SPONSOR:

TITLE: A Phase II Study to evaluate the efficacy and safety of pembrolizumab in combination with mitotane in patients with advanced adrenocortical carcinoma

IND NUMBER: EXEMPT

Documentation History Page

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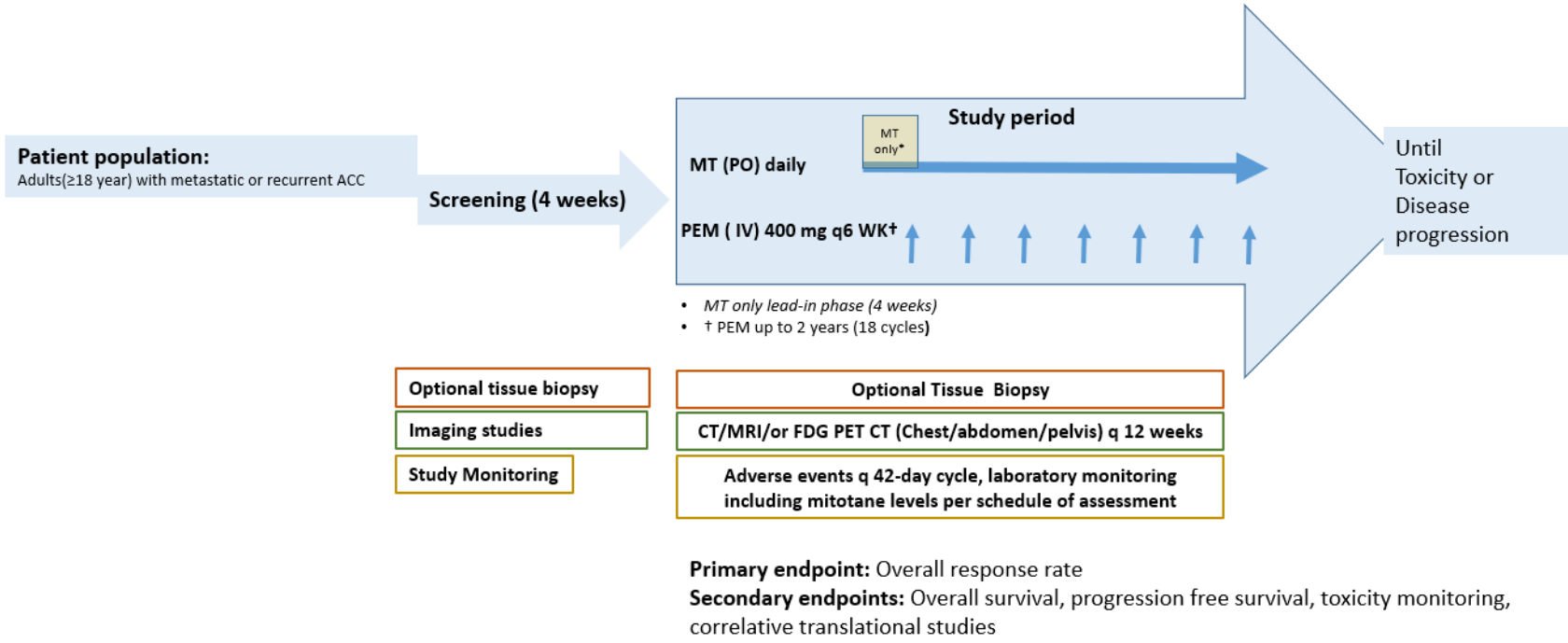
1.0 TRIAL SUMMARY

Abbreviated Title	Pembrolizumab plus mitotane for adrenocortical carcinoma
Trial Phase	II
Clinical Indication	Recurrent/Metastatic Disease
Trial Type	Single arm, open label
Type of control	Historical control
Route of administration	Mitotane: PO. Pembrolizumab: IV
Treatment Groups	1
Number of trial participants	Up to 50
Estimated enrollment period	48 months
Estimated duration of trial	60 months
Duration of Participation	Up to 24 months
Estimated average length of treatment per patient	12 months

2.0 TRIAL DESIGN

2.1 Trial Schema

Phase 2 trial of mitotane (MT) plus pembrolizumab (PEM) in advanced adrenocortical carcinoma (ACC)



Primary endpoint: Overall response rate
Secondary endpoints: Overall survival, progression free survival, toxicity monitoring, correlative translational studies

2.2 Schedule of Activities

Table 1 Study Schedule of Activities

	Screening	Lead-in phase	Treatment Period (cycles are 42 days) +/-5 -day window *All CXD1 assessments may be performed up to 7 days before infusion*					Progression	Study Completion /Early Termination Visit	Follow-Up [12]
Day	-28 through day -1	(Days 1-28 days± 5)	C1 D1	C2 D1	C3 D1	C4 D1	C5D1 -last course [h]			
Informed consent	x									
Inclusion/exclusion criteria	x	X *								
Demographic data	x									
Pregnancy test [1]	x	x	x	x	x	x	x			
Physical Examination & ECOG PS [2]	x		x	x	x	x	x		x	
Routine labs [3]	x		x	x	x	x	x		x	
Fasting Lipid Panel [4]	x			x		x	x[4]			
Adrenal Hormones Panel [5]	x		x		x		x [5]			
Mitotane level [6]	x [6]		x	x	x	x	x		x	
12-lead ECG [7]	x									
Mitotane therapy [8]		x	x	x	x	x	x			

Pembrolizumab infusion [9]			x	x	x	x	x			
Response assessment [10]	x	x [11]	Scans will be done every 12 weeks (+/-7 days) starting on C2D1							
Concomitant medications	x		x	x	x	x	x		x	
Adverse events	x		x	x	x	x	x		x	x
Optional Biopsy	x					x		x		

[1] Pregnancy test, serum or urine at baseline, urine or blood within 72 hours prior to every cycle for women of child-bearing potential; All WOCBP must have a negative serum or urine pregnancy test within 72 hours prior to start of study drug.

[2] Physical examination at screening and day 1 of each cycle (+/- 7 days). ECOG performance status must be documented within 10 days prior to each cycle and can be obtained remotely or in person.

[3] Hemoglobin, hematocrit, platelet count, RBC count, WBC count, percent and absolute differential count, sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, total and direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, TSH, free T4.

[4] Fasting Lipid panel at screening, Cycle 2, Cycle 4, and Cycle 6. May be repeated with every other cycle per treating physician discretion.

[5] Adrenal Hormones Panel: ACTH, Cortisol, plasma renin activity, plasma aldosterone concentration, DHEA-Sulfate, testosterone (in women), estradiol (in men and postmenopausal women), and 11-deoxycortisol. All patients must have full hormonal evaluation at screening. Adrenal Hormonal labs may be repeated (complete or partial panel) every other cycle starting Cycle 1 per treating physician discretion.

[6] Serum mitotane level: Only patients who are already on mitotane at time of screening will have mitotane level checked during screening. Otherwise, mitotane level will be checked cycles 1-5 with the option of having mitotane levels checked every other cycle starting Cycle 5 per treating physician discretion.

[7] All patients will undergo 12-lead EKG at screening. Further, evaluation of EKG can be repeated with other cycles per treating physician discretion.

[8] Patients who were on mitotane prior to consent and meet eligibility criteria do not need to have lead-in phase (including leading phase assessments) and can start on combination therapy if completed 28 days of mitotane therapy

[9] Patients will be treated for a maximum of 18 cycles with pembrolizumab but may continue mitotane beyond the 18 cycles per treating physician discretion outside the clinical trial

[10] Response assessment by cross-sectional imaging such as CT, MRI, or PET-CT as per standard of care for each patient. Screening assessment must occur within 28 days prior to lead-in phase and imaging to be repeated within 7 days of Cycle 1 Day 1 of combination therapy. PET/CTs may be substituted for CT or MRI at baseline and re-staging, if in the opinion of the treating physician.

[11] Response assessment by cross-sectional imaging will consider baseline scan as the study done within 7 days of Cycle 1 Day 1 of combination therapy.

[12] All patients who discontinue treatment without objective disease progression will be followed up with tumor assessment every 12 weeks (±14 days) or as determined by the principal investigator or designee) until disease progression or the start of a different anti-cancer therapy. Survival follow-up via phone call, medical record review, or visit with physician will occur every 3 months for 2 years once they are off study treatment or until patient death, withdrawal of consent, patient is lost to follow-up, or study termination, whichever occurs first.

* Please refer to Table.5. The lead-in phase is primarily designed to ensure patients safety and to have initial evaluation of potential AEs attributed to MT use with particular attention to liver enzymes. If MT use caused elevated ALT or AST during the lead-in phase not meeting eligibility criteria for LFTs or if participants developed ≥ G3 non-hematological toxicity, then these patients will not go through the combination therapy and may come off protocol at the discretion of the PI and will be replaced if excluded by other patients and considered as screen failure. Patients who were on prior MT therapy must complete 28 days of MT use prior to moving to combination therapy and must meet eligibility criteria stated at screening phase and will not need to have the lead-in phase assessment.

Table 2 Study Schedule of Activities: Survival Status

Study Period	Screening Phase	Lead-in phase	Treatment Cycles (6-Week Cycles) [1]						EOT	Post Treatment Visits [2]		
Treatment Cycle	Screening (Visit 1)		1	2	3	4	5	6 to 18	DC	Safety Follow-up	Survival Follow-up	Notes:
Scheduling Window (Days):	-28 to -1	Days 1-28 days (± 5)	±5	±5	±5	±5	±5	±5	Time of DC	30 Days from the last dose (±7days)	Every 12 Weeks (±14 days)	
Subsequent Anti-neoplastic Therapy Status									X	X		

[1] [1]

Patients will be treated for a maximum of 18 cycles with pembrolizumab but may continue on mitotane beyond the 18 cycles per treating physician discretion outside the clinical trial.

[2]All patients who discontinue treatment without objective disease progression will be followed up with tumor assessment every 12 weeks (±14 days) or as determined by the principal investigator or designee) until disease progression or the start of a different anti-cancer therapy. Survival follow-up via phone call, medical record review, or visit with physician will occur every 3 months for 2 years once they are off-study treatment or until patient death, withdrawal of consent, patient is lost to follow-up, or study termination, whichever occurs first.

Table 3 Study Schedule of Activities: Tumor Imaging

Study Period:	Screening Phase	Lead-in phase	Combination Treatment Cycles (6-Week Cycles)						End of Treatment	
Treatment Cycle/Title [1]:	Screening (Visit 1)	28 days	1	2	3	4	To be repeated beyond 6 cycles		Discon	Survival Follow-Up
							5	6		
[1] Scheduling Window (Days):	-28 to -1	X [3]		±7		±7		±7	At time of discontinuation ±7	[2] Every 12 weeks post discontinuation ±14

[1] Baseline assessment must occur within 28 days prior to day 1 of lead-in phase. After baseline assessment during screening, scans will be done during the lead-in phase within 7 days of combination therapy and then every 12 weeks (+/-7 days) starting on C2D1. Response assessment by cross-sectional imaging such as CT, MRI, or PET-CT as per standard of care for each patient. PET/CTs may be substituted for CT or MRI at baseline and re-staging, if in the opinion of the treating physician.

[2] All patients who discontinue treatment without objective disease progression will be followed up with tumor assessment every 12 weeks (±14 days) or as determined by the principal investigator or designee) until disease progression or the start of a different anti-cancer therapy. Survival follow-up via phone call, medical record review, or visit with physician will occur every 3 months for 2 years once they are off-study treatment or until patient death, withdrawal of consent, patient is lost to follow-up, or study termination, whichever occurs first.

[3] Patients who start with lead-in phase need to have imaging within 7 days of C1D1 of combination therapy as a baseline to assess response to therapy. Patients who were on mitotane prior to consenting will not need lead-in phase and will go directly to combination therapy and the screening phase imaging will be considered the baseline for future tumor measurement.

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

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

(1) **Objective:** Assess the clinical efficacy of the combined use of MT with PEM in patients with advanced ACC.

Hypothesis: We hypothesize that adding PEM will enhance the clinical efficacy of MT. This additive/synergistic effect could be related to the intrinsic adrenolytic activity of MT that could lead to antigens exposures to immune cells. Furthermore, the cortisol lowering effect of mitotane is expected to alter the tumor microenvironment leading to a change the milieu of the tumor infiltrating immune cells to make ACC more susceptible to PEM. Also, cortisol lowering can reduce lymphocytes inhibition and enhances the efficacy of PEM.

Primary Endpoint: Overall response rate (ORR) assessed objectively using RECIST 1.1 criteria defined as the percentage of patients who have a partial or complete response to the combined treatment of MT plus PEM

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

(1) **Objective**: Evaluate the safety and efficacy of the combined use of MT plus PEM in patients with advanced ACC.

Hypothesis: The optimal MT plasma levels have not been established prospectively in metastatic ACC. We hypothesize that mitotane level of 14-20 mg/L is associated with oncological responses, but we also anticipate that the combined use of PEM MT could be associated with responses at lower levels of MT which might be associated with more favorable AE profile of MT.

Secondary Endpoints:

1. Overall survival (OS), defined as the time from combination therapy to death from any cause.
2. Progression Free Survival (PFS), defined as the time from the start of combination therapy phase to disease progression or death from any cause.
3. Explore the association between MT level and response to therapy
4. Safety assessment by the Common Terminology Criteria for Adverse Events (CTCAE) V5.0

3.3 Exploratory Objective(s)

(1) **Objective:** Correlate safety and efficacy data with steroid profile, immune markers and MT levels.

1. Obtain optional tumor biopsy prior to, during, and after treatment with MT/PEM combination to study immune markers such as infiltrating tumor lymphocytes, and other immune markers during therapy.

2. Study the changes in circulating markers (MT level, immune cytokines, steroid profile) in blood samples obtained prior to, during, and after treatment with MT/PEM combination

4.0 BACKGROUND & RATIONALE

4.1 Background

Adrenocortical carcinoma (ACC) is a rare endocrine malignancy with high recurrence rates and mortality. ACC has an annual incidence of about 1-2 cases per million (Else T et al. Endocr Rev. 2014). ACC patients often cluster in few centers across the world with known experience in managing this disease. Currently, ACC patients receive systemic therapy that has suboptimal and short-lived benefit.

Mitotane (MT) (Lysodren®) (o,p′-DDD or 1,1-dichloro-2[o-chlorophenyl]-2-[p-chlorophenyl]ethane) is a pesticide isomer that is directly toxic to adrenocortical cells. MT is a unique drug with dual benefit in ACC. MT has an adrenolytic activity in addition to its ability to block steroidogenesis enzymes and thus it reduces circulating cortisol levels. Furthermore, MT changes the peripheral metabolism of cortisol and reduces circulating cortisol levels. MT is administered orally in tablets of 500 mg. MT is the only FDA-approved drug to treat advanced ACC and considered the standard of care in these patients. MT has been in use for almost 5 decades and is associated with objective response rate of 11-20.5% and median progression free survival of 4.1 months (Reidy-Lagunes et al. 2017; Megerle et al. 2018). MT is often combined with cytotoxic chemotherapy. The most commonly used regimen is (etoposide, doxorubicin, and cisplatin) [MT-EDP]. This regimen is associated with response rate of 23% with median time to progression of about 5 months while 58% of patients had serious AEs (Fassnacht et al. 2012). Considering the limited efficacy and the high toxicity of the commonly used therapy (MT-EDP), the lack of highly effective second line therapy, and the paucity of available clinical trials for ACC patients, there is a critical unmet need to provide an effective and less toxic systemic therapy to ACC patients as an alternative to MT-EDP.

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).

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 T-cells/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, Freeman, and Sharpe 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; 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, Sage, and Sharpe 2010). Therefore, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in ACC.

4.1.2 Preclinical and Clinical Trial Data

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

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Population

Recently, two phase II studies showed that PEM monotherapy in ACC resulted in objective response rates of 14-23% and disease control/clinical benefit rates of 52-57% while the risk of serious AEs was low and seen in only 13% of patients in both studies (Habra et al. 2019; Raj et al. 2019).

The combined use of MT with PEM has not been studied prospectively. A retrospective case series of 6 patients with metastatic ACC, for whom MT alone or with chemotherapy failed, and who were subsequently treated with a combination of PEM and MT. Two patients had a partial response and the remaining 4 patients had prolonged stable disease (8 to 19 months). All 6 patients lived for at least 16 months after adding PEM to MT therapy. The combination was reported to be appeared to be effective in both microsatellite instability-high and microsatellite stable tumors, suggesting some synergistic effect with mitotane (Head et al. 2019).

We anticipate that MT will have synergistic effect when combined with PEM through at least two different mechanisms. 1- In the first few weeks of MT use, mitotane is expected to exert a steroidogenesis blocker effect leading to reduced cortisol levels in the tumor microenvironment and blood this could enhance efficacy of PEM by reducing the immunosuppressive effects of cortisol on lymphocytes. 2- With prolonged MT use, the adrenolytic activity of mitotane is usually seen when serum MT level approaches 14 mg/L and this could release adrenal specific antigens that can further enhance the efficacy of PEM.

4.2.2 Justification for Dose

The planned dose of PEM for this study is 400 mg IV every 6 weeks (Q6W). Based on the totality of data generated in the Keytruda development program, both PEM 200 mg Q3W and PEM 400 mg Q6W are approved for clinical use. The FDA granted accelerated approval of the 400 mg Q6W for PEM (KEYTRUDA, Merck) across all currently approved adult indications, in addition to the 200 mg Q3W dosing regimen. The approval was based on pharmacokinetic modeling and exposure-response analyses that compared the predicted exposure of pembrolizumab 400 mg Q6W to observed exposures of pembrolizumab in patients who received pembrolizumab at 2 mg/kg every three weeks, 200 mg Q3W, and 10 mg/kg administered every 2 weeks. The pharmacokinetic modeling was supported by additional exposure-response analyses across the PEM development program and an interim analysis of pharmacokinetics and overall response rate (ORR) in a cohort of patients (Cohort B) enrolled in Study KEYNOTE-555 (NCT03665597). Cohort B of Study KEYNOTE-555 was an international, single-arm, multi-center study that enrolled 101 patients with advanced or metastatic melanoma who had not received prior PD-1, PD-L1, or CTLA-4 inhibitors (other than CTLA-4 inhibitors in the adjuvant setting). The ORR was 39% (95% CI: 24, 55) in the first 44 patients enrolled in KEYNOTE-555.

MT will be administered orally to reach a plasma level of 14–20 mg/L (or the maximum tolerated dose if unable to reach therapeutic levels). Analysis of serum mitotane levels will be performed by a CLIA certified laboratory to reflect standards of care of mitotane management. In general, mitotane starting dose will be 1-2 grams per day to be escalated up to 6 grams per day according to the treating physician's judgment if the levels remain below 14 mg/L. Reduction of mitotane dosage should be considered for asymptomatic plasma levels over 30 mg/L or for significant mitotane-related adverse effect. Asymptomatic mitotane levels of 20-30 mg/L may not require dose reduction at the discretion of the site principal investigator.

4.2.3 Rationale for Endpoints

ACC has low response to currently available treatments. MT has adrenolytic activity in addition to hormonal control efficacy by blocking multiple steps in the steroidogenesis pathways. The efficacy of

single agent MT in advanced ACC has been seen in 11-20.5% range with median progression free survival of 4.1 months (Reidy-Lagunes et al. 2017; Megerle et al. 2018; Fassnacht et al. 2012). The combined use of MT with EDP chemotherapy is associated with low response rate (23%) and serious AEs seen in 56% of patients (Fassnacht et al. 2012).

PEM monotherapy in ACC is associated with response rate of 14-23% with favorable AE profile (severe AEs in 13%) of subjects. The combined use of MT as standard of care with PEM has not been studied prospectively. We hypothesize that MET use with PEM will have synergistic effect. We would like to assess the overall response rate of MT combined with PEM in ACC patients. In addition, we would like to assess other endpoints related to efficacy and safety as well as study exploratory markers to assess immune changes during the combination therapy.

4.2.3.1 Efficacy Endpoints

In addition to the intrinsic adrenolytic activity of MT, we hypothesize that adding PEM will enhance the clinical efficacy of MT. The cortisol lowering effect of mitotane is expected to alter the tumor microenvironment leading to a change the milieu of the tumor infiltrating immune cells to make ACC more susceptible to PEM.

Primary Endpoint: Overall response rate (ORR) assessed objectively using RECIST 1.1 criteria defined as the percentage of patients who have a partial or complete response to the combined treatment of MT plus PEM.

Efficacy Secondary Endpoints:

Overall survival (OS), defined as the time from the start of combination therapy to death from any cause.
Progression Free Survival (PFS), defined as the time from the start of combination therapy phase to disease progression or death from any cause.

4.2.3.2 Planned Exploratory Biomarker Research

As an exploratory objective, we also aim to generate crucial data about the changes in immune markers in association with MT-PEM therapy. The adrenal gland can be recognized by the immune system and develop autoimmune adrenalitis and adrenal insufficiency (Addison's disease). Mononuclear cells infiltrating (mainly CD3+) the adrenal glands on autopsies are more common in people 60 years and older (63%) compared to subjects <49 years old (7%). CD4+ cells are more common than CD8+ cells and are thought to have been activated by interleukin 2 receptor (Feldmeyer et al. 2016) . It remains unknown if MT has any direct or indirect effects on immune cells in ACC. We presume that MT cortisol reduction will affect have immunomodulatory effect that enhances the sensitivity of tumor cells to T cell-mediated lysis. Thus, data generated from patients in this study can further our understanding of the complex effect of MT on tumor immune infiltrate and could lead to new treatment combinations in the future.

Analyses of tumor and blood samples: These studies will be performed at MDACC in collaboration with Translational Molecular Pathology - Immunoprofiling Laboratory (TMP-IL). Patient samples will be collected to perform immunologic analyses. The study will allow for the collection of blood samples to

be drawn at the time of routine blood-draw to assess circulating immune markers. Whole blood, plasma, serum, peripheral blood mononuclear cells (PBMCs) and other secreted markers (such as cytokines) may be collected at 3 time points (before and during treatment and at time of disease progression) and processed at the TMP-IL for further downstream analyses.

Optional biopsies will be used for immune-profiling analysis (core needle biopsies (CNBs). Fresh tissue samples will be sent immediately after collection to TMP-IL. Core biopsy is typically performed using 21-18-gauge needle and with condition permitting, up to 5 cores should be collected, including 2 for clinical processing and 3 additional passes will be attempted to obtain the research core samples.

> Cores 1 and 2: Immediate and overnight fixation in 10% buffered formalin for paraffin embedding, usually within 20-24 hour after fixation. For biopsies performed on Friday, fixation time may extend to 48 hours (FFPE samples)
>
> Cores 3-4: Flash freezing in liquid nitrogen.
>
> Core 5: Flow cytometry analysis of TIL and TME on fresh tissue.

All tissue specimens collected will be reviewed by reference pathologists. At least, three types of QC activities for specimens collected will be performed: a) histology/cytology examination of the tissues and cells to confirm the presence of tumor cells, as well as their abundance (tumor cellularity); b) tissue quality assessment of fresh specimens for extraction of DNA, RNA and proteins, and to prepare histology specimens such as whole sections for immunohistochemistry and immunofluorescence; and, c) quality assessment of DNA, RNA and protein extracted. All histology stained samples will be scanned, and digital images will be available for review.

Using immunohistochemistry (IHC) and multiplex immunofluorescence (IF) approach that is available in the TMP-IL, we will quantitatively assess multiple immune markers. Fresh frozen tissues will be also used for analysis of immune markers. IHC and IF will be performed using autostainers. All antibodies used will be optimized for IHC/IF by examination of positive and negative controls and testing of the antibodies standard methods, including Western blotting. All pathology slides will be scanned into a digital image scanner and analyzed using image analysis software; IHC analysis will be performed using the Aperio Image Toolbox™ (Leica Biosystems) and IF analysis using the Vectra Inform™ (Perkin-Elmer) software. Nucleic acids (DNA and RNA) and protein extraction: Blood (plasma and PMBCs) and tumor (CNB) samples will be subjected to extraction using standard methods. DNA and RNA quantity and integrity will be assessed using NanoDrop 1000 spectrophotometer (Nanodrop technologies) and Pico-green analyses. Also, protein lysate will be extracted using standard methods.

High order flow cytometry panels will focus on 1) delineation of major immune cell types (T cells, B cells, NK cells, DC), 2) determination of T cell differentiation status and limited functionality (IFNγ,

TNFα, GB) and 3) defining the expression level of costimulatory and coinhibitory molecules on T cells and their respective receptors such as PD-L1 on infiltrating myeloid cells or tumor. Briefly, 50 cc of heparinized peripheral blood from cancer patients prior to the initiation of treatment, during treatment, and at time of progression will be processed fresh (within 24h of being drawn) for PBMC isolation by ITB. PBMCs will be cryopreserved and stored in Liquid Nitrogen until use. Flow cytometric analysis will be conducted retrospectively on cryopreserved PBMCs. When appropriate, cells will be thawed and stained immediately. All time points belonging to a patient will be stained and acquired at the same time to avoid any technical variation (sample at time of progression will be omitted for responders if analysis needs to be completed when patient is still responding). We expect that half of the study participants will agree to have the optional biopsies and we anticipate collecting blood samples from all participants.

Steroid profiling will be done on the stored plasma samples at the end of the study. In addition to the standard of care check of select steroid hormones as standard of care while managing ACC.

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 ACC 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 an additional 180 days after the last dose of study treatment 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. 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 plus 180 days after the last dose of study treatment.

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

5. Have measurable disease based on RECIST 1.1. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

6. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Evaluation of ECOG is to be performed within 10 days prior to the first dose of MT therapy.

7. Have adequate organ function as defined in the following table (Table 4). Specimens must be collected within 10 days prior to the start of study intervention.

8. The study will accept therapy naïve patients with metastatic ACC, patients who failed one prior line of therapy not including immunotherapy, patients who started MT within 4 weeks for metastatic disease, and patients who developed metastases while on adjuvant mitotane therapy. Patients who failed platinum-based chemotherapy combined with MT may be eligible to join the study at the discretion of the PI if their treatment ended > 6 months before consenting for this study or if did not achieve therapeutic MT levels during prior treatment (MT level ≥ 14 mg/L).

9. For patients receiving therapeutic anticoagulation: stable anticoagulant regimen in the 28 days immediately preceding initiation of study treatment

10. Criteria for known Hepatitis B and C positive subjects

    Hepatitis B and C screening tests are not required unless:

    •Known history of HBV or HCV infection

    •As mandated by local health authority

    10.1 Hepatitis B positive subjects

    - Participants who are HBsAg positive are eligible if they have received HBV antiviral therapy for at least 4 weeks and have undetectable HBV viral load prior to randomization.
    - Participants should remain on anti-viral therapy throughout study intervention and follow local guidelines for HBV anti-viral therapy post completion of study intervention.

    10.2 Participants with history of HCV infection are eligible if HCV viral load is undetectable at screening.

    Participants must have completed curative anti-viral therapy at least 4 weeks prior to randomization.

Table 4 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
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 urine pregnancy test within 72 hours prior to pembrolizumab treatment (see Appendix 3). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
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 (eg, CTLA-4, OX-40, CD137).
3. Has received prior systemic anti-cancer therapy including investigational agents within 4 weeks
4. Has received prior radiotherapy within 2 weeks of start of study intervention. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.

5. Has received a live vaccine or live-attenuated vaccine within 30 days before the first dose of study intervention. Administration of killed vaccines is allowed.
6. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study intervention.
7. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent at the time of screening) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug. Higher dose of steroid may be permitted as replacement doses while on mitotane therapy to follow acceptable standards of care while on mitotane Known additional malignancy that is progressing or has required active treatment within the past 2 years. Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin *or* carcinoma in situ, excluding carcinoma in situ of the bladder, that have undergone potentially curative therapy are not excluded.
8. 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.
9. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.
10. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment and is allowed.
11. Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.
12. Has an active infection requiring systemic therapy.
13. Has a known history of Human Immunodeficiency Virus (HIV) infection
14. Concurrent active Hepatitis B (defined as HBsAg positive and/or detectable HBV DNA) and Hepatitis C virus (defined as anti-HCV Ab positive and detectable HCV RNA) infection.

    Note: Hepatitis B and C screening tests are not required unless:

    - Known history of HBV and HCV infection
    - As mandated by local health authority

15. Has a history or current evidence of any condition, therapy, or laboratory abnormality or other circumstance that might confound the results of the study, interfere with the participant's

participation for the full duration of the study, such that it is not in the best interest of the participant to participate, in the opinion of the treating investigator.

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

17. 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.

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

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 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).

5.1.4 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab, 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** 5

Table 5 Trial Intervention(s) Drug		Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Mitotane		1000-6000 mg	Daily	PO	4 weeks lead-in phase* (+/-5 days) followed by maintenance therapy per acceptable clinical standards	Standard of Care
Pembrolizumab		400 mg	Q6W	IV infusion	Day 1 of each 6-week cycle (after MT lead-in phase)	Experimental

* The lead-in phase is primarily designed to ensure patients safety and to have initial evaluation of potential AEs attributed to MT use with particular attention to liver enzymes. If MT use caused elevated ALT or AST during the lead-in phase not meeting eligibility criteria for LFTs or if participants developed ≥ G3 non-hematological toxicity, then these patients will not go through the combination therapy and may come off protocol at the discretion of the PI and will be replaced if excluded by other patients and considered as screen failure. Patients who were on prior MT therapy must complete 28 days of MT use prior to moving to combination therapy and must meet eligibility criteria stated at screening phase and will not need to have the lead-in phase assessment.

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

5.2.1 Treatment

- Pembrolizumab will be given for a maximum of 2 years i.e. a total of 18 cycles of pembrolizumab with the Q6 week dosing.
- Mitotane will be given following standards of clinical practice and could extend beyond the study period

5.2.2 Second Course

N/A

5.2.3 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 2.2. Trial interventions may be administered up to 5 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 400 mg will be administered as a 30-minute IV infusion every 6 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).

MT use will follow acceptable clinical practice pattern with starting dose of 500 mg PO BID or TID to be titrated every to achieve therapeutic serum level of 14-20 mg/L (maximum dose 6,000 milligrams per day). For MT naïve patients, the first 4 weeks (+/- 5 days) will be a lead-in phase then they will continue MT therapy in combination with PEM in 6-week cycles.

5.2.4 Dose Modification and toxicity management for immune-related AEs associated with pembrolizumab and IO combination partners

AEs associated with pembrolizumab or IO/IO combination exposure, may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab/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 6.

Attribution of Immune-Related Toxicity:

When study interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to the combination, to pembrolizumab, or to MT, all IO drugs must be held according to the criteria in [Table 6 Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated with Pembrolizumab].

Holding Study IO Interventions:

When study interventions are administered in combination, if the AE is considered immune-related, all IO interventions should be held according to recommended dose modification criteria

If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must discontinue all IO therapy.

Restarting Study Interventions:

Participants may restart pembrolizumab and MT as described below.

- If the toxicities do resolve and conditions are aligned with what is defined in [Table 6], the study interventions may be restarted at the discretion of the investigator.

Table 6 Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab and IO combination partners

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. All IO treatments 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 IO treatments have 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 + all IO Drugs	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever)

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab + all IO Drugs	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
	Recurrent Grade 3 or Grade 4	Permanently discontinue		and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
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	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab + all IO Drugs	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
	associated with evidence of β-cell failure		• Administer antihyperglycemic in participants with hyperglycemia	
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3 or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: 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		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab + all IO Drugs	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (previously CTCAE v4.0 Grade 1)	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

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

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

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

[a] AST/ALT: >3.0 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 or its IO combination partner is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab or its IO combination partner may be resumed.

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

CT

Table 7 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	No subsequent dosing

renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Corticosteroids 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 monotherapy or in combination 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.

5.3 Randomization or Treatment Allocation

N/A

5.4 Stratification

N/A

5.5 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The 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.

5.5.1 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.

5.5.2 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 is discouraged but radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion,
- Live or attenuated vaccines within 30 days before the first dose of study intervention and while participating in the study.

- Systemic glucocorticoids except when used for the following purposes:
    - To modulate symptoms of an AE that is suspected to have an immunologic etiology
    - For the prevention of emesis
    - To premedicate for IV contrast allergies
    - To treat COPD exacerbations (only short-term oral or IV use in doses >10 mg/day prednisone equivalent)
    - For chronic systemic replacement while on MT therapy

- Other glucocorticoid use except when used for the following purposes:
    - For topical use or ocular use
    - Intraarticular joint use
    - For inhalation in the management of asthma or chronic obstructive pulmonary disease

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. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, the Sponsor and the participant. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

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

5.5.3 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 5.2.4, [Table 6].

5.6 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 2.2 unless the participant has withdrawn from the study (Section 5.7).

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 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 5.2.4.
- 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

5.7 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.

5.8 **Participant Replacement Strategy:** Patients who cannot join the combination of the study and deem ineligible to move from the lead-in phase to the combination therapy phase of the study will be replaced by other participants.

5.9 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, Section 2.2.
- Adherence to the study design requirements, including those specified in the Schedule of Activities 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 must ensure appropriate consent is in place.

6.1.1.2 General Informed Consent

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 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.

There is a potential for enrollment of cognitively impaired subjects, whose disease may directly benefit from trial procedures that would be unavailable outside the research context. Risks to subjects are reasonable in relation to anticipated benefits. Available systemic therapies are limited and not curative. The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches.

This trial is not prohibited by law. Subjects will be particularly closely monitored per stated protocol procedures and assessment plans and will be withdrawn if they appear to be unduly distressed or unable to follow protocol requirements.

These subjects will be informed about the research to the extent compatible with the subject's understanding. The consent document includes a signature line for a Legally Authorized Representative (LAR). If capable, the subject will sign and personally date the written informed 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 that are considered to be clinically important 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.

If a medical condition is diagnosed at the time of screening due to the physical examination, laboratory tests, radiologic assessment, other assessment, and/or a combination of these evaluations, the medical condition is to be recorded as a baseline condition along with the participant's other medical history unless due to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in).

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. In addition, new medication started during the Second Course should be recorded. 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

6.1.1.8 Assignment of Randomization Number

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

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 2). 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 [specify if there are specific assessments that must be conducted as a minimum] [systems/evaluations]. 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 2.4. 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 2.2, 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 2.2). 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 2.2).

6.1.2.7 Electrocardiograms

A single 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA (see Section 2.2) using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and [QTc] intervals.

6.1.2.8 Elevated Transaminases With Treated HBV or HCV

Participants who were treated for HBV or HCV, enrolled in the study, and present with elevated transaminases according to the criteria below should be evaluated for viral hepatitis exacerbation/reactivation.

- If baseline AST/ALT <2×ULN and an increase of AST/ALT ≥5×ULN
- If baseline AST/ALT ≥2×ULN and an increase of AST/ALT >3 × baseline level
- AST/ALT ≥2×ULN and an increase of AST/ALT >3 × baseline level

Viral load testing and additional hepatitis serologies should be included as required.

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 SoA.

- If laboratory values from nonprotocol-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. Refer to the Study Flow Chart (Section 2.2) for the timing of laboratory assessments.

6.1.3.2 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

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

6.1.3.3 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. If a urine test is positive or not evaluable, a serum test will be required. 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). MRI imaging as well as FDG-PET CT are alternative modalities per PI discretion. 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.

Expedited confirmation of measurable disease based on RECIST 1.1 at Screening should be used to determine participant eligibility. Confirmation that the participant's imaging shows at least 1 lesion that is appropriate for selection as a target lesion per RECIST 1.1 is highly recommended prior to participation [randomization/allocation].

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 28 days prior to the date of MT treatment. 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 28-days prior to the date of treatment.

6.1.4.2 Tumor Imaging During the Study

For patients who start with lead-in phase, the first on-study imaging assessment should be performed at the onset of the combination therapy phase (C1D1 +/- 7 days) and then every 12 weeks (+/-7 days). Response assessment by cross-sectional imaging such as CT, MRI, or PET-CT as per standard of care for each patient. PET/CTs may be substituted for CT or MRI at baseline and re-staging, if in the opinion of the treating physician.

Patients who were on mitotane prior to consenting will not need lead-in phase and will go directly to combination therapy and the screening phase imaging will be considered the baseline for future tumor measurement.

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 12weeks, 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 6.1.4.6.

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 12 weeks ±14 days) 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 Second Course (Retreatment) Tumor Imaging

N/A

6.1.4.5 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.

6.1.4.6 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.

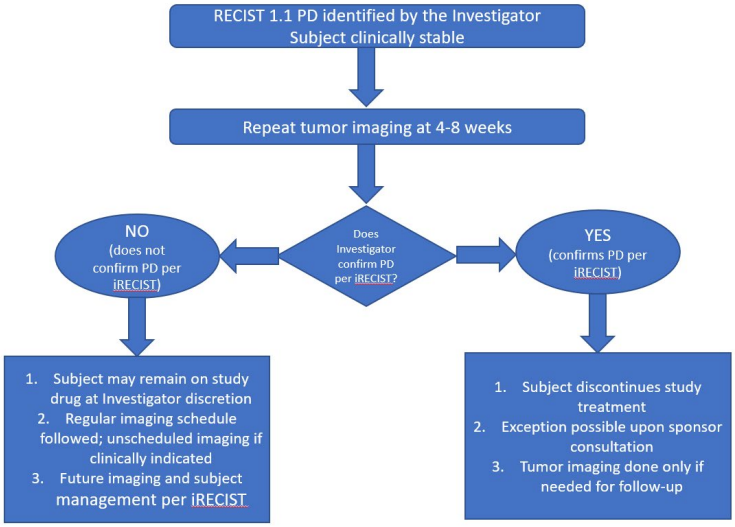
A description of the adaptations and iRECIST process is provided in Appendix 4. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 8 and illustrated as a flowchart in Figures 1 and 2.

Table 8 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	[For those studies in which PFS is the primary endpoint, add this: Submit the imaging to BICR for verification] 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	[For those studies in which PFS is the primary endpoint, add this: Submit the imaging to BICR for verification] 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	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.

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of disease progression by RECIST 1.1 per investigator assessment	[For those studies in which PFS is the primary endpoint, add this: Submit the imaging to BICR for verification] 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	[For those studies in which PFS is the primary endpoint, add this: Submit the imaging to BICR for verification] Repeat imaging at 4 to 8 weeks to confirm disease progression per investigator's discretion only.	Discontinue treatment
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

Per SoA

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.

6.1.6.2 Blinding/Unblinding: N/A

6.1.7 Visit Requirements

Visit requirements are outlined in Section 2.2 – 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: 28 days prior to the initiation of MT therapy. Patients who have been on MT therapy can proceed to PEM therapy when completing 28 days of MT therapy

6.1.7.2 Treatment Period: Daily oral MT therapy to follow acceptable standards of care for mitotane therapy including concomitant steroid replacement and periodic MT levels check. PEM will be given 400 mg IV on D1 (+/- 5 days) in 6 weeks cycles for total of 18 cycles.

Post-Treatment Visits: All patients who discontinue treatment without objective disease progression will be followed up with tumor assessment every 12 weeks (±14 days) or as determined by the principal investigator or designee) until disease progression or the start of a different anti-cancer therapy. Survival follow-up via phone call, medical record review, or visit with physician will occur every 3 months for 2 years once they are off-study treatment or until patient death, withdrawal of consent, patient is lost to follow-up, or study termination, whichever occurs first.

6.1.7.3

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. Participants who are eligible for retreatment/crossover with pembrolizumab (as described in Section 5.2.2) may have up to two safety follow-up visits, one after the Initial Treatment Period and one after the Second Course Treatment.

6.1.7.3.2 Efficacy Follow-up Visits

All patients who discontinue treatment without objective disease progression will be followed up with tumor assessment every 12 weeks (±14 days) or as determined by the principal investigator or designee) until disease progression or the start of a different anti-cancer therapy. Survival follow-up via phone call, medical record review, or visit with physician will occur every 3 months for 2 years once they are off-study treatment or until patient death, withdrawal of consent, patient is lost to follow-up, or study termination, whichever occurs first.

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 within 30 days after the last dose of study intervention for the poststudy visit. If the poststudy visit occurs less then 14 days after the last dose of study intervention, a subsequent follow-up telephone call should be made at 30 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.**Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information**

All AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before intervention allocation/randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause 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 time of intervention allocation/randomization through 30 days following cessation of study intervention must be reported by the investigator.

- All AEs meeting serious criteria, from the time of intervention allocation/randomization 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.
- All pregnancies and exposure during breastfeeding, from the time of intervention allocation/randomization through the time required to eliminate systemic exposure after cessation of study intervention as described in Section 5.11, or 30 days after 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** .

Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention.

Table 9 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period:** **Consent to Randomization/ Allocation**	**Reporting Time Period:** **Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period:** **After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Merck:**
Serious Adverse Event (SAE) including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or 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 receipt of information
Pregnancy/Lactation Exposure	Report if: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/termination; report outcome	Within 2 business days but no longer than 3 calendar days of receipt of information
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 receipt of information

6.1.2 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.

6.1.3 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.

6.1.4 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.

6.1.5 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 the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, 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

6.1.6 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. 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.

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

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

7.0 STATISTICAL ANALYSIS PLAN

We will simultaneously monitor efficacy and toxicity using the Bayesian optimal phase 2 (BOP2) design (Zhou, Lee and Yuan, 2017). Specifically, let n denote the interim sample size, and N denote the maximum sample size. Let Y_{eff} and Y_{tox} denote the binary efficacy and toxicity endpoints, with $Y_{eff} = 1$ and $Y_{tox} = 1$ indicating that patients experience efficacy and toxicity, respectively. We assume that the joint distribution of (Y_{eff}, Y_{tox}) follows a multinomial distribution with four elementary outcomes: (Y_{eff}, Y_{tox}) = (1, 1), (1, 0), (0, 1) and (0, 0). Let $\mathbf{p} = (P_{11}, P_{10}, P_{01}, P_{00})$ denote the probabilities of observing the four outcomes, and let $p_{eff} = Pr(Y_{eff} = 1)$, $p_{tox} = Pr(Y_{tox} = 1)$ and $p_{efftox} = Pr(Y_{eff} = 1, Y_{tox} = 1)$. When efficacy and toxicity endpoints are monitored separately, the joint distribution reduced to marginal distribution of efficacy and marginal distribution of toxicity, respectively. For trial monitoring and decisions, extreme toxicities (TOX) will be defined as any grade 3 or higher adverse event that is possibly, probably, or related to therapy received on this protocol. Any grade 3 or higher adverse event that is potentially treatable with steroids or hormonal replacement will only count as an extreme toxicity if it does not improve to grade 1 or better within 2 weeks of therapy.

The treatment is deemed unacceptable if $p_{eff} \leq 0.23$ or $p_{tox} > 0.5$. Thus, we will stop enrolling patients and claim that the treatment is unacceptable if

$$Pr(p_{eff} > 0.23|data) < \lambda\left(\frac{n}{N}\right)^{\alpha},$$

or

$$Pr(p_{tox} \leq 0.5|data) < \lambda\left(\frac{n}{N}\right)^{\alpha/3},$$

where λ=0.5 and α=1 are design parameters optimized to maximize the study power, i.e., probability of correctly concluding an efficacious and safe treatment as acceptable when $p_{eff} = 0.3$, $p_{tox} = 0.3$ and $p_{efftox} = 0.18$, while controlling that the probability of incorrectly claiming an inefficacious and toxic treatment, i.e., type I error, with $p_{eff} = 0.23$, $p_{tox} = 0.5$ and $p_{efftox} = 0.15$, to 9.5%. Note that in the safety stopping rule, the original publication of the design used the probability cutoff $\lambda(n/N)^{\alpha}$, here the attenuation factor 3 is added (i.e., α/3) to obtain stricter interim stopping boundaries to enhance safety.

For the purposes of interim monitoring, toxicities and responses will be monitored for 24 weeks post start of the combination therapy.

This optimization is performed assuming a vague Dirichlet prior $Dir(0.15,0.08,0.35,0.42)$ for **p**. The prior is chosen such that it corresponds to a prior effective sample size of 1 patient, and the prior estimates of p_{eff} and p_{tox} match the values specified when the treatment is unacceptable. The above decision rule leads to the following optimal stopping boundaries:

Table 1: Optimized stopping boundaries

# patients treated	Stop if # response <=	OR # toxicity >=
10	0	6
20	3	11
35	7	18
50	11	25

When the total number of patients reaches the maximum sample size of **50**, we conclude that the treatment is acceptable if the number of responses are greater than 11, and the number of toxicities are less than 25; otherwise we conclude that the treatment is unacceptable. The go/no-go criteria in Table 1 are non-binding.

Below are the operating characteristics of the design based on 10000 simulations using the BOP2 web application (BOP2 V1.4.7.0), which is available at http://www.trialdesign.org.

Table 2: Operating characteristics

Scenario	Pr(Eff)	Pr(Tox)	Pr(Eff & Tox)	Early Stopping (%)	Claim Acceptable (%)	Average Sample Size
1	0.23	0.5	0.15	83.15	9.47	23.0
2	0.30	0.3	0.18	24.46	71.38	42.9

ORR will be summarized with a 95% confidence interval (Clopper-Pearson exact method).

Analysis of Secondary Endpoints: OS and PFS will be analyzed using Kaplan-Meier survival curves. T-tests and dot plots will be used to associated mitotane levels (specify time of measurement) with overall response. Adverse events will be summarized with frequencies tables. Highest grade adverse event will be determined for each subject and the count of all adverse events and related adverse events will be computed.

8.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

8.1 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 product in accordance with the protocol and any applicable laws and regulations.

Pembrolizumab will be provided by Merck as summarized in Table 10.

Table 10 Product Descriptions

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

8.2 Packaging and Labeling Information

Supplies will be labeled in accordance with regulatory requirements.

8.3 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.

8.4 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.

8.5 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.

9.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.0 REFERENCES

At the end of protocol

11.0 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 11 will be performed [by the central laboratory] [by the local laboratory].
- [Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.]
- 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 11 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	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/SGPT	Total Protein
	Glucose [Indicate if fasting, or nonfasting]	Calcium	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick • Microscopic examination (if blood or protein is abnormal)			
Pregnancy Testing	• [Highly sensitive serum or urine] hCG pregnancy test (as needed for WOCBP)			
Other Screening Tests	• FSH (as needed in WONCBP only) • [Serum or urine] [alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) if applicable] • [Serology [(HIV antibody, HBsAg, and hepatitis C virus antibody)] [or specify other tests] [if applicable]			

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 12 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 method of contraception that has a low user dependency consistently and correctly as described in Table 12 during the protocol-defined time frame in Section 5.11.

Table 12 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 [190 days, corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential] after the last dose of study treatment.

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 13 during the protocol-defined time frame in Section 5.11.

Table 13 Highly Effective Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent [a]

Failure rate of <1% per year when used consistently and correctly.
● Combined (estrogen- and progestogen- containing) hormonal contraception [b, c] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception [b, c] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant [b, c] ● 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) Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly). 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 [190 days, corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential] after the last dose of study treatment. c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use one of the contraception methods described in Table 14 consistently and correctly during the protocol-defined time frame in Section 5.11.

Table 14 Contraceptive Methods

Acceptable Contraceptive Methods *Failure rate of >1% per year when used consistently and correctly.*
● Male or female condom with or without spermicide ● Cervical cap, diaphragm or sponge with spermicide
Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen- containing) hormonal contraception [b] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception [b] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant [b, c] ● 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) Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly).

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 190 days, corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential] after the last dose of study treatment .
c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

Pregnancy Testing

Female Participant: Pregnancy test, serum or urine at baseline, urine prior to every cycle for women of child-bearing potential; All WOCBP must have a negative serum or urine pregnancy test within 72 hours prior to start of pembrolizumab.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

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 8 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 (Seymour et al. 2017).

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

11.1.1 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, medical device, combination product, or protocol specified procedure whether investigational or marketed (including placebo, 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.

11.1.2 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.

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.

11.1.3 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

11.1.4 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 1 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.

11.1.5 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.

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