SPONSOR: Merck

TITLE: IMRT followed by Pembrolizumab in the Adjuvant Setting in Anaplastic Cancer of the Thyroid (IMPAACT): Phase II trial adjuvant Pembrolizumab after IMRT in ATC

Principal Investigator: Maria E. Cabanillas

Co-Investigators:
Brandon Gunn (co-PI)
Michael Spiotto
Naifa Busaidy
Ramona Dadu
Mark Zafereo
Jennifer Rui Wang

Documentation History Page

TABLE OF CONTENTS

1.0 TRIAL SUMMARY

Abbreviated Title	IMPAACT
Trial Phase	2
Clinical Indication	Anaplastic Thyroid Cancer (ATC)
Trial Type	Interventional Unblinded Open-label
Type of control	Historical control
Route of administration	IV
Treatment Groups	Post-IMRT (unresected) stratified by dose and Exploratory post-IMRT (resected)
Number of trial participants	35
Estimated enrollment period	2021-2024
Estimated duration of trial	23.5 months
Duration of Participation	36 months
Estimated average length of treatment per patient	12 months (average)

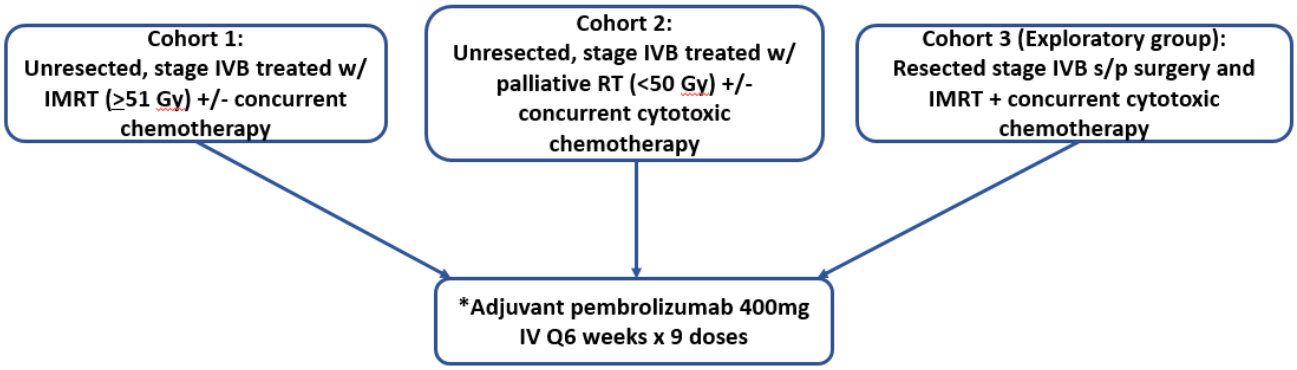
2.0 TRIAL DESIGN

2.1 Trial Design

This is an open label, single center, phase 2 trial of adjuvant pembrolizumab after external beam radiation to the primary tumor in patients with stage IVB (disease localized to the neck) ATC. Eligible patients include those with gross, local disease who are planned for or have completed treatment with IMRT plus or minus concurrent cytotoxic chemotherapy (radiosensitizing/low dose; usually paclitaxel +/- carboplatin; doxorubicin +/- docetaxel or single agent cisplatin). Patients will start treatment with adjuvant pembrolizumab after 2-6 weeks after completion of radiation, (+2-week window). Patients will be enrolled by dose of radiation in cohort 1 (high dose group), cohort 2 (palliative dose group), and cohort 3 (surgery plus IMRT plus concurrent chemotherapy). The main assessment will focus on cohort 1 and 2. Cohort 3 will be an exploratory set of patients who have completed treatment with surgery and IMRT plus concurrent cytotoxic chemotherapy. Patients may be consented for screening for this trial prior/during (preferable) or after completion of radiation. Patients will be treated with pembrolizumab 400mg IV Q6 weeks for 9 cycles or until progression (whichever occurs first). Patients will then be followed for survival for up to 5 years.

2.2 Trial Schema

Figure 1. Trial Schema



*patients will start pembrolizumab after completion of radiation and recovery from adverse effects

2.3 Schedule of Activities

Trial Period:	**Screening Phase**	**Treatment Cycles (42-day cycles)**									**End of Treatment and Safety Follow Up[4]**	**Post-Treatment**	
Treatment Cycle/Title:	Main Study Screening (Visit 1)	1	2	3	4	5	6	7	8	9		Efficacy Follow Up Visits[4]	Survival Follow-Up[6]
Scheduling Window (Days):	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	30 days post discontinuation[5]	Every 12 +/- 4 weeks post discontinuation	Every 12 +/- 4 weeks
Administrative Procedures													
Informed Consent	X												
Inclusion/Exclusion Criteria	X												
Medical History	X												
Prior and Concomitant Medication Review	X												
Pembrolizumab Administration		X	X	X	X	X	X	X	X	X			
Subsequent Anti-neoplastic Therapy Status											X	X	X
Survival Status													X
Clinical Procedures/Assessments													
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	
Full Physical Examination including weight[7]	X	X	X	X	X	X	X	X	X	X	X		
Directed Physical Examination												X[3]	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X[3]	
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X		X	
12-lead ECG	X		X		X		X		X				
[HIV, hepatitis B and C screen (per site SOP)]	X												

Trial Period:	**Screening Phase**	**Treatment Cycles (42-day cycles)**									**End of Treatment and Safety Follow Up[4]**	**Post-Treatment**	
Treatment Cycle/Title:	Main Study Screening (Visit 1)	1	2	3	4	5	6	7	8	9		Efficacy Follow Up Visits[4]	Survival Follow-Up[6]
Scheduling Window (Days):	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	30 days post discontinuation[5]	Every 12 +/- 4 weeks post discontinuation	Every 12 +/- 4 weeks
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory													
Pregnancy Test –Serum β-HCG	X	X	X	X	X	X	X	X	X	X			
PT/INR and aPTT	X												
CBC with Differential	X	X	X	X	X	X	X	X	X	X			
Comprehensive Serum Chemistry Panel	X	X	X	X	X	X	X	X	X	X			
Urinalysis	X	X	X	X	X	X	X	X	X	X			
Thyroid Function Tests (TSH, free T4; thyroglobulin)	X	X	X	X	X	X	X	X	X	X			
Efficacy Measurements													
Tumor Imaging	X[1]	X[2]										X[3]	

1 Pre-treatment imaging to occur no less than 14 days prior to C1D1

2 imaging to occur after 6 weeks (cycle 2) and then every 12 weeks thereafter (regardless of cycle start dates). MRI brain will be repeated every 6 months +/- 1 month in the absence of evidence of symptoms or progression. Imaging continues every 12 weeks during the post-treatment phase, up until 1 year.

[3] may be performed locally

[4] patients will continue to be seen in follow-up for 1 year after study treatment discontinuation; patients continuing pembrolizumab past 9 cycles, outside of the protocol, will be considered off study treatment. Every effort will be made to follow these patients according to the efficacy follow-up schedule for 1 year following their 9 cycles of pembrolizumab. After 1 year patients will go into survival follow-up. Note that patients starting a **new** anti-neoplastic therapy following 9 cycles of pembrolizumab will go straight into the survival follow-up phase.

[5] this may be done by video or phone call telehealth visit

[6] survival follow-up will continue for up to 5 years following treatment discontinuation (ie, following up to 9 cycles of pembrolizumab)

[7] After C1D1, these examinations may be done via telemedicine. A physical exam is not necessary unless clinically indicated.

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

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

(1) **Objective:** To estimate the median progression-free survival (PFS) (from the start of adjuvant pembrolizumab until locoregional progression, development of distant metastatic disease, or death) in stage IVB ATC patients with gross disease, treated with external beam radiation (+/- concomitant chemotherapy) followed by adjuvant pembrolizumab. Patients will be patients enrolled from cohort 1 and 2 (cohort 1: ≥51 Gy; cohort 2: ≤50 Gy).

Hypothesis: The use of adjuvant pembrolizumab after completion of radiation +/- concurrent cytotoxic chemotherapy will lead to an improvement in median PFS in unresectable stage IVB patients, compared to historical controls.

Primary Endpoint: Median Progression-free survival (PFS), from the start of adjuvant pembrolizumab until disease progression or death

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

(1) **Objective**: To estimate median overall survival in stage IVB ATC patients treated with external beam radiation (+/- concurrent chemotherapy) followed by adjuvant pembrolizumab. Patients will be stratified by dose of external beam radiation.

Hypothesis: The use of adjuvant pembrolizumab after completion of radiation +/- concurrent cytotoxic chemotherapy will lead to an improvement in median OS in unresectable stage IVB patients, compared to historical controls.

Secondary Endpoint: median OS

Exploratory Objective(s)

(1) **Objective:** To estimate the median disease-free survival (DFS) in patients with stage IVB ATC treated with surgery/external beam radiation/concomitant chemotherapy followed by adjuvant pembrolizumab (cohort 3).

(2) Objective: Translational endpoints: cell-free DNA changes, resistance markers, and immune biomarkers will be studied.

4.0 BACKGROUND & RATIONALE

4.1 Pregnancy est

4.2 Background

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).

4.2.1 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 et al., 2005; Okazaki et al., 2001].

The structure of murine PD-1 has been resolved [Zhang et al., 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [Okazaki et al., 2001; Chemnitz et al., 2004; Sheppard et al., 2004; and Riley, 2009]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry et al., 2005; Francisco, 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in anaplastic thyroid cancer.

4.2.2 Preclinical and Clinical Trial Data

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

4.3 Rationale

4.3.1 Rationale for the Trial and Selected Population

Recently, our group has found that over 90% of ATCs express PD-L1, with 43% having expression levels greater than 50% (Dadu et al, ATA 2016). In Head and neck squamous cell carcinoma, expression of PD-L1 is associated with resistance to radiotherapy (Skinner et al., *CCR*, 2017). A clinical trial with the anti-PD1 drug, spartalizumab, in ATC patients with measurable, active disease showed that patients with ATC had a response rate of 19%. In those with high PD-L1 expression (≥50%), the response rate was 35%, the 1-year PFS rate was 29% and the median OS was not yet reached (Capdevila et al, JCO 2020). Taken together, we believe that anti-PD1/L1 drugs can be used in the setting of radiation.Thus, we believe that pembrolizumab in the adjuvant setting is a safer and feasible option. Additionally, as tumor PD-L1 expression has been linked to radioresistance, the addition of adjuvant pembrolizumab may also provide a local control benefit, in addition to targeting micrometastatic disease.

4.3.2 Justification for Dose

The planned dose of pembrolizumab for this study is 400 mg Q6W.

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

As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5 fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics

and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

A 400 mg Q6W dosing regimen of pembrolizumab is expected to have a similar benefit-risk profile as 200 mg Q3W, in all treatment settings in which 200 mg Q3W pembrolizumab is currently appropriate [Lala et al, 2018]. Specifically, the dosing regimen of 400 mg Q6W for pembrolizumab is considered adequate based on modeling and simulation (M&S) analyses, given the following rationale:

• Pharmacokinetic (PK) simulations demonstrating that in terms of pembrolizumab exposures:

- Average concentration over the dosing interval (Cavg) (or area under the curve [AUC]) at 400 mg Q6W is similar to the approved 200 mg Q3W dose, thus bridging efficacy between dosing regimens.

- Trough concentrations (Cmin) at 400 mg Q6W are generally within the range of those achieved with 2 mg/kg or 200 mg Q3W in the majority (>99%) of patients.

- Peak concentrations (Cmax) at 400mg Q6W are well below the Cmax for the highest clinically tested dose of 10 mg/kg Q2W, supporting that the safety profile for 400 mg Q6W should be comparable to the established safety profile of pembrolizumab.

- Exposure-response (E-R) for pembrolizumab has been demonstrated to be flat across indications, and OS predictions in melanoma and non-small cell lung cancer (NSCLC) demonstrate that efficacy at 400 mg Q6W is expected to be similar to 200 mg or 2mg/kg Q3W, given the similar exposures; thus, 400 mg Q6W is expected to be efficacious across indications.

4.3.3 Rationale for Endpoints

Overall survival (OS) and progression-free survival (PFS) are important endpoints for evaluating anticancer therapies, particularly in ATC where these events occur relatively rapidly. Although OS is considered to be the most clinically relevant endpoint in ATC trials, it is affected by the use of multiple post-progression therapies.

PFS, which measures the time to disease progression or death after treatment with the trial drug, is a useful endpoint because it can demonstrate a clinical benefit and is more rapidly assessable than OS and is unaffected by post-progression therapies.

4.3.3.1 Efficacy Endpoints

Based on historical data, the median PFS for unresected, stage IVB patients is approximately 6 months. We anticipate that these patients (cohorts 1 and 2) under adjuvant pembrolizumab will improve their median PFS to be approximately 10 months.

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 the following criteria apply:

1. Male/female participants who are at least 18 years of age on the day of signing informed consent with Pathologic findings supporting the clinical impression of anaplastic thyroid carcinoma will be enrolled in this study. Diagnosis may include consistent with or suggestive of terminology associated with: anaplastic thyroid carcinoma, undifferentiated carcinoma, squamous carcinoma; carcinoma with spindled, giant cell, or epithelial features; poorly differentiated carcinoma with pleomorphism, extensive necrosis with tumor cells present.

2. Stage IVB disease (no convincing evidence of metastatic disease outside of the neck) who have unresectable disease are eligible in groups 1 or 2. Previous excisional biopsy is permitted.

3. Stage IVB disease (no convincing evidence of metastatic disease outside of the neck) who have undergone complete resection of tumor (no convincing evidence of metastatic disease in the neck) are eligible in group 3

4. Patient must have completed external beam radiation with or without concomitant cytotoxic chemotherapy to participate in groups 1 and 2. Those who have completed these treatment after surgical resection of primary tumor may participate in group 3.

5. Patients may enroll only after completing radiation. Study drug may start from 2-6 weeks (+2 weeks) after radiation is completed and can only be started once radiation and chemotherapy-related toxicities are grade 2 or less (with the exception of

alopecia). If a subject is consented but AEs are not grade 2 or less by 8 weeks after RT is completed, that subject is not eligible and should not start pembrolizumab.

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

   a. Not a woman of childbearing potential (WOCBP) as defined in Appendix 3
   OR
   b. A WOCBP who agrees to follow the contraceptive guidance in Appendix 3 during the treatment period and for at least 120 days after the last dose of study treatment.

7. A male participant must agree to use a contraception as detailed in Appendix 3 of this protocol during the treatment period and for at least 32 weeks (5 terminal half-lives for pembrolizumab plus an additional 90 days) from the last dose of study treatment and refrain from donating sperm during this period.

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

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

10. Adequate organ function as defined in the following table (Table 1). Specimens must be collected within 10 days prior to the start of study intervention.

Table 1: 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 first dose of pembrolizumab (see Appendix 3). 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 a live vaccine or live-attenuated vaccine within 30 days prior to the first dose of study drug. Administration of killed vaccines is allowed.
4. 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.
5. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.
6. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.
7. 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 (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment and is allowed.
8. Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease, not related to radiation.
9. Has an active infection requiring systemic therapy.
10. Has a known history of Human Immunodeficiency Virus (HIV) infection.
11. Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA qualitative is detected) infection.

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

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

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

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

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** 2

Table 2 Trial Intervention(s)

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	400 mg	Q6W	IV infusion	Day 1 of each 6-week cycle	Experimental

5.2.1 Timing of Dose Administration

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

All trial interventions will be administered on an outpatient basis.

Pembrolizumab 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).

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

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

AEs associated with pembrolizumab exposure, including coadministration with additional compounds, may represent an immunologic aetiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of

pembrolizumab/combination treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab/combination treatment, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab/combination treatment are provided in Table 6.

Table 3 Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab monotherapy and IO Combinations

General instructions:

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

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Use of other immunosuppressant drugs such as vedolizumab may be considered	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
AST or ALT Elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper Other immunosuppressive agents such as Imuran may be considered	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper Other immunosuppressive agents such as Imuran may be considered	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypothyroidism	Grade 2, 3 or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold		

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

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

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

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

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

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

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

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

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

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 4.

Table 4 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., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately.	No subsequent dosing

	Participant is permanently discontinued from further study drug intervention.	
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

Other allowed dose interruption for pembrolizumab

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

5.3 Treatment Allocation

Treatment with adjuvant pembrolizumab will start 2 weeks after completion of radiation, up until 6 weeks (+2 weeks) after radiation is completed and can only be started once radiation and chemotherapy-related toxicities are grade 2 or less (with the exception of alopecia). Pembrolizumab will be administered via IV infusion, 400 mg q6weeks x 9 cycles.

5.4 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.

5.4.1 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.

5.4.2 Prohibited Concomitant Medications

Participants are prohibited from receiving the following therapies during the Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy

- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
- The use of anti-colitis drugs such as vedolizumab are allowed, as they are not absorbed systemically.

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.

5.4.3 Rescue Medications & Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2.2, [Table 3]. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes

such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the Investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the Investigator does not need to follow the treatment guidance. Refer to [Table 3] in Section 5.2.2 for guidelines regarding dose modification and supportive care.

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

5.5 Participant Discontinuation Criteria

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to be monitored in this study and participate in the study visits and procedures as specified in Section 2.3 unless the participant has withdrawn from the study (Section 5.6).

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

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention
- After prolonged study intervention interruption that prohibits restarting study intervention if agreed upon with the Sponsor
- Radiographic disease progression outlined in Section 6.1.4.
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 5.2.2.

- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, placed the participant at unnecessary risk from continued administration of study treatment.
- The participant has a confirmed positive serum pregnancy test

Completion of pembrolizumab Q6W monotherapy consists of 9 treatments (approximately).

5.6 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.

5.7 Participant Replacement Strategy

Patients who have signed informed consent but are unable/unwilling to participate in the trial (never received a dose of pembrolizumab) during/after radiation will be replaced but this information will be collected and reported.

5.8 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 2.3.
- 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.

Remote consenting is permitted and will adhere to IRB/ERC standards.

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 significant by the Investigator. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

6.1.1.5 Prior and Concomitant Medications Review

6.1.1.5.1 Prior Medications

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

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

6.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the trial. 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. Once new anti-cancer therapy has been initiated the participant will move into survival follow-up.

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. 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.

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

6.1.2.3 After C1D1, these examinations may be done via telemedicine. A physical exam is not necessary unless clinically indicated. Full Physical Exam

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

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

6.1.2.4 After C1D1, these examinations may be done via telemedicine. A physical exam is not necessary unless clinically indicated.Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Schedule of Activities (Section 2.3). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure.

6.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

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

6.1.2.6 Electrocardiograms

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

6.1.3 Clinical Safety Laboratory Assessments

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

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

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

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 60 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.

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

Baseline cross-sectional imaging of the neck, chest and abdomen and MRI of the brain will be performed prior to starting protocol-related treatment. Restaging scans (CT or MRI of the neck, chest, abdomen or PET/CT) will be performed at 6 weeks after enrollment, then every 12 weeks. Brain imaging is required for all participants at screening. MRI is preferred; however, CT imaging will be acceptable, if MRI is medically contraindicated. MRI brain will be repeated every 6 months +/- 1 month in the absence of evidence of symptoms of metastatic brain metastases or progression.

Participant eligibility will be determined using local assessment (Investigator assessment) based on RECIST 1.1. In addition, images (including via other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons, but which demonstrate radiologic progression, should also be used to determine progression.

6.1.4.1 Initial Tumor Imaging

Initial tumor imaging at Screening must be performed within 14 days prior to the date of first dose of pembrolizumab.

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 14 days prior to the date of first dose of pembrolizumab and can be assessed by the central imaging vendor.

6.1.4.2 Tumor Imaging During the Study

The first on-study imaging assessment should be performed at 6 weeks ([42] days ±7 days]) from the date of first dose of pembrolizumab. Subsequent tumor imaging should be performed every 12 weeks ([84] days ±7 days) or more frequently if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the Investigator.

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.

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 in Year 1 or every 12 weeks after Year 1) to monitor disease status until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

6.1.4.4 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used as the primary measure for assessment of stability or progression and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study treatment). Progression of disease should be noted as unequivocal. If progression is equivocal progression it will be considered stable disease until biopsy proven or until it becomes unequivocal.

6.1.4.5 Clinical Stability

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status (unless decline is related to an AE)
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any participant deemed clinically unstable should have imaging to determine if they have progressed.

6.1.5 Other Procedures

6.1.5.1 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.

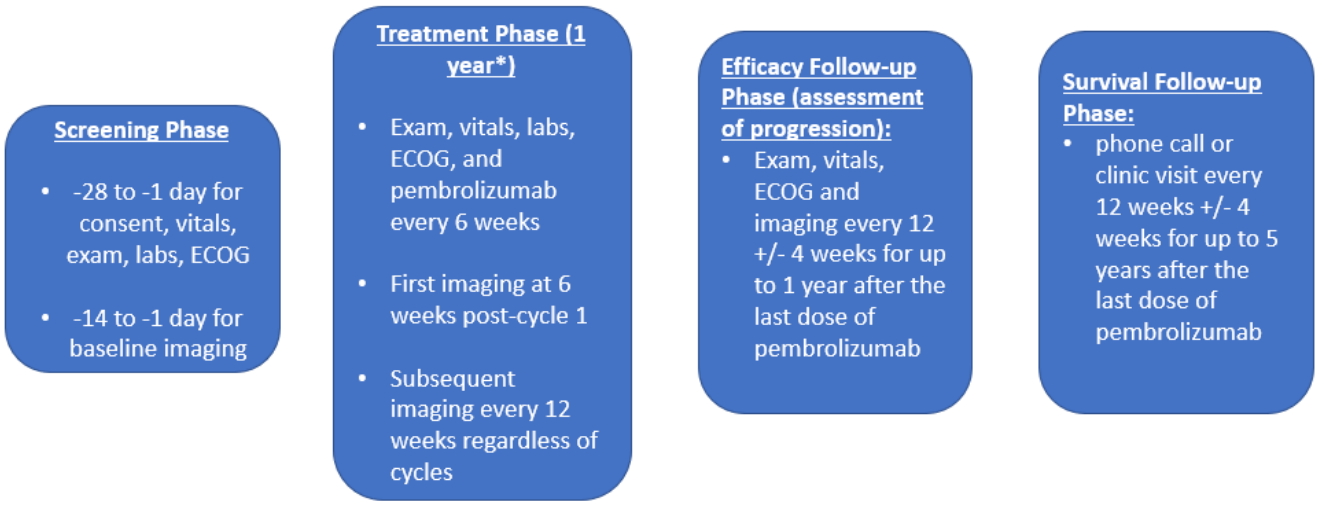
Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the final study visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 6.2.

6.1.6 Visit Requirements

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

6.1.6.1 Screening, Treatment, Efficacy Follow-up and Survival Phases

Figure 2



*Patients who discontinue treatment for any reason other than progression will enter the Efficacy Follow-up Phase and Survival Follow-up Phase

6.1.5.3.1 Safety Follow-Up Visit

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

6.1.5.3.2 Efficacy Follow-up Visits (assessment of progression)

Participants who complete the protocol-required cycles of study intervention or who discontinue study intervention for a reason other than disease progression will begin the Efficacy Follow-Up Phase and should be assessed every 12 weeks (84 ± 7 days) by radiologic imaging to monitor disease status for 1 year after the last dose of pembrolizumab. Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, or end of the study. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated. Participants who completed all efficacy assessments will not have further efficacy assessments must enter the Survival Follow-up Phase.

6.1.5.3.3 Survival Follow-up Phase

Participant survival follow-up status will be assessed approximately every 12 +/- 4 weeks to assess for survival status for a period of up to 5 years in total following the study treatment phase, or until death, withdrawal of consent, or the end of the study, whichever occurs first. Note that the first year of the survival follow-up phase is replaced by the efficacy phase for those not starting new antineoplastic therapy, and those not removed from trial due to progression. Those continuing on pembrolizumab outside of the trial will be followed in accordance with the efficacy phase as per physician discretion, and then go to the survival follow-up phase.

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

- For participants who completed assessments in the Efficacy Follow-up Phase, the first survival follow-up contact will be scheduled 12 +/- 4 weeks after the last efficacy assessment follow-up visit has been performed. Patients will be contacted by phone or in person when they are seen in the clinic.

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

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

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

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

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

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

All AEs, SAEs, and other reportable safety events 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 120 days following cessation of study intervention, or 30 days following cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to Merck if the event is considered drug-related.

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

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to Merck within the time frames as indicated in **Table 5** .

Table 5: 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 learning of event
Pregnancy/Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 2 business days but no longer than 3 calendar days of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential drug-induced liver injury (DILI) - require regulatory reporting	Not required	Within 2 business days but no longer than 3 calendar days of learning of event

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

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events including pregnancy and exposure during breastfeeding, events of clinical interest (ECIs), cancer, and overdose will be followed

until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up.. In addition, the investigator will make every attempt to follow all nonserious AEs that occur in allocated or randomized participants for outcome. Further information on follow-up procedures is given in Appendix 5.

6.2.4 Sponsor Responsibility for Reporting Adverse Events

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

6.2.5 Pregnancy and Exposure During Breastfeeding

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

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

6.2.6 Events of Clinical Interest (ECIs)

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

Events of clinical interest for this study include:

1. An overdose of pembrolizumab that is not associated with clinical symptoms or abnormal laboratory results. For purposes of this study, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥2.5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated. If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

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

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

7.0 STATISTICAL ANALYSIS PLAN

7.1 Statistical Analysis Plan Summary

Power Calculation

This is a phase II trial investigating adjuvant pembrolizumab after completion of radiation +/- concomitant cytotoxic chemotherapy in the treatment off stage IVB ATC. The primary endpoint is the progression-free survival (PFS), which is from the start of the adjuvant pembrolizumab till the disease progression or completion of follow-up. We will estimate the median PFS and focus on unresected patients from cohort 1 and 2 for our primary analysis and futility monitoring. Resected patients from cohort 3 will serve as patients for exploratory analysis. Based on historical data, the median PFS for unresected patients is 6.8 months. We anticipate unresected patients under adjuvant pembrolizumab will improve their median PFS to be 10.5 months. Assuming an accrual rate is one patient per month and 12 months additional follow-up after the last patient being enrolled, with 30 evaluable patients we would have 80.0% power using 1-sided 10% alpha for a one-sample log rank test (calculated using trialdesign.org). The required number of events is 24 and exponential survival time is assumed.

Futility Monitoring

We will enroll at least 10 subjects and at most 30 (cohorts 1 and 2 will enroll 15 subjects each) subjects at a rate of one patient per month and we will follow all patients for at least 12 months for the purposes of the futility monitoring rule. We will use the methods described by Thall et al. [14] to monitor progression-free survival from the date of start of adjuvant pembrolizumab and will stop enrolling subjects early if, based on the available data, we have reason to believe that the median PFS is less than that observed by historical therapy (i.e, 6.8 months). Formally, we will stop enrolling patients early if:

$$\Pr(\text{median PFS}_{\text{experiemtnal}} > \text{median PFS}_{\text{historical}} \mid \text{data from the trial}) < 0.05.$$

That is, if there is less than 5% chance that the median PFS is more than that observed with historical therapy (6.8 months), then we will stop enrolling subjects. Details of how this monitoring rule was constructed are explained in the "*Technical Details*" section below. The operating characteristics of this monitoring rule are shown in the table below and are based on 1,000 simulations of the monitoring rule using the One-Arm Time-to-Event Simulator (PID-359): Version 3.0.9. developed in the Department of

Biostatistics at MD Anderson and available at the following website (https://biostatistics.mdanderson.org/SoftwareDownload/).

Table 6. Operating characteristics of the futility monitoring rule

Scenario	True Median PFS (Months)	Pr(Stop Early)	Mean # Patients	Trial Duration (Months)
1	1	>0.99	10.00	22.20
2	3	0.99	12.49	25.23
3	6	0.23	26.46	38.92
4	7	0.11	28.19	40.55
5	10	0.01	29.75	42.06
6	11	0.01	29.84	42.04
7	12	<0.01	29.92	42.11

We will use the Clinical Trial Conduct (CTC) website, which is housed on a secure server at MD Anderson and maintained by the Department of Biostatistics, to implement the futility monitoring rule. The CTC website is found at https://biostatistics.mdanderson.org/ClinicalTrialConduct/. Access to the CTC website will be gained through usernames and passwords provided by the MD Anderson Department of Biostatistics to study personnel responsible for enrolling patients and updating, reviewing, and analyzing patient data. Training on the use of the CTC website will be provided by the study statisticians, with

particular attention to the importance of timely updating of follow-up dates and recording events. Monitoring will occur at each patient accrual so all previous patient's data will be updated at each patient accrual.

Technical details

At any point in the trial the PFS can be calculate for each patient, with the time interval regarded as censored at the date of last clinic-visit assessed for progression if the patient is still alive without progressive disease. At each interim analysis, we will apply a Bayesian method for updating prior information with PFS observed at that time. We assume that the PFS for each patient is exponentially distributed with a median of λ_H months for the historical treatment and a median of λ_E for the experimental treatment. We assume λ_H follows an inverse gamma distribution with mean 6.8 months and standard deviation of 1 month. The middle 95% of this distribution is between 5.12 and 9.02 months. We assume λ_E follows an inverse gamma distribution with mean 6.8 months and standard deviation of 10 months. The middle 95% of this distribution is between 1.57 and 24.77months.

The goal of the futility monitoring rule is to guard against a median PFS rate less than that observed by historical therapy. Patients enrolled will be stopped early if based on the available data, $Pr(\lambda_E > \lambda_H \mid \text{data from the trial}) < 0.05$. This rule was chosen to achieve a high early-stopping probability if the true median PFS is less than 6.8 months for the experimental treatment, while maintaining a relatively low early-stopping probability if the median PFS is greater than 6.8 months for the experimental treatment.

Analysis

We will use descriptive statistics to summarize the demographic and clinical characteristics of the subjects. Cohorts 1 and 2 will consist of our primary analysis set. We will estimate the median PFS with a 95% confidence interval and report the posterior probability that the median PFS is > 6.8 months. We will also estimate PFS with the methods of Kaplan and Meier and model PFS as a function of potential prognostic factors using Cox proportional hazards regression. PFS will be calculated as the time from date of start of pembrolizumab to the earliest date of last clinic visit assessed for progression, date of progression, or date of death. Secondary objectives consist of overall survival and disease-free survival. OS will be calculated as the time from date of start of pembrolizumab to the earliest date of death or last conduct. DFS will be calculated as time from disease-free status to earliest date of last clinic visit assessed for disease, date of recurrence, date of metastasis, or date of death. OS and DFS will analyzed similarly as PFS. Cohort 3 will include 5 subjects and will be analyzed descriptively.

Evaluable Analysis Set: Our evaluable patient population will be subjects who start pembrolizumab and have one follow up imaging visit to assess for disease progression. Subjects who do not start pembrolizumab will be replaced.

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 7.

Table 7. 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 REFERENCES

[1] Disis ML. Immune regulation of cancer. J Clin Oncol 2010;28(29):4531-8.

[2] Dudley ME, Wunderlich JR, Yang JC, Sherry RM, Topalian SL, Restifo NP, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol 2005;23(10):2346-57.

[3] Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med 2008;358(25):2698-703.

[4] Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annu Rev Immunol 2005;23:515-48.

[5] Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. Proc Natl Acad Sci U S A 2001;98(24):13866-71.

[6] Zhang X, Schwartz J-CD, Guo X, Bhatia S, Cao E, Chen L, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. Immunity 2004;20:337-47.

[7] Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. J Immunol 2004;173:945-54.

[8] Sheppard K-A, Fitz LJ, Lee JM, Benander C, George JA, Wooters J, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. FEBS Lett. 2004;574:37-41.

[9] Riley JL. PD-1 signaling in primary T cells. Immunol Rev 2009;229:114-25.

[10] Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Mol Cell Biol 2005;25(21):9543-53.

[11] Lala M, Li M, Sinha V, de Alwais D, Chartash E, Jain L. A six-weekly (Q6W) dosing schedule for pembrolizumab based on an exposure-response (E-R) evaluation using modeling and simulation. Presented at: 2018 American Society of Clinical Oncology (ASCO) Annual Meeting; 2018 Jun 1 – 5. J Clin Oncol. 2018: 36 (15 suppl) Abstract no. 3062.

[12] Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 2010;236:219-42.

[13] Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017;18(3):e143-e152. Epub 2017 Mar 2.

10.0 APPENDICES

Appendix 1: ECOG Performance Status

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

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

Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 8 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 8 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	Calcium	Alkaline phosphatase	TSH, Free T4, thyroglobulin
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)			
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

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 9 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). 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

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

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

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

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

10.1.1 Definition of AE

AE definition

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

10.1.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the participant's medical history.

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

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

f. Other important medical events

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

10.1.3 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

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

- Is a new cancer (that is not a condition of the study)
- Is associated with an overdose of pembrolizumab

10.1.4 Recording AE and SAE

AE and SAE recording

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

Assessment of intensity/toxicity

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

1. The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI Common Terminology for Adverse Events (CTCAE), version 5. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.
    - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
    - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
    - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
    - Grade 4: Life threatening consequences; urgent intervention indicated.
    - Grade 5: Death related to AE.

Assessment of causality

1. Did Merck product cause the AE?

2. The determination of the likelihood that Merck product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

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

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

    - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?

- **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.
- **Dechallenge:** Was Merck product discontinued or dose/exposure/frequency reduced?
- If yes, did the AE resolve or improve?
- If yes, this is a positive dechallenge.
- If no, this is a negative dechallenge.
- (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Merck product; (3) the study is a single-dose drug study; or (4) Merck product(s) is/are only used 1 time.)
- **Rechallenge:** Was the participant re-exposed to Merck product in this study?
- If yes, did the AE recur or worsen?
- If yes, this is a positive rechallenge.
- If no, this is a negative rechallenge.

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

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

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

5. The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.

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

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

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

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

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

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

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

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

10. The causality assessment is 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.

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

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

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally, investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215-661-6229) at the time of submission to FDA.