanced solid tumors. This clinical trial showed that Lenvatinib 20 mg/day + pembrolizumab 200 mg IV every 3 weeks exhibited an acceptable safety profile and significant preliminary anti-tumor efficacy. Subsequent clinical trials in patients with advanced endometrial carcinoma and renal cell carcinoma confirmed excellent anti-tumor activity. These results led to the FDA approval of Lenvatinib + Pembrolizumab for patients with metastatic endometrial cancer and metastatic renal cell carcinoma [23].

4.1.4 Preclinical and Clinical Trial Data

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

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Population

The combination of Lenvatinib + pembrolizumab has demonstrated excellent clinical efficacy in patients with metastatic endometrial cancer as well as metastatic renal cell carcinoma. Of note, it appears that the combination of these drugs may result in a synergistic therapeutic effect rather than merely an additive benefit. Consequently, this combination is now being evaluated across a broad range of advanced solid tumors.

Uveal melanomas express high levels of the immunosuppressive molecules VEGF and FGF [24]. Consequently, targeting VEGF and FGF signaling pathways in the tumor microenvironment represents an attractive approach to decrease the local immunosuppression. The anticipated effect of blockade of both VEGF and PD-1 signaling will be to modulate the tumor microenvironment by increasing tumor infiltration of CD8+ T cells, decreasing intratumoral Tregs and TAMs and reinvigorating exhausted tumor-specific CD8+ T cells. It is noteworthy that high numbers of Tregs in uveal melanoma metastases has been correlated with poor response to immune checkpoint inhibitors [25]. As such, the capacity of Lenvatinib to decrease the number of tumor infiltrating Tregs may represent a significant mechanism of enhancing anti-tumor immunity when used in combination with pembrolizumab.

4.2.2 Justification for Dose

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies in melanoma and NSCLC indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg Q2W, representing an approximate 5- to 7.5-fold exposure range (refer to IB, Section 5.2.2)
- Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W

The dose for Lenvatinib in this clinical trial will be 20 mg daily. This dose of Lenvatinib has been shown to be safe and well tolerated by several clinical trials using this combination [26]. The combination of Lenvatinib 20 mg PO daily with Pembrolizumab 200 mg IV every 3 weeks has been approved by the

FDA for treatment of patients with metastatic renal cell carcinoma and metastatic endometrial carcinoma that is not microsatellite instability-high or mismatch repair deficient (see Lenvatinib package insert).

4.2.2.1 Planned Exploratory Biomarker Research

Paired fresh tumor biopsy specimens will be collected (pre-treatment and cycle 3 day 8) from at least 15 subjects (in no certain order). Subjects with tumor metastases that are not amenable to image guided biopsies or who have a contraindication to biopsy (such as anticoagulation therapy that cannot be interrupted for a biopsy) are still eligible for participation in the clinical trial without the biopsies. Archival tissue may be used in place of pre-treatment biopsy. These specimens will be banked for biomarker analysis that will include tumor immune cell profiling and gene expression analysis. Biomarker analysis will be performed for evaluation of predictive and/or prognostic biomarkers of tumor response and survival.

5.0 METHODOLOGY

5.1 Study Population

5.1.1 Participant Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Male/female participants who are at least 18 years of age on the day of signing informed consent with histologically confirmed diagnosis of uveal melanoma that is unresectable or metastatic will be enrolled in this study.

2. Male participants:

   A male participant must agree to use a contraception as detailed in Appendix 3 of this protocol during the treatment period and for at least 120 days after the last dose of Lenvatinib and refrain from donating sperm during this period.

3. Female participants:

   A female participant is eligible to participate if she is not pregnant (see Appendix 3), not breastfeeding, and at least one of the following conditions applies:

   a. Not a woman of childbearing potential (WOCBP) as defined in Appendix 3 OR
   b. A WOCBP who agrees to follow the contraceptive guidance in Appendix 3 during the treatment period and for at least 120 days post pembrolizumab or post Lenvatinib whichever occurs last.

4. The participant (or legally acceptable representative if applicable) provides written informed consent for the trial.

5. Have measurable disease based on iRECIST. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

6. Have provided archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. Formalin-fixed, paraffin embedded (FFPE) tissue blocks are preferred to slides. If slides are only available, ten slides would be required. Newly obtained biopsies are preferred to archived tissue.

7. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Evaluation of ECOG is to be performed within 7 days prior to the first dose of study intervention.

8. Have adequate organ function as defined in the following table (Table 2). Specimens must be collected within 7 days prior to the start of study intervention.

9. Paired fresh tumor biopsy specimens (to be collected pre- treatment and cycle 3 day 8) will be collected for at least 15 patients (in no certain order) who consent. Subjects with tumor metastases that are not amenable to image guided biopsies or who have a contraindication to biopsy (including but not limited to anticoagulation therapy that cannot be interrupted for a biopsy) are still eligible for participation in the clinical trial without undergoing biopsies. Archival tissue may be used in place of pre-treatment biopsy.

Table 2 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/μL
Platelets	≥100 000/μL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine OR Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN (patients with clinical evidence of Gilbert's syndrome and elevated bilirubin are eligible for participation).
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)

Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal.

[a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.

[b] Creatinine clearance (CrCl) should be calculated per institutional standard.

Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

5.1.2 Participant Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. A WOCBP who has a positive serum pregnancy test within 24 hours prior to the first dose of study intervention (see Appendix 3).
2. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX-40, CD137). Prior therapy with Tebentafusp is permitted. Prior liver directed therapy is permitted (including but not limited to radioembolization, chemoembolization, immunoembolization, radio-frequency ablation, external beam radiation and resection).
3. Participants previously treated with radiation therapy must have recovered from all radiation-related toxicities and not require corticosteroids.
4. Has received a live vaccine or live-attenuated vaccine within 30 days prior to the first dose of study drug. Administration of killed-virus vaccines and mRNA vaccines are allowed.
5. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.
6. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years. Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, early stage bladder cancer, or carcinoma in situ (e.g., breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.
7. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, i.e.

without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study intervention.

8. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.

9. 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 and is allowed.

10. Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.

11. Has an active infection requiring systemic therapy.

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

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

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

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

16. Uncontrolled blood pressure (Systolic BP>140 mmHg or diastolic BP >90 mmHg) in spite of an optimized regimen of antihypertensive medication.

17. Significant cardiovascular impairment: history of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina, myocardial infarction or stroke within 6 months of the first dose of study drug, or cardiac arrhythmia requiring medical treatment at Screening.

18. Bleeding or thrombotic disorders or subjects at risk for severe hemorrhage. The degree of tumor invasion/infiltration of major blood vessels (e.g. carotid artery) should be considered because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis following lenvatinib therapy.

19. Subjects having ≥2+ proteinuria on urine dipstick testing. However, subjects with ≥2+ proteinuria on urine dipstick testing may undergo a 24-hour urine collection for quantitative assessment of proteinuria. Subjects with <1 g/24-hour proteinuria are eligible for participation.

20. Subjects who have not recovered adequately from any toxicity from other anti- cancer treatment regimens and/or complications from major surgery prior to starting therapy. Withhold lenvatinib for at least 1 week prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing.

21. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [ß-hCG] (or human chorionic gonadotropin [hCG]) test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG [or hCG]).

22. Females of child-bearing potential must be willing to use effective contraception during study and for 120 days after the last dose

23. The participant has severe hypersensitivity (≥Grade 3) to lenvatinib and/or any of its excipients

5.1.3 Lifestyle Considerations

5.1.3.1 Meals and Dietary Restrictions

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

5.1.3.2 Contraception

Pembrolizumab and lenvatinib may have adverse effects on a fetus in utero. Refer to Appendix 3 for approved methods of contraception.

For this study, male participants 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).

5.1.3.3 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab and lenvatinib, the participant will be immediately discontinued from study intervention(s). The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Merck within 2 working days if the outcome is a serious adverse experience (e.g. death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to Merck. If a male participant impregnates his female partner, the

study personnel at the site must be informed immediately and the pregnancy must be reported to Merck and followed as described in Section 6.2.

5.2 Trial Intervention(s)

The intervention(s) to be used in this trial is outlined below in Table 3.

Table 3 Trial Intervention(s)

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Lenvatinib	20 mg	QD	Oral	QD, no treatment duration limit	Experimental
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3-week cycle for 2 years maximum	Experimental
Abbreviations: IV = intravenous; QD = once daily					

Trial intervention(s) should begin on the day of or as close as possible to the date on which intervention is allocated/assigned.

5.2.1 Timing of Dose Administration

Trial interventions should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Schedule of Activities, Section 2.3. Trial interventions may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial interventions will be administered on an outpatient basis.

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.

Lenvatinib 20 mg will be administered in an oral dose to be taken once daily. Capsules are packaged in cold form blisters or high-density polyethylene bottles with a polypropylene cap and desiccant. The blisters and bottles should be stored under room temperature.

5.2.2 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 etiology. 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 4.

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 lenvatinib or to pembrolizumab alone, both interventions must be held according to the criteria in Table 4 Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated with Pembrolizumab.

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 4.

- 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 4, the combination of lenvatinib and pembrolizumab may be restarted at the discretion of the investigator. In these cases where the toxicity is attributed to the combination or to lenvatinib alone, re-initiation of pembrolizumab as a monotherapy may be considered at the principal investigator's discretion.

Table 4 Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab monotherapy and Immunotherapy (IO) Combinations

General instructions:

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

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 (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e., peritoneal signs and ileus)

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
	Recurrent Grade 3 or Grade 4	Permanently discontinue		· 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
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 b-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]		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hyperthyroidism	Grade 2	Continue	· Treat with nonselective beta-blockers (e.g., propranolol) or thionamides as appropriate	· Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3 or 4	Continue	· Initiate thyroid replacement hormones (e.g., 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		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
All Other irAEs	Persistent Grade 2	Withhold	· Based on severity of AE administer corticosteroids	· Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

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 (e.g., vasculitis and sclerosing cholangitis).

Dose modification and toxicity management of infusion-reactions related to pembrolizumab

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

hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 5.

Table 5 Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug intervention**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of study intervention with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g.,	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids	No subsequent dosing

renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug intervention.**	
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

Other allowed dose interruption for pembrolizumab

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

Dose Modifications for Overlapping Toxicities Pembrolizumab-Lenvatinib:

Based on the known toxicity profiles of pembrolizumab and lenvatinib, certain treatment-related AEs are uniquely associated with one drug versus the other. For example, hypertension, arterial thrombotic events, proteinuria, and hemorrhagic events are known risks for lenvatinib treatment, while immune-related AEs are risks for pembrolizumab treatment. However, certain AEs, such as such as diarrhea, hypothyroidism, and liver enzyme elevation, may be initially considered attributable to either study drug. Therefore, evaluation of attribution is important for determining the study drug most likely related to the AE, or an alternative etiology, and subsequently proper clinical management. The following aspects should be considered:

1. Timing of AE onset

   Since lenvatinib is dosed daily and continuously due to a relatively short half-life (28 hours), and pembrolizumab is dosed Q3W due to a long half-life, lenvatinib can be interrupted to assess whether an AE improves/resolves with dechallenge (ie, interruption of treatment) based on the following two scenarios:
   - If an AE is identified during a treatment cycle (ie, between 2 pembrolizumab doses), only lenvatinib dose interruption is needed.
   - If an AE is identified at the beginning of a treatment cycle, lenvatinib can be interrupted and dosing of pembrolizumab should be held.

   If the subject recovers from an AE in response to lenvatinib interruption (ie, positive dechallenge), the event is more likely to be related to lenvatinib. Otherwise, after excluding other alternative explanations, an immune-related AE should be considered.

2. Severity of AE

   If an AE is suspected to be treatment related and is severe/life threatening at the time of onset or is rapidly worsened, action including interrupting both drugs and initiating treatment with a corticosteroid (with exception of hypothyroidism, TIDM) and other supportive care should be taken promptly.

3. Participants receiving the combination therapy (pembrolizumab + lenvatinib) must discontinue study therapy if any of the following occur:
   - ALT or AST >5 X ULN for more than 2 weeks.
     Pembrolizumab will have already been permanently discontinued per Table 6,[X], but

lenvatinib may be administered at a reduced dose by the time this criterion is met and must be permanently discontinued immediately.

- ALT or AST >3 X ULN and (TBL >2 X ULN or INR >1.5).
  Although Table [X] advises pembrolizumab to be withheld (interrupted), and Table [X] advises lenvatinib to have no dose modification or a reduction, if this criterion is met, both drugs must be permanently discontinued immediately.

5.2.3 Monitoring Recommendations on lenvatinib

- BP should be well-controlled prior to the start of lenvatinib. Blood pressure should be monitored after 1 week of treatment with lenvatinib, then every 2 weeks for the first 2 months and monthly thereafter while on treatment. If a patient develops systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg active management is indicated.

- Urine protein should be monitored regularly. If urine dipstick ≥2+ is detected, dose interruptions, adjustments, or discontinuation may be necessary. Discontinue in the event of nephrotic syndrome.

- Monitor and correct all electrolyte abnormalities in all patients.

- Liver function tests should be monitored before initiation of treatment, then every 2 weeks for the first 2 months and monthly thereafter during treatment. In the case of hepatotoxicity, dose interruptions, adjustments, or discontinuation may be necessary.

- Thyroid function, T4 and TSH should be monitored before initiation of, and periodically throughout treatment with lenvatinib. Hypothyroidism should be treated according to standard medical practice to maintain euthyroid state.

- Monitor patients for clinical symptoms or signs of cardiac dysfunction as dose interruptions, adjustments, or discontinuation may be necessary.

- Gastrointestinal toxicity should be actively managed in order to reduce the risk of development of renal impairment or renal failure. Dose interruptions, adjustments, or discontinuation may be necessary.

- Withold lenvatinib for at least 1 week prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of lenvatinib after resolution of wound healing complications has not been established.

- Events of osteonecrosis of the jaw (ONJ) have been observed with lenvatinib. Invasive dental procedures are an identified risk factor for the development of ONJ. An oral dental examination and appropriate preventive dentistry should be considered prior to initiation of lenvatinib. Patients should be advised regarding periodic dental examinations and oral hygiene practice during lenvatinib therapy. Avoid invasive dental procedures during lenvatinib treatment, if possible. Use caution in patients receiving agents associated with ONJ, such as bisphosphonates and denosumab.

- **Lenvatinib Dose Reductions/ Interruptions/ Discontinuation**:
  - Dose reductions of Lenvatinib for treatment related toxicities will proceed as follows:
    - First dose reduction: 14 mg daily
    - Second dose reduction: 10 mg daily
    - Third dose reduction: 8 mg daily
  - Discontinuation: lenvatinib should be discontinued in case of life-threatening reactions (e.g., Grade 4) with the exception of laboratory abnormality judged to be nonlife-threatening, in which case they should be managed as severe reactions (e.g., Grade 3).
  - Dose interruption: Lenvatinib may be interrupted for situations other than treatment-related AEs such as medical/surgical events and/or unforeseen circumstances not related to study intervention. However, intervention is to be restarted within 2 weeks of treatment hold, unless otherwise discussed with the Sponsor Investigator. The reason for study intervention interruption is to be documented in the patient's study record.

5.2.4 Labeling, Packaging, Storage and Return Of Clinical Supplies

5.2.4.1 Investigational Product

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

Pembrolizumab and Lenvatinib will be provided by Merck as summarized in Table 8.

Table 8 Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 100 mg/ 4mL	Solution for Injection
Lenvatinib 10 and 4 mg capsules	Oral

5.2.4.2 Packaging and Labeling Information

Supplies will be labeled in accordance with regulatory requirements.

5.2.4.3 Clinical Supplies Disclosure

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

5.2.4.4 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.

5.2.4.5 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 participants 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.

5.3 Concomitant Medications/Vaccinations (allowed & prohibited)

The investigator or qualified designee will record medication, if any, taken by the participant during the study. Concomitant medications will be recorded for 30 days after the last dose of study intervention. 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 final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

5.3.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a participant'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 prior to the first dose of trial intervention and up to 30 days after the last dose of trial intervention should be recorded. If participants experience an SAE or ECI, concomitant medications administered30 days after the last dose of trial intervention are to be recorded as defined in Section 6.2.

5.3.2 Prohibited Concomitant Medications

Participants are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) 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
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza and mRNA vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. All treatments that the Investigator considers necessary for a participant's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care.

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.3.3 Rescue Medications & Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2.2, [Table 4]. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the Investigator determines the events to be related to pembrolizumab.

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

5.4 Participant Discontinuation Criteria

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to be monitored in this study and participate in the study visits and procedures as specified in Section 2.3 unless the participant has withdrawn from the study (Section 5.5).

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

A participant must be discontinued from study treatment but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention
- After prolonged study intervention interruption that prohibits restarting study intervention if agreed upon with the Sponsor
- Radiographic disease progression outlined in Section 6.1.4.
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 5.2.2.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, placed the participant at unnecessary risk from continued administration of study treatment.
- The participant has a confirmed positive serum pregnancy test

Completion of pembrolizumab Q3W monotherapy consists of 35 treatments (approximately 2 years). Discontinuation of treatment may be considered for participants who have attained a confirmed complete response (CR) and have been treated for at least 8 cycles (at least 24 weeks), receiving [for monotherapy: at least 2 doses of pembrolizumab; for combination treatment: 2 cycles of the combination including 2 doses of pembrolizumab and at least 80% of the planned doses of lenvatinib beyond the date when the initial CR was declared.

5.5 Participant withdrawal From Study

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

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

Specified details regarding procedures to be performed at the time of withdrawal from the study are outlined in Section 6.1.6.1.

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

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

6.0 TRIAL ASSESSMENTS AND PROCEDURES

6.1 Trial Procedures

- Study procedures and their timing are summarized in the Schedule of Activities (SoA), Section 2.3.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria

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

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

6.1.1 Administrative and General Procedures

6.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical trial. If there are changes to a participant's status during the study (e.g. health requirements) the investigator or medically qualified designee must ensure appropriate documented informed consent is in place.

6.1.1.2 General Informed Consent

Informed consent must be documented by the participant's dated signature or by the participant'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 participant (or their legally acceptable representative) before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the participant must receive the IRB/ERC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant'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 participant's dated signature or by the participant'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.

If the investigator recommends continuation of study intervention beyond disease progression, the participant or his/her legally acceptable representative will be asked to sign consent.

6.1.1.3 Inclusion/Exclusion Criteria

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

6.1.1.4 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 until the first dose of study treatment (C1D1) that are considered to be clinically significant by the Investigator. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

6.1.1.5 Prior and Concomitant Medications Review

6.1.1.5.1 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 participant within 28 days before starting the trial. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

6.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 6.2.

6.1.1.6 Disease Details and Treatments

6.1.1.6.1 Disease Details

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

6.1.1.6.2 Prior Treatment Details

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

6.1.1.6.3 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 participant 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 participant will move into survival follow-up.

6.1.1.7 Assignment of Screening Number

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

6.1.2 Clinical Procedures/Assessments

6.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each participant 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 5.0 (see Appendix 5). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to section 6.2 for detailed information regarding the assessment and recording of AEs.

6.1.2.2 Physical Exam

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard. Height and weight will also be measured and recorded.

A brief directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard [specify if there are specific assessments that must be conducted as a minimum].

Investigators should pay special attention to clinical signs related to previous serious illnesses.

6.1.2.3 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical exams are described in Section 2.3. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

6.1.2.4 Directed Physical Exam

For cycles that do not require a full physical exam per the Section 2.3, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to study intervention administration. New clinically significant abnormal findings should be recorded as AEs.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

6.1.2.5 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 Schedule of Activities (Section 2.3). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

6.1.2.6 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix 1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Schedule of Activities (Section 2.3).

6.1.2.7 Electrocardiograms and ECHO or MUGA

12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals.

A MUGA scan (using technetium-based tracer) or an echocardiogram will be performed to assess LVEF as designated in the SoA. MUGA or echocardiogram scans should be performed locally in accordance with the institution's standard practice. MUGA scans are the preferred modality; however, whichever modality is used for an individual participant at baseline should be repeated for all subsequent LVEF assessments for that participant. LVEFs as assessed by the institution will be entered onto the CRF. Investigator assessment will be based upon institutional reports.

6.1.3 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed

with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

- If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (e.g., SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

Details regarding specific laboratory procedures/assessments to be performed in this study are provided below. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant can be found in the Lab Manual. Refer to the SoA (Section 2.3) for the timing of laboratory assessments.

6.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, and urinalysis are specified in Appendix 2.

6.1.3.2 Pregnancy Testing

All women who are being considered for participation in the study, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy within 72 hours or the first dose of study intervention. Participants must be excluded/discontinued from the study in the event of a positive test result. Repeated pregnancy test (such as monthly testing) may be conducted if required by local regulation.

6.1.4 Tumor Imaging and Assessment of Disease

Tumor imaging is strongly preferred to be acquired by computed tomography (CT). For the abdomen and pelvis, contrast-enhanced magnetic resonance imaging (MRI) may be used when CT with iodinated contrast is contraindicated, or when local practice mandates it. MRI is the strongly preferred modality for imaging the brain. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the

reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging.

Brain imaging is required for all participants at screening. MRI is preferred; however, CT imaging will be acceptable, if MRI is medically contraindicated. Participant eligibility will be determined using local assessment (Investigator assessment) based on RECIST 1.1. In addition, images (including via other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons, but which demonstrate radiologic progression, should also be used to determine progression.

When the Investigator identifies radiographic progression per RECIST 1.1, efforts should be made to verify radiologic PD. Treatment should continue until PD has been verified. Regardless of whether PD is verified, if the Investigator considers the participant has progressed, but elects to implement iRECIST, the Investigator will assess for confirmation of progression by iRECIST at subsequent time points.

6.1.4.1 Initial Tumor Imaging

Initial tumor imaging at Screening must be performed within 30 days prior to the date of allocation. The site study team must review screening images to confirm the participant has measurable disease per RECIST 1.1.

Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if they are of diagnostic quality and performed within 30 days prior to C1D1.

Brain imaging is required to rule out radiographically detectable brain metastases. Magnetic resonance imaging is preferred; however, CT imaging will be acceptable, if MRI is medically contraindicated or CT is mandated by local practice.

6.1.4.2 Tumor Imaging During the Study

The first on-study imaging assessment should be performed at 9 weeks (±7 days) from the date of allocation. Subsequent tumor imaging should be performed every 9 weeks (±7 days) or more frequently if clinically indicated. After 1 year (±7 days), participants who remain on treatment will have imaging performed every 12 weeks (±7 days). Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the Investigator.

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response is observed. Participants will then return to regular scheduled imaging every 9 weeks, starting with the next scheduled imaging time point. Participants who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

Per iRECIST (Section 6.1.4.6), disease progression should be confirmed by the site 4 to 8 weeks after first radiologic evidence of PD in clinically stable participants. Participants who have unconfirmed disease progression may continue on treatment at the discretion of the investigator until progression is confirmed by the site provided they have met the conditions detailed in Section 6.1.4.6. Participants who receive confirmatory imaging do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point, if clinically stable. Participants who have confirmed disease progression by iRECIST, as assessed by the site, will discontinue study treatment. Exceptions are detailed in Section 6.1.4.5.

6.1.4.3 End of Treatment and Follow-up Tumor Imaging

In participants who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (± 4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. In participants who discontinue study treatment due to documented disease progression and the investigator elects not to implement iRECIST, this is the final required tumor imaging.

For participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while on treatment (every 9 weeks in Year 1 or every 12 weeks after Year 1) to monitor disease status until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

6.1.4.4 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used 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 (eg, discontinuation of study treatment). Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, the Sponsor allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden. The first half of the flowchart in [Figure 2] illustrates the imaging flow involving verification of PD for clinically stable participants.

6.1.4.5 iRECIST Assessment of Disease

iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the investigator to assess tumor response and progression and make treatment decisions. When clinically stable, participants should not be discontinued until progression is confirmed by the investigator, working with local radiology, according to the rules outlined in Appendix 4. This allowance to continue treatment despite initial radiologic disease progression takes into account the observation that some participants can have

a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. This data will be captured in the clinical database.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any participant deemed clinically unstable should be discontinued from study intervention at central verification of site-assessed first radiologic evidence of disease progression, and is not required to have repeat tumor imaging for confirmation of disease progression by iRECIST.

If the investigator decides to continue treatment, the participant may continue to receive study intervention and the tumor assessment should be repeated 4 to 8 weeks later to confirm disease progression by iRECIST, per investigator assessment. Images should continue to be sent in to the iCRO for potential retrospective BICR.

If repeat imaging does not confirm disease progression per iRECIST, as assessed by the investigator, and the participant continues to be clinically stable, study intervention may continue and follow the regular imaging schedule. If disease progression is confirmed, participants will be discontinued from study intervention.

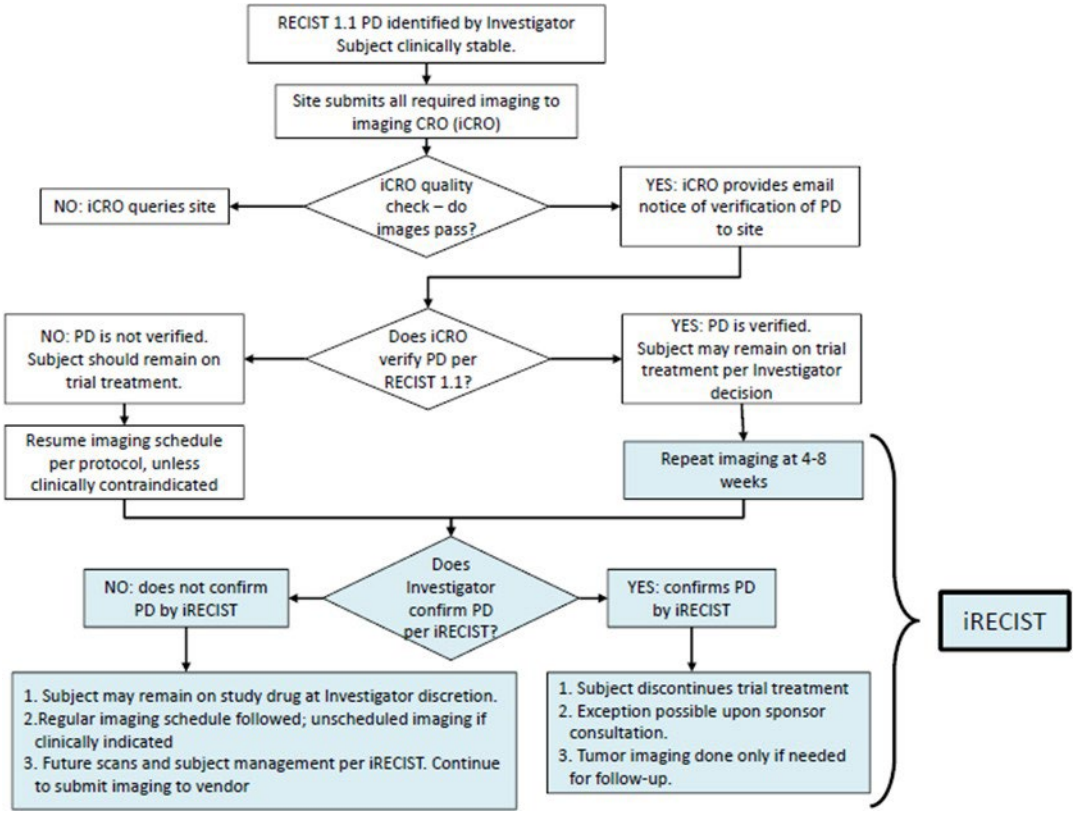
If a participant has confirmed radiographic progression (iCPD) as defined in Appendix 4, study intervention should be discontinued; however, if the participant is achieving a clinically meaningful benefit, an exception to continue study intervention may be considered following consultation with the Sponsor. In this case, if study intervention is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 6 and submitted to the iCRO.

A description of the adaptations and iRECIST process is provided in Appendix 4. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 6 and illustrated as a flowchart in Figures 1 and 2.

Table 6 Imaging and Treatment After First Radiologic Evidence of Progressive Disease

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of disease progression by RECIST 1.1 per investigator assessment	Repeat imaging at 4 to 8 weeks to confirm disease progression	May continue study treatment at the assessment of the investigator and after the participant's consent	Repeat imaging at 4 to 8 weeks to confirm disease progression per investigator's discretion only.	Discontinue treatment
First radiologic evidence of disease progression by RECIST 1.1 [For those studies in which PFS is the primary endpoint, add the following: which has been verified by the central imaging vendor].	Repeat imaging at 4 to 8 weeks to confirm disease progression.	May continue study intervention at the investigator's discretion while Awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm disease progression per investigator's discretion only.	Discontinue treatment
Repeat tumor imaging confirms disease progression (iCPD) by iRECIST per investigator assessment.	No additional imaging required.	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional imaging required.	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per investigator assessment.	Repeat imaging at 4 to 8 weeks to confirm disease progression. May occur at next regularly scheduled imaging visit.	Continue study intervention at the investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm disease progression per investigator's discretion only.	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study intervention at the investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study intervention if condition has improved and/or clinically stable per investigator's discretion. Next tumor imaging should occur according to the regular imaging schedule.
iCPD=iRECIST confirmed progressive disease; iCR=iRECIST complete response; iRECIST=modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD=iRECIST stable disease; iUPD=iRECIST unconfirmed progressive disease; RECIST 1.1=Response Evaluation Criteria in Solid Tumors 1.1; VOP=verification of progression [For studies in which PFS is the primary endpoint, add the following: Note: If progression has been centrally verified, further management is by the site, based on iRECIST. Any further imaging should still be submitted to the iCRO, but no rapid review will occur. If RECIST 1.1 disease progression has not been centrally verified, the site should continue treatment. Whether or not treatment continues, imaging should be collected and submitted to the iCRO with VOP request until RECIST 1.1 progression is verified by BICR.]				

Figure 1: Imaging and Treatment for Clinically Stable Participants after First Radiologic Evidence of PD Assessed by the Investigator



6.1.5 Tumor Tissue Collection and Correlative Studies Blood Sampling

Tumor tissue and blood specimens will be collected and banked for correlative research studies. An additional optional collection for specimen banking will be collected for those who consent for at least 15 subjects (in no certain order). Fresh tumor biopsy samples will be collected prior to initiating treatment. Archival tissue may be used in place of pre-treatment biopsy. A second biopsy will be collected on cycle 3 day 8 (+/- 1 day). Blood specimens including the optional specimen banking samples will be collected during screening and on day 1 of cycles 1-6.

Correlative and optional specimen banking samples collected for Screening may be used for C1D1 if the collection is within 3 days prior to C1D1.

6.1.6 Other Procedures

6.1.6.1 Discontinuation and withdrawal

Participants who discontinue study intervention prior to completion of the treatment period should be

encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 6.2.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the final study visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 6.2.

6.1.7 Visit Requirements

Visit requirements are outlined in Section 2.3 – Schedule of Activities. Specific procedure-related details are provided above in Section 6.1 - Trial Procedures.

6.1.7.1 Screening

6.1.7.1.1 Screening Period

Please reference schedule of activities in section 2.3.

6.1.7.2 Treatment Period

Please reference schedule of activities in section 2.3

6.1.7.3 Post-Treatment Visits

6.1.7.3.1 Safety Follow-Up Visit

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

6.1.7.3.2 Efficacy Follow-up Visits

Participants who complete the protocol-required cycles of study intervention of who discontinue study intervention for a reason other than disease progression will begin the Efficacy Follow-Up Phase and should be assessed every 6 weeks (42 ± 7 days) by radiologic imaging to monitor disease status. After 1 year, the imaging time point will occur every 9 weeks (± 7 days). Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, end of the study or if the participant begins retreatment with pembrolizumab as detailed in Section 5.2.3. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated. Participants who completed all efficacy assessments and/or will not have further efficacy assessments must enter the Survival Follow-up Phase.

6.1.7.3.3 Survival Follow-up Contacts

Participant survival follow-up status will be assessed approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

The first survival follow-up assessment should be scheduled as described below:

- For participants who discontinue treatment intervention and who will not enter the Efficacy Follow-up Phase, the first survival follow-up contact will be scheduled 12 weeks after the discontinuation visit and/or safety follow-up visit (whichever is last).

For participants who completed assessments in the Efficacy Follow-up Phase, the first survival follow-up contact will be scheduled 12 weeks after the last efficacy assessment follow-up visit has been performed.

6.1.7.3.4 Post Study

Participants will be required to return to clinic approximately 14 days after the last dose of study intervention for the poststudy visit. If the poststudy visit occurs less than 14 days after the last dose of study intervention, a subsequent follow-up telephone call should be made at 14 days post the last dose of study intervention to determine of any AEs have occurred since the poststudy clinic visit.

6.2 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 5.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

6.2.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs and other reportable safety events must be reported starting after the first dose of study intervention on C1D1. AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before first dose of study intervention must be reported by the investigator only if the participant is receiving other run-in treatment, if the event causes the participant to be excluded from the study, or is the result of a protocol- specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the first dose of study intervention through 30 days following cessation of study intervention or until initiation of new anticancer therapy, whichever is earlier, must be reported by the investigator.

- All AEs meeting serious criteria, from the first dose of study intervention through 90 days following cessation of study intervention or 30 days following cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.
    - Of note, progression of disease under study does not meet the definition of an Adverse Event, therefore death due to progression of disease under study is not reportable as an SAE.
- All pregnancies and exposure during breastfeeding, from the first dose of study intervention through 120 days following cessation of study intervention, or 30 days following cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to Merck if the event is considered drug-related.

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

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to Merck within the time frames as indicated in Table 7 via fax (Attn: Worldwide Product Safety; Fax 215-661-6229).

Table 7 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period:** **Consent to First Dose of Study Intervention**	**Reporting Time Period:** **First Dose of Study Intervention through Protocol-specified Follow-up Period**	**Reporting Time Period:** **After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Merck:**
Serious Adverse Event (SAE) including New Cancer Diagnosis and Overdose	Report if: - due to protocol-specified procedure/intervention - causes exclusion - participant is receiving other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 2 business days but no longer than 3 calendar days of learning of event
Pregnancy/Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 2 business days but no longer than 3 calendar days of learning of event

Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention causes exclusion	Report - potential drug-induced liver injury (DILI) require regulatory reporting	Not required	Within 2 business days but no longer than 3 calendar days of learning of event

6.2.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

6.2.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events including pregnancy and exposure during breastfeeding, events of clinical interest (ECIs), cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up.. In addition, the investigator will make every attempt to follow all nonserious AEs that occur in allocated or randomized participants for outcome. Further information on follow-up procedures is given in Appendix 5.

6.2.4 Sponsor Responsibility for Reporting Adverse Events

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

6.2.5 Pregnancy and Exposure During Breastfeeding

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

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.

6.2.6 Events of Clinical Interest (ECIs)

Selected nonserious and SAEs are also known as ECIs and must be reported to Merck.

Events of clinical interest for this study include:

1. An overdose of pembrolizumab that is not associated with clinical symptoms or abnormal laboratory results. For purposes of this study, 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. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated. If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

2. For the purpose of this study, an overdose will be defined as any dose exceeding the prescribed dose for:

    - Lenvatinib: any dose above the protocol-prescribed dose if associated with an adverse event

    There is no specific antidote for an overdose of lenvatinib. Due to its high degree of plasma protein binding, lenvatinib is not expected to be dialyzable. Adverse reactions in patients receiving single doses of lenvatinib as high as 40 mg were similar to those in clinical studies at the recommended dose for differentiated thyroid cancer, RCC, and HCC.

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

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

7.0 STATISTICAL ANALYSIS PLAN

7.1 Statistical Analysis Plan Summary

For this exploratory pilot study, sample size was calculated based on a hypothesis of anticipated clinical efficacy and compared with historical clinical trial data. As this is a single arm study, no formal statistical comparisons will be made.

7.2 Statistical Analysis Plan

This represents a single-arm signal finding pilot study. As such, no formal statistical comparisons will be conducted. However, using historical data from prospective clinical trials and retrospective case series reported in the literature, therapy with PD-1 inhibitors results in objective response rates of approximately 10% and median progression free survival of approximately 3.5 months (reviewed by Wessely A., et al. International Journal of Molecular Sciences 2020) [27].

In this 30 patient pilot study, using a one-sided test with a type I error of 0.05, the power for detecting a difference in the ORR compared with the historical average of 10% ORR with anti-PD-1 monotherapy varies with the hypothetical experimental ORR as follows:

Hypothetical experimental ORR	Historical average ORR	Power
20%	10%	0.55
25%	10%	0.78
30%	10%	0.91

Interim futility analysis/stopping rules: After 15 evaluable subjects have been enrolled and treated (defined as having received scheduled treatment per protocol for at least 1 cycle and have completed restaging imaging) - an interim futility analysis will be conducted. If the objective response rate is less than 20% (3 of 15 subjects) or the median progression free survival is less than 6 months - enrollment will stop.

8.0 ADMINISTRATIVE AND REGULATORY DETAILS

8.1 Data Reporting

RedCap will be the electronic data capture (EDC) system utilized for data collection. Clinical data will be entered on electronic, study-specific case report forms (eCRFs) built and maintained in the eResearch application. All data entries to CRFs must be supported by a clinical source document. No direct entry of patient data to the CRF is permitted.

8.2 Continuing Review and Final Reports

An annual progress report (continuing review) will be submitted to the FDA annually for the duration of the study and to the IRB of record at the interval it determines, but at least annually. Continuing review reports to the FDA will comply with Title 21, Part 312.33 of the Code of Federal Regulations.

8.3 Protocol Modifications and Amendments

All modifications or amendments to the protocol or informed consent document must be approved by the Principal Investigator and submitted to the IRB for review and approval. All modifications and amendments will be documented with a new version number and date. All changes to the informed consent document will include the date of the revision on the form.

No changes will be implemented until IRB approval is obtained except when a potential threat to patient safety exists.

The IRB will be notified of any significant deviations from the approved protocol. Documentation of all IRB correspondence will be maintained in a central regulatory file.

8.4 Record Retention

According to 21 CFR 312.62(c), the investigator shall retain required 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. If no application is to be filed or if the application is not approved for such indication, the investigator shall retain these records until 2 years after the investigation is discontinued (IND is withdrawn) and the FDA is notified.

The investigator must retain protocols, amendments, IRB/IBC approvals, copies of the Form FDA 1572, completed, signed, dated consent forms, patient source documents, case report forms, quality monitoring reports, drug accountability records and all documents of any nature regarding the study or patients enrolled. All records will be maintained under restricted access by the Clinical Trials Department at Providence Portland Medical Center while the study remains active. Records may be placed in long-term storage after the study is completed. The location of long-term storage will be secure and easily accessed for regulatory purposes.

8.5 Study Monitoring

Clinical research staff members who have completed specialized training in study monitoring procedures and human subjects' protections perform study monitoring activities (Quality Control Reviews). Individuals who perform study monitoring activities do not report to Principal Investigators or research scientists and may not monitor studies for which they have direct responsibility.

Study monitoring activities are conducted regularly and include (but are not limited to) review and verification of the following:

- Eligibility
- Informed Consent process
- Adherence to protocol treatment plan
- Case Report Forms (CRFs)
- Source Documentation
- Adverse Events
- Regulatory Reporting

Results of study monitoring activities will be reported to applicable study personnel, the Administrative Director of Clinical Research and Quality Assurance. Quality Assurance (QA) personnel review study monitoring reports and, if necessary, determine follow-up actions to resolve significant findings. QA has the authority to request immediate corrective action if significant patient safety issues are identified.

QA will track and trend results from study monitoring reports as well as associated corrective and preventive actions. A QA summary report will be provided to the IRB at the time of continuing review.

QA personnel do not have a direct reporting relationship to the Principal Investigator and are not responsible for enrollment or coordination of care for study participants.

External sites

Monitoring will occur at intervals stipulated in the monitoring plan for the study. Monitoring may be performed on-site or remotely. Monitoring will include: review regulatory documentation, CRFs, source documentation, and investigational product storage, preparation, and accountability. The CRFs will be reviewed for completeness and accuracy compared to the source documents.

8.6 Quality Assurance Plan

The Providence Health System Quality Assurance (QA) plan for cancer clinical trials comprises Standard Operating Procedures (SOPs) that require ongoing review of activities associated with all investigator-initiated trials including protocol compliance, accuracy of data and safety of participants.

Quality Assurance (QA) personnel review study monitoring reports and if necessary, determine follow-up actions to resolve significant findings. QA has the authority to request immediate corrective action if significant patient safety issues are identified.

QA will track and trend results from study monitoring reports as well as associated corrective and preventive actions. A QA summary report will be provided to the IRB at the time of continuing review.

QA personnel do not have a direct reporting relationship to the Principal Investigator and are not responsible for enrollment or coordination of care for study participants.

All case report forms will undergo quality assurance review. All quality assurance reviews will include verification of the accuracy and integrity of data entered to case report forms. Incorrect data will be identified and corrected. The existence of adequate source documents for all data will be verified. A staff person not associated with patient care coordination, data completion or submission will review all annual reports.

8.7 Safety Monitoring Plan

Oversight of participant safety will include review of adverse events as well as study progress and outcomes.

Adverse events, outcomes, and recruitment and retention of patients will be reviewed on a weekly basis by the PI, research nurse, and data coordinator. Protocol deviations are reviewed monthly at the Cancer Research Meeting.

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10.0 APPENDICES

Appendix 1: ECOG Performance Status

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

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

Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 9 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 9 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	BUN	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the ULN)
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	ALT (including LFT)/SGPT	Total Protein
	Glucose [Indicate if fasting, or nonfasting]	Calcium	Alkaline phosphatase	Thyroid Funtion Tests (LDH, Free T4, TSH)
	INR or PT and aPTT			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal) • 24-hour urine collection for quantitative assessment of proteinuria may also be required at screening to determine eligibility			
Pregnancy Testing	• Highly sensitive serum hCG pregnancy test (as needed for WOCBP)			
Other Screening Tests	• FSH (as needed in WOCBP only)			

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle-stimulating hormone; hCG=human chorionic gonadotropin; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; RBC=red blood cell; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; ULN=upper limit of normal; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

Appendix 3: Contraceptive Guidance and Pregnancy Testing

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

Male Participants:

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol defined time frame in section 5.11:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 10 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

- Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective (with a failure rate of <1% per year) method of contraception that has a low user dependency consistently and correctly as described in Table 10 during the protocol-defined time frame in Section 5.1.3.2.

Table 10 Highly Effective Contraceptive Methods That Have Low User Dependency

Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen- only contraceptive implant [a, b] • Intrauterine hormone-releasing system (IUS) [b] • Intrauterine device (IUD) • Bilateral tubal occlusion
• **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
• **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least 120 days after the last dose of study treatment.

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive serum pregnancy test.

Following initiation of treatment, pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected; at the time points specified in the Schedule of Activities (Section 2.3), and as required locally.

Appendix 4: Description of the iRECIST Process for Assessment of Disease Progression

Assessment at Screening and Prior to RECIST 1.1 Progression

Until radiographic progression based on RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST 1.1 Progression

In participants who show evidence of radiological PD by RECIST 1.1 the Investigator will decide whether to continue a participant on study treatment until repeat imaging 4 to 8 weeks later is obtained (using iRECIST for participant management (see Table 6 and Figures 1 and 2). This decision by the Investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

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

If the Investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per Investigator assessment.

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥ 20% and ≥ 5 mm from nadir
    - Please note: the iRECIST publication uses the terminology "sum of measurements", but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and non-target lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

Assessment at the Confirmatory Imaging

On the confirmatory imaging, the participant will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
  - For target lesions, worsening is a further increase in the sum of diameters of ≥ 5 mm, compared to any prior iUPD time point
  - For non-target lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
  - For new lesions, worsening is any of these:
    - An increase in the new lesion sum of diameters by ≥ 5 mm from a prior iUPD time point
    - Visible growth of new non-target lesions
    - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the scan on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the

subsequent confirmation scan proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is "reset". This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management Following the Confirmatory Imaging

If repeat imaging does not confirm PD per iRECIST, as assessed by the Investigator, and the participant continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study treatment.

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 6.

Detection of Progression at Visits After Pseudo-progression Resolves

After resolution of pseudo-progression (ie, achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
  - Sum of diameters reaches the PD threshold (≥ 20% and ≥ 5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudo-progression.
- Non-target lesions
  - If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.

  - If non-target lesions had shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.

- New lesions
  - New lesions appear for the first time
  - Additional new lesions appear
  - Previously identified new target lesions show an increase of ≥ 5 mm in the new lesion sum of diameters, from the nadir value of that sum
  - Previously identified non-target lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, except in one respect. If new lesions occurred at a prior instance of iUPD, and at the confirmatory scan the burden of new lesions has increased from its smallest value (for new target lesions, their sum of diameters is ≥5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Additional details about iRECIST are provided in the iRECIST publication [28].

Appendix 5: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.1.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- NOTE: For purposes of AE definition, study intervention (also referred to as Merck product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, or protocol specified procedure whether investigational or marketed (including active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by Merck for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology “accidental or intentional overdose without adverse effect.”

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.
- Progression of disease under study.

10.1.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met. For example, death or hospitalization due to progression of disease under study would not be considered an SAE.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

- The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing 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 an SAE. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the participant's medical history.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a

substantial disruption.

e. Is a congenital anomaly/birth defect

- In offspring of participant taking the product regardless of time to diagnosis.

f. Other important medical events

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.1.3 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to Merck in the same time frame 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 of pembrolizumab

10.1.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- There may be instances when copies of medical records for certain cases are requested by the Merck. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Merck.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

1. The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI Common Terminology for Adverse Events (CTCAE), version 5. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.
    - 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 activities of daily living (ADL).
    - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
    - Grade 4: Life threatening consequences; urgent intervention indicated.
    - Grade 5: Death related to AE.

Assessment of causality

1. Did Merck product cause the AE?

2. The determination of the likelihood that Merck product caused the AE 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 product and the AE based upon the available information.

3. The following components are to be used to assess the relationship between Merck's product and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Merck product caused the AE:

    - **Exposure:** Is there evidence that the participant was actually exposed to Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

    - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies 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.
- **Dechallenge:** Was Merck product discontinued or dose/exposure/frequency reduced?
- If yes, did the AE resolve or improve?
- If yes, this is a positive dechallenge.
- If no, this is a negative dechallenge.
- (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Merck product; (3) the study is a single-dose drug study; or (4) Merck product(s) is/are only used 1 time.)
- **Rechallenge:** Was the participant re-exposed to Merck product in this study?
- If yes, did the AE recur or worsen?
- If yes, this is a positive rechallenge.
- If no, this is a negative rechallenge.

(Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study; or (3) Merck product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY MERCK PRODUCT, OR IF RE-EXPOSURE TO MERCK'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE INIRB/IEC.

4. **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding Merck product or drug class pharmacology or toxicology?

5. 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.

6. Use the following scale of criteria as guidance (not all criteria must be present to be indicative of Merck product relationship).

- Yes, there is a reasonable possibility of Merck product relationship:

- There is evidence of exposure to the Merck product. The temporal sequence of the AE onset relative to the administration of Merck product is reasonable. The AE is more likely explained by Merck product than by another cause.

- No, there is not a reasonable possibility of Merck product relationship:

- Participant did not receive the Merck product OR temporal sequence of the AE onset relative to administration of the Merck product is not reasonable OR the AE is more likely explained by another cause than the Merck product. (Also entered for a participant with overdose without an associated AE.)

7. For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

8. There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Merck. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Merck.

9. The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

10. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

11. For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.

- The investigator will submit any updated SAE data to Merck within 2 business days but no longer than 3 calendar days of receipt of the information.

10.1.5 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Merck

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-661-6229

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. (Attn: Worldwide Product Safety; FAX 215-661-6229) at the time of submission to FDA.