Mayo Clinic Cancer Center

MC200708 Phase II Study of Pemetrexed and Pembrolizumab in Recurrent and/or Metastatic Salivary Gland Malignancies

Sponsor/Principal Investigator: [redacted]

Co-Principal Investigator: [redacted]

Co-Investigators: [redacted]

Statistician: [redacted]

FDA IND #: 155730 EXEMPT

√Study contributor(s) not responsible for patient care

Trial Supported by:
Funding: Merck (MISP 59947)

Drug Availability:
Commercial Agents: pemetrexed
Drug Company Supplied: pembrolizumab

Site Investigators & Participating sites:

[redacted]

Document History	Approval Date	Effective Date
Activation	30Apr2021	23Jul2021
MCCC Amendment 1	12Nov2021	22Nov2021
MCCC Amendment 2	06May2022	09May2022
MCCC Amendment 3	06May2024	07May2024

Protocol Resources

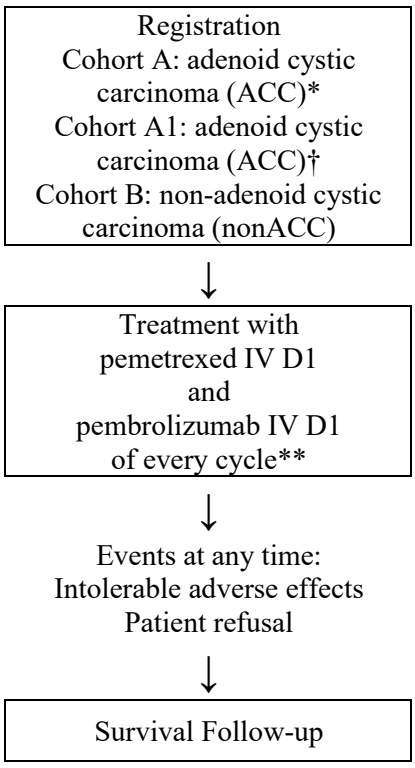
Questions:	Contact Name:
Patient eligibility*, test schedule, treatment delays/interruptions/adjustments, dose modifications, adverse events, forms completion and submission	[redacted]
Clinical coordinators (lead site first)	[redacted]
Forms completion and submission (lead site first)	[redacted]
Protocol document, consent form, regulatory issues	[redacted]
Laboratory Contact	[redacted]
Serious Adverse Event Reporting	[redacted]

*No waivers of eligibility allowed

Table of Contents

.

Schema



Cycle = 21 ± 3 days

*Cohort A: Adenoid cystic carcinoma is permanently closed as of 06Apr2022.

†Cohort A1: Adenoid cystic carcinoma (ACC) is re-opened to Rochester only with MCCC Amendment 3

**Up to maximum of 35 total doses of pembrolizumab

Generic name: pembrolizumab Brand name(s): Keytruda® Availability: Provided by Merck & Co.	Generic name: pemetrexed Brand name(s): Alimta® and others Availability: Commercial

1.0 Background

1.1 Recurrent and/or metastatic (R/M) salivary gland cancer (SGC)

Salivary gland malignancies are a heterogeneous group of rare cancers that arise from major and minor salivary glands predominantly in the head and neck. They are morphologically and clinically varied neoplasms and account for approximately 5–7 % of head and neck cancers. The heterogeneity of salivary malignancies is underscored by the World Health Organization classification, which categorizes these tumors into 24 subtypes with varying biologic characteristics, clinical behaviors, and survival outcomes [1]. Many malignant salivary cancers are largely cured with surgery alone but medical oncologists routinely encounter such subtypes as adenoid cystic carcinoma (ACC), adenocarcinoma NOS, carcinoma ex-pleomorphic adenoma, mucoepidermoid carcinoma (MEC), and salivary duct carcinoma (SDC) in the recurrent and metastatic setting (R/M). The clinical behaviors of R/M SGCs range from aggressive to indolent, with heterogeneity even within any given subtype, making treatment standardization a challenge. Regardless of the type of salivary cancer, the majority of patients with metastatic salivary gland cancer will succumb to the disease, and metastatic disease remains incurable. The rarity of the cancers and the varying responses of the different subtypes have made it difficult to prospectively design and study treatment options through clinical trials, thus resulting in a paucity of standardized treatment options for clinicians treating R/M SGC.

1.2 Chemotherapy responses for R/M salivary gland cancer

Treatment options for recurrent and/or metastatic (R/M) salivary gland cancer (SGC) are limited and to date there are no clear standard treatment options. A review of chemotherapy for R/M SGC reported with response rates to chemotherapy low at 10-30% [2]. The chemotherapy responses do vary by histologic subtype with adenoid cystic carcinoma being the most resistant to chemotherapy and having the lowest response rate and non-ACC histologies such as adenocarcinoma being relatively chemosensitive.[3,4] The most studied chemotherapeutic regimen was the historic salivary cancer regimen cyclophosphamide, doxorubicin, and cisplatin [5, 6] but recent reviews concluded that there is no clear benefit for the use of triplet therapy over double or single agent regimens [2].

1.3 Pemetrexed and R/M salivary gland cancer

Pemetrexed is a multitargeted antifolate chemotherapy widely used in lung cancer, but its efficacy in SGC is unknown. A recent publication reported on two patients with R/M SGC (adenocarcinoma) with marked and sustained responses to pemetrexed [7]. The first patient had widely metastatic adenocarcinoma of the parotid gland with diffuse liver, skin, and lymph node metastases, who progressed through two prior lines of cytotoxic chemotherapy including platinum chemotherapy, and who achieved a rapid complete response with single agent pemetrexed that was sustained for 8 months. The second patient had androgen receptor-positive adenocarcinoma with diffuse bony metastases who initially responded then progressed through two lines of hormone therapy. This patient also had complete resolution of disease within 2 months of pemetrexed therapy resulting in marked improvement in bone pain, and maintained the complete response for 8 months. These two cases represent the clinical rationale for further investigation of pemetrexed in R/M SGC.

1.4 Rationale for combination of pembrolizumab and pemetrexed for R/M SGC

Immunotherapy is not part of standard of care treatment for R/M SGC. Limited data is available for the use of checkpoint inhibitors in the treatment of patients with R/M SGC. A published phase 1b study reported a response rate (RR) of 12% for patients with R/M SGC treated with pembrolizumab monotherapy.[8] Partial responses were observed in patients with adenocarcinoma and high-grade serous carcinoma. The rationale for combining pembrolizumab with pemetrexed came out of the now standard of care treatment for non-small cell lung cancer. The phase III KEYNOTE-189 study demonstrated the safety and superiority of pembrolizumab and pemetrexed-based chemotherapy on overall survival (OS) and progression-free survival (PFS) in advanced non-squamous non-small cell lung cancer with a RR that was more than doubled in the chemo-immunotherapy arm.[9] Given the modest single agent RR of both chemotherapy and immunotherapy in R/M SGC, this study will look at the combination to see if chemoimmunotherapy will result in improved efficacy.

1.5 Pembrolizumab

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. Pembrolizumab (Keytruda®) 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.

1.6 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [10]. 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 [11, 12].

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) [13, 14].

The structure of murine PD-1 has been resolved [15]. 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 [14-18]. 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 [19, 20]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in R/M SGC.

1.7 Study Summary

This is a phase II, single arm, study of the combination of pembrolizumab and pemetrexed in patients with recurrent or metastatic salivary gland cancer. Patient will be enrolled and analyzed in two separate cohorts based on historical response rates. Cohort A will be for patients with adenoid cystic carcinoma (ACC), and Cohort B will be for patients with all other histologies (non-ACC). The treatment will be identical for both cohorts. Treatment is once every three weeks with tumor response assessments every 3 cycles. Primary endpoint is response rate and secondary endpoints include overall survival, progression-free survival, and safety/tolerability. Correlative studies to identify biomarkers for response will include PDL1, thymidylate synthase, and MTAP loss. Blood for future immunophenotyping and circulating tumor DNA will be collected and banked.

1.71 Justification for Dose

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

- Clinical data from 8 randomized studies in melanoma and NSCLC indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W), representing an approximate 5- to 7.5-fold exposure range (refer to IB, Section 5.2.2)
- 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
- Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W

1.72 Rationale for Additional Accrual of ACC Patients (Cohort A1)

We originally closed the study to further enrollment of adenoid cystic carcinoma (ACC) patients due to failure to pass the interim analysis that required at least one (1) confirmed partial response in the first 7 patients. However, as the study continued it was noted that several patients in the ACC arm had prolonged stable disease and clinical benefit from the treatment in the absence of an objective response. Given this observation, we elected to re-open the ACC cohort to enroll the remaining 9 patients with a modified primary

endpoint for the ACC cohort (Cohort A1) of clinical benefit rate (CBR). CBR is the sum of patients who respond and who have stable disease in order to capture treatment benefit even outside of a response.

1.8 Rationale for correlative studies

Given the heterogeneity of SGCs, it is important to try and identify clinically-accessible biomarkers of response to any systemic therapy. The following correlative studies will provide hypothesis-generating data for potential biomarkers of response for pembrolizumab or pemetrexed in R/M disease.

1.81 MTAP loss

Methylthioadenosine phosphorylase (MTAP) loss has been described in many solid tumors, and has been reported in salivary gland malignancies (Nichols 2013). However, the prevalance of MTAP loss is not well-characterized for salivary gland malignancies. MTAP loss has been shown to correlate with response to anti-folate therapy in bladder cancer. This study will investigate the frequency of MTAP loss by immunohistochemistry in salivary cancer and whether it correlates with enhanced response to pemetrexed.

1.82 Thymidylate synthase

A high level of thymidylate synthase (TS) expression in malignant tumours has been suggested to be related to a reduced sensitivity to the antifolate drug pemetrexed [Johnson, Pestalozzi] but this has not been explored in SGC. This study will investigate the degree of expression of TS and whether it correlates with response to pemetrexed.

1.83 PDL1

The only published study of pembrolizumab in R/M SGC was a phase 1b study in patients whose tumors expressed PDL1. This study will treat patients irrespective (Alhalabi *J Clin Oncol* 37, 2019 suppl; abstr 4521) of the PDL1 status which will allow exploration of whether PDL1 expression is necessary for a response to the combination of pembrolizumab and pemetrexed. PDL1 expression will be determined using the PDL1 IHC 22C3 pharmDx assay using formalin-fixed tumor samples and the degree of expression will be correlated with response.

1.84 Circulating tumor DNA

Circulating tumor DNA is being increasingly utilized to monitor response to anti-cancer therapy and disease progression, but this area is undefined for salivary gland tumors. We will collect blood and store for future ctDNA analysis.

1.85 PSMA

Prostate-specific membrane antigen (PSMA) is a transmembrane glycoprotein of the prostate secretory acinar epithelium that is used diagnostically and therapeutically for prostate cancer and is a promising tool for salivary gland cancer (Tan et al. 2022).

1.851 PSMA expression by immunohistochemistry

Nulent and colleagues retrospectively analyzed FFPE tissue from 110 consecutive patients with adenoid cystic carcinoma from 1990-2017 for PSMA expression by immunohistochemistry (Klein Nulent et al. 2020). Expression was intracellular in a granular fashion in the cytoplasm or at the luminal side of the cell membrane. PSMA expression was seen in 94% of primary tumors with a median expression of 31% (range 15-60%). PSMA expression was seen in 80%

of recurrent tumors and 90% of samples from distant metastatic disease. The median PSMA expression of the recurrent samples overall was 60% and 23% for the metastatic samples. PSMA expression was not associated with pathologic stage, tumor grade, or the risk of recurrence.

1.852 PSMA uptake by nuclear imaging

Several reports have shown the feasibility of imaging adenoid cystic carcinoma with PSMA PET/CT (Klein Nulent et al. 2017, van Boxtel et al. 2020). A phase 2 prospective imaging study using ^{68}GA-PSMA HBED-CC PET/CT imaging for adenoid cystic carcinoma and salivary duct carcinoma (SDC) showed that 93% of patients with ACC and 40% of patients with SDC had relevant PSMA-ligand uptake (defined as a tumor/liver ratio of >1).(van Boxtel et al. 2020)There was a significant range of uptake in ACC patients (SUV_{max} 1.1-30.2) and in SDC patients (SUV_{max} 0.3-25.9). PSMA expression by immunohistochemistry was not predictive of ligand uptake for either histology, suggesting that patients who could be candidates for treatment with radionuclide therapy should be identified through imaging.

1.853 PSMA extracellular vesicles (EVs) as potential biomarker of disease burden and response

Extracellular vesicles are lipid-bound vesicles secreted by cancer and non-cancer cells as a means of cellular communication and are emerging as potential circulating biomarkers of disease, with the largest body of literature in prostate cancer. PSMA expression on salivary gland cancers has been previously described, with initial attempts at PSMA radioligand therapy under investigation. However, the use of PSMA EVs as a potential biomarker of disease for salivary cancer has not yet been described. In an exploratory analysis, we analyzed PSMA EVs in patients with ACC in the original Cohort A and in patients treated on Cohort B and found expression across all salivary histologies. In pre- and post-treatment samples in patients with ACC, the direction of change appeared to correlate with clinical response, and in two patients with prolonged stable disease there was either a decline or only small increase in PSMA EV levels, suggesting that PSMA EVs could be a useful marker of disease burden and treatment response, particularly in slower growing histologies such as ACC where imaging and determination of progression can be challenging. As such, Cohort A (ACC) was re-opened and renamed Cohort A1, with patients continuing to receive the same protocol therapy but with serial PSMA EV measurements in the blood and PSMA PET imaging as correlates.

2.0 Goals

2.1 Primary Goal

2.11 Groups A/A1 (ACC)

To determine the clinical benefit rate (CBR) of the combination of pembrolizumab and pemetrexed in patients with recurrent or metastatic adenoid cystic salivary gland cancer

2.12 Group B (non-ACC)

To determine the response rate of the combination of pembrolizumab and pemetrexed in patients with recurrent or metastatic salivary gland cancer (R/M SGC).

2.2 Secondary Goals

2.21 To determine the progression-free survival (PFS), overall survival (OS), response rate (ACC cohort), CBR rate (non-ACC), and adverse events of the combination of pembrolizumab and pemetrexed in patients with recurrent or metastatic salivary gland cancer (R/M SGC).

2.22 To assess safety and tolerability of the combination of pembrolizumab and pemetrexed in patients with recurrent or metastatic salivary gland cancer (R/M SGC).

2.3 Correlative Research

2.31 To investigate the frequency of MTAP loss by immunohistochemistry in R/M SGC and whether it correlates with enhanced response to pemetrexed.

2.32 To measure the degree of PDL1 expression using formalin-fixed tumor samples, and determine the extent of PDL1 expression correlates with response to study treatment.

2.33 To investigate expression of thymidylate synthase by immunohistochemistry in R/M SGC and whether it correlates with enhanced response to pemetrexed.

2.34 To investigate circulating tumor DNA (ctDNA) and correlation with response to study treatment.

2.35 To prospectively investigate circulating PSMA EVs and correlate with disease burden and treatment response for patients with adenoid cystic carcinoma in Cohort A1.

2.36 To prospectively investigate PSMA PET/CT as an imaging modality for patients with adenoid cystic carcinoma in Cohort A1.

3.0 Eligibility

3.1 Registration – Inclusion Criteria

3.11 Age ≥18 years

3.12 Disease Characteristics

3.121 All patients: Histologically confirmed diagnosis of recurrent or metastatic salivary gland cancer not amenable to curative-intent therapy

3.122 Cohort A1: Rochester Minnesota only: Diagnosis of adenoid cystic carcinoma (ACC)

3.13 Measurable disease as defined by RECIST v1.1 criteria (See Section 11.0)
NOTE: Tumor lesions in a previously irradiated area are considered measurable disease if progression has been demonstrated in such lesions. Disease that is measurable by physical examination only is not eligible.

3.14 Prior treatment:
- Prior treatment with checkpoint inhibitor(s) allowed
- Any number of lines of prior therapy in the recurrent/metastatic setting is permitted at the investigator's discretion

3.15 ECOG Performance Status (PS) 0 or 1 (Appendix I).
NOTE: PS must be assessed again within 7 days prior to first dose of study drug.

3.16 The following laboratory values obtained ≤8 days prior to registration:
- Hemoglobin ≥9.0 g/dL
  NOTE: Must be met without growth factor support and no transfusions <14 days prior to testing
- Absolute neutrophil count (ANC) ≥1500/mm^3
- Platelet count ≥100,000/mm^3
- Total bilirubin ≤1.5 x ULN
- Alanine aminotransferase (ALT) and aspartate transaminase (AST) ≤2.5 x ULN (≤5 x ULN for patients with liver involvement)
- PT/INR/aPTT ≤1.5 x ULN OR if patient is receiving anticoagulant therapy and INR or aPTT is within target range of therapy
- Creatinine ≤1.5 x ULN **OR**
  Calculated creatinine clearance ≥45 ml/min using the Cockcroft-Gault formula below:

Cockcroft-Gault Equation:	
Creatinine clearance for males =	$\frac{(140 - age)(weight\ in\ kg)}{(72)(serum\ creatinine\ in\ mg/dL)}$
Creatinine clearance for females =	$\frac{(140 - age)(weight\ in\ kg)(0.85)}{(72)(serum\ creatinine\ in\ mg/dL)}$

3.17 Negative pregnancy test done ≤7 days prior to registration, for persons of childbearing potential only.
Note: If testing done for eligibility is >72 hours prior to first dose, then pregnancy testing must be repeated and result must be negative for patient to receive treatment.

3.18 Persons able to become pregnant OR able to father a child must be willing to use an adequate method of contraception while on treatment and for 180 days after last treatment.

3.19a Life expectancy ≥12 weeks.

3.19b Provide written informed consent.

3.19c Willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).

3.19d Willingness to provide mandatory blood specimens for correlative research (see Section 14.0).

3.19e Willingness to provide mandatory tissue specimens for correlative research (see Section 17.0).

3.2 Registration - Exclusion Criteria

3.21 Any of the following because this study involves an agent that has known genotoxic, mutagenic, and teratogenic effects:
- Pregnant persons
- Nursing persons
- Persons of childbearing potential and persons able to father a child who are unwilling to employ adequate contraception
- Persons expecting to conceive or father children during study treatment or within 180 days (6 months) after the last treatment

3.22 Any of the following prior therapies:
- Surgery <3 weeks prior to registration
- Systemic anti-cancer therapy <3weeks prior to registration
- Radiotherapy <2 weeks prior to registration
  OR Palliative radiation <1 week prior to registration
  NOTES: Must have recovered from all radiation related adverse effects (≤Grade 1)
  Must not currently require corticosteroids
  Must not have had radiation pneumonitis
- Live vaccine <4 weeks prior to registration
  NOTES: Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette-Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.
- Received an investigational agent or used an investigational device or participated in a study of an investigational agent <4 weeks prior to registration

3.23 Known active human immunodeficiency virus (HIV) infection (defined as patients who are not on anti-retroviral treatment and have detectable viral load and CD4+ <500/ml).
NOTE: HIV-positive patients who are well controlled on anti-retroviral therapy are allowed to enroll.

3.24 Active autoimmune disease requiring systemic treatment <2 years prior to registration, documented history of severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents with use of disease modifying agents, corticosteroids or immunosuppressive drugs

NOTE: Exceptions are allowed for:

- Vitiligo
- Resolved childhood asthma/atopy
- Intermittent use of bronchodilators or inhaled steroids
- Daily steroids at dose of ≤10mg of prednisone (or equivalent)
- Local steroid injections
- Stable hypothyroidism on replacement therapy
- Stable diabetes mellitus on therapy (with or without insulin)
- Sjögren's syndrome
- Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment and is allowed

3.25 Current or prior use of immunosuppressive medication <14 days prior to registration

NOTE: The following are exceptions to this criterion:

- Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intraarticular injection)
- Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
- Steroids as premedication for hypersensitivity reactions (e.g., premedication for CT scans)

3.26 Uncontrolled intercurrent illness including, but not limited to:

- Ongoing or active infection requiring systemic therapy
- Interstitial lung disease or clinically significant pleural effusion
- Clinically significant ascites
- Serious, chronic gastrointestinal conditions associated with diarrhea (e.g., Crohn's disease or others)
- Known history of hepatitis B (i.e., known positive HBV surface antigen (HBsAg) reactive)
- Known active hepatitis C (i.e., positive for HCV RNA detected by PCR)
- Known active tuberculosis (TB)
- Symptomatic congestive heart failure
- Unstable angina pectoris
- Unstable cardiac arrhythmia or
- Psychiatric illness/social situations that would limit compliance with study requirements (e.g., substance abuse)

3.27 Co-morbid systemic illnesses or other severe concurrent disease or current evidence of any condition, therapy, or laboratory abnormality which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

3.28 Failure to recover to ≤Grade 1 (or baseline) from adverse events due to previously administered therapies or prior surgery.
Exceptions: Neuropathy, fatigue, and/or alopecia may be Grade 1

3.29a Known active central nervous system (CNS) metastases
NOTE: Patients with previously treated brain metastases may participate provided all of the following are true:

- They are stable (without evidence of progression by imaging ≤4 weeks prior to registration and any neurologic symptoms have returned to baseline)
- Have no evidence of new or enlarging brain metastases, and
- Are not using steroids ≤14 days prior to registration.

3.29b Known leptomeningeal disease

3.29c Hypersensitivity (≥Grade 3) to pembrolizumab or any of its excipients

3.29d Previous serious adverse event (≥Grade 3) attributed to prior checkpoint inhibitor therapy.

3.29e History of (non-infectious) pneumonitis that required steroids or has current pneumonitis

3.29f History of Grade ≥3 immune-related adverse event or any grade of immune-related neurologic or ocular adverse event while receiving immunotherapy
Note: Patients who had endocrine adverse events ≤Grade 2 are allowed to enroll if they are stable on appropriate replacement therapy and asymptomatic.

3.29g Other active malignancy <2 years prior to registration.
EXCEPTIONS: Non-melanotic skin cancer, superficial bladder cancer, papillary thyroid cancer, or carcinoma-in-situ of the cervix or others curatively treated and now considered to be at less than 30% risk of relapse.

3.29h History of allogenic tissue/solid organ transplant.

4.0 Test Schedule

4.1 Test schedule for Salivary Gland Malignancies

			Active Monitoring Phase				
Tests and procedures[1]	≤28 days prior to Registration	≤8 days prior to Registration	After Reg prior to Treatment on C1D1	End of every cycle	End of every third cycle[2]	Safety follow-up[3]	End of initial treatment[4]
Window				±3 days	±7 days	+5	
History and exam, wt, PS	X		X[5]	X			X
Height	X						
Adverse event assessment		X		X	X	X	X
Pregnancy test[6]		X	X				
Hematology: CBC with 5-part differential		X		X			X
Comprehensive Metabolic Panel (CMP) (80053) plus magnesium (83735)[7]		X		X			X
Coagulation: PT/INR/aPTT		X					
Thyroid testing (TSH; reflex per clinical care)		X[8]		X			
Tumor measurement[9] (See Section 11.0)	X				X		X
Clinical genetic testing and PD-L1 testing[10]							
Research imaging: PSMA-PET (Rochester only)[11]			X		X		
Mandatory research blood specimens[12,R]			X		X[13]		X

[1] All tests and procedures are clinically indicated and can be performed more often at the treating physician's discretion, unless noted with an R to indicate funding by research
[2] End of Cycle 3, 6, 9, etc.
[3] Follow-up visit at least 30 days after last dose for safety monitoring – may be in person or by telephone or virtual visit
[4] End of initial treatment on this study.
[5] Physical exam and performance status must be assessed within 7 days prior to first dose of study drug, Do not repeat if previous exam and PS are ≤7 days prior to C1D1
[6] For persons of childbearing potential only. Must be done ≤7 days prior to registration and must be repeated prior to C1D1 if previous test was >72 hours prior to first study treatment. NOTE: Result must be negative for patient to receive treatment.
[7] Order additional testing as needed for clinical care
[8] TSH obtained anytime ≤28 days prior to registration may be used for baseline value.
[9] Standard clinical imaging should be used, including brain imaging at baseline to check for metastases. Contrast-enhanced CT/MRI is acceptable as a baseline scan if done ≤28 days prior to C1D1. Tumor measurements are repeated at the end of every third cycle starting at end of Cycle 3. Once patient has achieved CR or SD, frequency may be reduced per clinical guidelines. Documentation (radiologic) must be provided for patients removed from study for progressive disease.
[10] Clinical genetic analysis (e.g. NGS) and clinical PD-L1 results may be submitted at any time
[11] Separately consented substudy for up to five patients in Cohort A1 only; two scans per patient at the interval specified in that study
[12] Blood samples are collected per Section 14.0.
[13] Research samples should be collected with imaging and clinical blood at end of every third cycle

Tests and procedures[1]			Active Monitoring Phase				
	≤28 days prior to Registration	≤8 days prior to Registration	After Reg prior to Treatment on C1D1	End of every cycle	End of every third cycle[2]	Safety follow-up[3]	End of initial treatment[4]
Mandatory research tissue specimens[14,R]					X[15]		

Cycle = 21±3 days; R = Research funded

[14] Tissue specimens are collected per Section 17.0.
[15] Archived tissue is submitted one time per patient anytime prior to end of Cycle 3

4.2 Survival Follow-up/Event Monitoring

	Survival Follow-up/Event Monitoring				
	q. 3 months until PD	At PD	After PD q. 6 months	Death	New Primary
Survival Follow-up	X	X	X	X	At each occurrence

1. If a patient is still alive 3 years after registration, no further follow-up is required.

5.0 Grouping Factor

Cohort assigned: Cohort A (adenoid cystic carcinoma) vs. Cohort A1 (ACC patients enrolled starting with MCCC Amendment 3) vs. Cohort B (non-adenoid cystic carcinoma)

NOTE: Cohort A (ACC) is permanently closed as of 06Apr2022. Cohort A1 (ACC) is reopened with MCCC Amendment 3.

6.0 Registration Procedures

6.1 Registration (Step 1)

To register a patient, access the Mayo Clinic Research Registration Application at [redacted] The Research Registration Application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the website. If unable to access the website,contact the Research Site Management Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

Access and training instructions for the Research Registration Application are available on the Office of Clinical Trials web page [redacted] nd detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and an MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the Research Registration Application can be confirmed in any of the following ways:

- Contact the Research Site Management Office [redacted] If the patient was fully registered, the Research Site Management Office staff can access the information from the centralized database and confirm the registration.
- Refer to “Instructions for Remote Registration” in section “Finding/Displaying Information about A Registered Subject.”

6.2 Verification of materials

Prior to accepting the registration, the Research Registration Application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.3 Documentation of IRB approval

Documentation of IRB approval must be on file in the Research Site Management Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Research Site Management Office ([redacted]) If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Research Site Management Office is no longer necessary.

6.4 Correlative Research

6.41 Mandatory

A mandatory correlative research component is part of this study, the patient will be automatically registered onto this component (see Sections 3.0, 14.0, and/or 17.0).

6.42 Banking

At the time of registration, the following will be recorded:

- Patient has/has not given permission to store and use his/her sample(s) for future research on cancer at Mayo Clinic
- Patient has/has not given permission to store and use his/her sample(s) for future research to learn, prevent, or treat other health problems.
- Patient has/has not given permission for MCCC to give his/her sample(s) to researchers at other institutions.

6.5 Treatment on protocol

Treatment on this protocol must commence at Mayo Clinic, under the supervision of a medical oncologist.

6.6 Treatment start

Treatment cannot begin prior to registration and must begin ≤10 days after registration.

6.7 Pretreatment

Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.8 Baseline symptoms

All required baseline symptoms (see Section 10.6) must be documented and graded.

6.9a Study drug

Study drug is available on site.

6.9b Study Conduct

The clinical trial will be conducted in compliance with regulations (21 CFR 312, 50, and 56), guidelines for Good Clinical Practice (ICH Guidance E6), and in accordance with general ethical principles outlined in the Declaration of Helsinki; informed consent will be obtained from all participating patients; the protocol and any amendments will be subject to approval by the designated IRB prior to implementation, in accordance with 21 CFR 56.103(a); and subject records will be stored in a secure location and subject

confidentiality will be maintained. The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

7.0 Protocol Treatment

7.1 Treatment Schedule for both Cohorts

7.11 Treatment medication table

Agent	Dose Level	Route	Day	ReRx
Pembrolizumab	200 mg	IV	1	Q3W*
Pemetrexed	500 mg/m^2	IV	1	Q3W

Cycle = 21 ± 3 days

Pembrolizumab should be administered first, followed by pemetrexed.
*NOTE: Pembrolizumab will stop when patient has received a total of 35 doses.

7.2 Pembrolizumab

Pembrolizumab will be administered as a 30 minute IV infusion once every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

Pembrolizumab may be administered for up to 2 years or a maximum of 35 doses.

7.3 Pemetrexed

Pemetrexed should be administered according to institutional guidelines.

Suggested administration is intravenously as a 10-minute infusion via an automatic dispensing pump (e.g., IMED, Harvard, Travenol).

7.4 PSMA PET/CT Substudy (Rochester only)

PSMA PET/CT may be offered to up to five (5) ACC patients in Cohort A1 who will be separately consented for this small substudy. Imaging may be collected at up to two timepoints: once prior to study treatment and one scan subsequent to treatment (per interval described in that study).

7.5 Return to consenting institution

For this protocol, the patient must return to the consenting institution for evaluation at least every 21 days during treatment and every 21 days during clinical follow-up (Active Monitoring Phase) unless patient withdraws consent.

7.6 Treatment by local medical doctor (LMD)

Treatment with pemetrexed and pembrolizumab on this trial by a local medical doctor (LMD) is not allowed.

Interim laboratory assessments for pemetrexed can be done locally and transmitted to Mayo Clinic, if needed for clinical management.

7.7 Safety Follow-up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of study treatment or before the initiation of a new anti-cancer treatment, whichever comes first. This visit may be done by telephone call or virtual visit as needed. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Participants with an AE of Grade >1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-cancer therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

8.0 Treatment Modification Based on Adverse Events

Strictly follow the modifications in this section for the first **two** cycles, until individual treatment tolerance can be ascertained. Thereafter, these modifications should be regarded as guidelines to manage mild-to-moderate, but not debilitating, side effects. If multiple adverse events are seen, administer dose based on greatest modification required for any single adverse event observed.

Special Considerations

- The treating investigator may modify/withhold/continue a patient's treatment for an AE of any grade/duration where s/he believes it to be in the best interests of the patient.
- Any consideration to modification of the above treatment modification guidelines should be discussed with the Principal Investigator for approval or disapproval in advance and documented in the patient's medical/clinical record.

→ ***ALERT:*** ***ADR reporting may be required for some adverse events (See Section 10.0)*** ←

8.1 Starting Dose Levels

Dose Level	Pembrolizumab*	Pemetrexed**
1	200 mg	500 mg/m^2

* There are no dose modifications for pembrolizumab

**Pemetrexed dose may be modified/omitted per clinical practice

NOTE: If either pembrolizumab or pemetrexed is discontinued, the patient can continue on the other drug, unless specified otherwise in the dose modification tables. If both are discontinued, the patient will go to survival follow-up/event monitoring (Section 4.2).

→ → ***Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) current version 5.0* unless otherwise specified*** ← ←

[redacted]

8.2 Treatment Modifications for Pembrolizumab and Combination Therapy

- See Section 9.0 for supportive care guidelines for irAEs listed below
- Pembrolizumab 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 pembrolizumab treatment.
- The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
- If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper

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 below.

CTCAE System/Organ/ Class (SOC)	Adverse Event	Hold Treatment for Grade	Timing for Restarting Treatment*	Treatment Discontinuation
Cardiac disorders	Myocarditis	Grade 1	Hold until AE resolves to Grade 0	Permanently discontinue if AE does not resolve rapidly with treatment
		Grade 2-4	Permanently discontinue	Permanently discontinue
Endocrine disorders	Adrenal insufficiency	Grade 2-4	Hold for new onset Resume when patients are clinically and metabolically stable at investigator's discretion	
Endocrine disorders	Hyperthyroidism	Grade 3 or 4	Hold or permanently discontinue at investigator's discretion	Hold or permanently discontinue at investigator's discretion
Endocrine disorders	Hypothyroidism	Grade 3 or 4	Hold until patient is metabolically stable. Then hold or permanently discontinue at investigator's discretion	Hold or permanently discontinue at investigator's discretion
Endocrine disorders	Endocrine disorders – Other, specify: Hypophysitis	Grade 2	Hold	
		Grade 3 or 4	Hold or permanently discontinue at investigator's discretion	Hold or permanently discontinue at investigator's discretion

CTCAE System/Organ/ Class (SOC)	Adverse Event	Hold Treatment for Grade	Timing for Restarting Treatment*	Treatment Discontinuation
Gastrointestinal disorders	Colitis or Diarrhea or Colonic perforation	Grade 2 or 3	Hold until AE resolves to Grade 0-1 See Section 9.0 for supportive care	Permanently discontinue if AE does not resolve to Grade 0-1 within 14 days
		Recurrent Grade 3 Grade 4	Permanently discontinue	Permanently discontinue
General disorders and administration site conditions	Infusion reaction	Grade 1	Interruption is not indicated Increase monitoring See Section 9.0 for more details	
		Grade 2	Temporarily interrupt until resolution If within 1 hour may restart at 50% of initial infusion rate See Section 9.0 for more details	Permanently discontinue if AE recurs despite adequate premedication See Section 9.0 for more details
		Grade 3 or 4	Permanently discontinue	Permanently discontinue
Investigations	Alanine aminotransferase (ALT) increased, or Aspartate aminotransferase (AST) increased or Blood bilirubin increased	Grade 2	Hold until AE resolves to Grade 0-1	Permanently discontinue if AE does not resolve within 6 weeks of last dose
		Grade 3 or 4	Permanently discontinue	Permanently discontinue
Investigations	Creatinine increased	Grade 2	Hold until AE resolves to Grade 0-1	Permanently discontinue if AE does not resolve within 6 weeks of last dose
		Grade 3 or 4	Permanently discontinue	Permanently discontinue
Metabolism and nutrition disorders	Glucose intolerance (Type 1 diabetes mellitus [if new onset]) or Hyperglycemia	T1DM or Grade 3 or 4	Hold for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure Resume when patients are clinically and metabolically stable (at investigator discretion)	

CTCAE System/Organ/ Class (SOC)	Adverse Event	Hold Treatment for Grade	Timing for Restarting Treatment*	Treatment Discontinuation
Nervous system disorders	Guillain-Barre syndrome or Myasthenia gravis or Other nervous system disorders	Grade 2	Hold until AE resolves to Grade 0-1	Permanently discontinue if AE does not resolve within 6 weeks of last dose
		Grade 3-4	Permanently discontinue	Permanently discontinue
Renal and urinary disorders	Acute kidney injury or Chronic kidney disease (e.g. Renal Failure or Nephritis)	Grade 2	Hold until AE resolves to Grade 0-1	Permanently discontinue if AE does not resolve within 6 weeks of last dose
		Grade 3 or 4	Permanently discontinue	Permanently discontinue
Respiratory, thoracic and mediastinal disorders	Pneumonitis	Grade 2	Hold until AE resolves to Grade 0-1 Decision to reinitiate will be based on treating physician's clinical judgment and after completion of steroid taper (if needed)	Permanently discontinue if AE does not resolve within 6 weeks of last dose
		Recurrent Grade 2 Grade 3 or 4	Permanently discontinue	Permanently discontinue
Skin and subcutaneous tissue disorders	Stevens-Johnson syndrome (SJS) or Toxic epidermal necrolysis (TEN) or Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) [or other exfoliative skin conditions	Suspected	Hold until AE resolves to Grade 0-1	Permanently discontinue if AE does not resolve within 6 weeks of last dose
		Confirmed	Permanently discontinue	Permanently discontinue

CTCAE System/Organ/ Class (SOC)	Adverse Event	Hold Treatment for Grade	Timing for Restarting Treatment*	Treatment Discontinuation
	All Other **Immune-Related** Adverse Events	Persistent Grade 2	Hold at physician discretion	Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose
		Grade 3	Hold or discontinue based on the type of event Events that require discontinuation include and are not limited to encephalitis, myelitis, vasculitis, sclerosing cholangitis	Permanently discontinue if AE does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
		Recurrent Grade 3 Grade 4	Permanently discontinue	Permanently discontinue
	All Other **NON-Immune-Related** Adverse Events	Grade 2	Hold until AE resolves to Grade 0-1	Permanently discontinue of AE does not resolve to Grade 0-1 within 14 days
		Grade 3	Hold until AE resolves to Grade 0-1 Resume if AE resolves to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days	Permanently discontinue of AE does not resolve within 14 days
		Grade 4	Discontinue (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor)	Permanently discontinue

8.21 Other allowed dose interruption for pembrolizumab

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

8.3 Suggested Treatment Modifications for Pemetrexed

Follow institutional guidelines for pemetrexed treatment modifications.

9.0 Ancillary Treatment/Supportive Care

9.1 Full supportive care

Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.2 Blood products and growth factors

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the Journal of Clinical Oncology, Volume 33, No 28 (October 1), 2015: pp. 3199-3212 (WBC growth factors) AND Journal of Clinical Oncology, Volume 28, No 33 (November 20), 2010: pp. 4955-5010 (darbepoetin/epoetin).

9.3 Antiemetics

Antiemetics may be used at the discretion of the attending physician.

NOTE: Steroids should not be used solely as prophylactic antiemetic therapy on this protocol.

9.4 Hypersensitivity reaction

Patients do not require premedication prior to study treatment, as hypersensitivity reaction is not expected. In the unlikely event of a hypersensitivity reaction, treatment with antihistamines, H2 blockers, and corticosteroids is recommended. Patients should be pre-medicated with the typical regimen for subsequent cycles.

If anaphylaxis is suspected, follow institutional guidelines, including discontinuing treatment infusion and instituting appropriate supportive measures.

9.5 Concurrent enrollment in other studies

Patients may not enroll in a different clinical study, including Cancer Control studies, in which investigational procedures or agents are being used, while participating in this study.

9.6 Concurrent radiation therapy

Patients must terminate study treatment if they are to receive radiation therapy for palliative reasons as it impacts evaluation of study endpoints.

9.7 General patient monitoring and supportive care guidelines

9.71 Patients should be carefully monitored during the treatment phase and then followed appropriately. Decisions for retreatment or dose modifications/interruption should follow the guidelines in Sections 8.2-8.3.

9.72 Patients who have an ongoing study agent-related serious adverse event upon study completion or at discontinuation from the study will be contacted by the treating physician or his/her designee at least every 2 weeks until the event is resolved or determined to be irreversible.

9.8 Side effect management for immune-related adverse events

These are to be regarded as guidelines for managing adverse events that occur with therapy and should not replace clinical judgement (e.g., patients with Grade 1 rash may require systemic steroids).

General recommendations.

Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events.

For persistent (>3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.

Some events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Consider, as necessary, discussing with the study physician, and promptly pursue specialist consultation.

If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [e.g., up to 2 to 4 mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (>28 days of taper).

More potent immunosuppressives such as TNF inhibitors (e.g., infliximab;) (also refer to the individual sections of the imAEs below for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when these events are not responding to systemic steroids.

With long-term steroid and other immunosuppressive use, consider need for Pneumocystis jirovecii pneumonia (PJP, formerly known as Pneumocystis carinii pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring.

Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (e.g., inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug/study regimen in this situation should be based upon a benefit-risk analysis for that patient.

9.81 Diarrhea/Colitis

All events of diarrhea or colitis should be thoroughly evaluated for more common etiologies other than drug-induced effects.

- For events of significant duration or severity or associated with signs of systemic inflammation or acute-phase reactants, check for immune-related colitis.

9.811 Grade 1- without abdominal pain/or blood in stool and symptoms. Infectious etiologies should be ruled out. Discontinue medications that may exacerbate colitis (e.g., NSAIDS) while investigating etiology. Patients may be managed symptomatically. Instruct patients to report any increase in stools.

9.812 Grade 2- without abdominal pain/or blood in stool and symptoms <1 week, and resolve to Grade 0 or 1. Continue to monitor. Infectious etiologies should be ruled out. Discontinue medications that may exacerbate colitis (e.g., NSAIDS) while investigating etiology.

9.813 Grade 2- symptoms >1 week, should be started on steroid therapy – first choice is budesonide at 12 mg once daily (if unable to obtain budesonide and/or patent continues to have diarrhea after 72 hours of use start systemic steroids at 0.5 mg/kg/day prednisone or equivalent- can be given in two doses- especially for patients that have nocturnal diarrhea).** Infectious etiologies should be ruled out. Discontinue medications that may exacerbate colitis (e.g., NSAIDS) while investigating etiology.

9.814 Grade 3 or greater- who have other etiologies ruled out should be started on systemic steroids at 1-2 mg/kg/day prednisone or equivalent (may be given in two daily doses-especially for patients that have nocturnal diarrhea).** Assess for dehydration. Patients may require hospitalization for IV steroids (1-2 mg/kg/day methylprednisolone). Discontinue medications that may exacerbate colitis (e.g., NSAIDS) while investigating etiology.

** Once patients have improvement of symptoms to Grade 0 or 1 taper of steroids should occur over at least 1 month. If patients have been started on budesonide in addition to systemic steroids, start tapering the prednisone FIRST.

Do NOT administer loperamide in patients with ≥Grade 2 diarrhea as this may cause toxic megacolon and/or perforation.

If at any time patients experience diarrhea with the following symptoms: fever or abdominal pain patients should have a CT scan of the abdomen to rule out perforation. Emergent surgical evaluation should be performed if

perforation is found. If a patient has bloody diarrhea, a Gastroenterology consult should be obtained. A Gastroenterology consult should be obtained if provider is considering infliximab for treatment of colitis.

For all patients- assess hydration status and monitor electrolytes, including magnesium.

9.82 Infusion Related Reactions

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 9.821.

9.821 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 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	**Stop Infusion** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilator support indicated	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 **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 [redacted]		

9.83 Hyperthyroidism

Hyperthyroidism is usually self-limiting, short-lived, and does not require intervention, unless symptomatic (e.g. tachycardia). If patient experiences tachycardia, treatment with low-dose beta blockade would be indicated. Refer patient to Endocrinology.

9.84 Hypothyroidism

Isolated hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids.

9.85 Immune-Mediated Hypophysitis/Adrenal Insufficiency

Refer patient to Endocrinology for treatment and monitoring.

9.86 Pneumonitis

Mild- to-moderate events of pneumonitis have been reported. All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia/infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. For events of pneumonitis, consider comprehensive infectious evaluation including viral etiologies.

9.861 Grade 1: No change in treatment

9.862 Grade 2: Initiate steroids at 0.5-1 mg/kg/day of prednisone or equivalent.

9.863 Grade 3 or greater: Consider hospitalization, and initiate systemic steroids

9.87 Liver Dysfunction

AST or ALT	Total Bilirubin	Action
≤3 x ULN	<2 x ULN	No change in treatment
>3 but <5 x ULN (Grade 2)	<2 x ULN	Initiate systemic steroids at 0.5-1mg/kg/day of prednisone or equivalent Monitor LFTs at least weekly and consider referral to Hepatology/biopsy

AST or ALT	Total Bilirubin	Action
≥5-10 x ULN (≥Grade 3)	<2 x ULN	Initiate systemic steroid therapy at 1-2 mg/kg/day of prednisone or equivalent Monitor LFTs at least weekly and consider referral to Hepatology/for biopsy
≤10 x ULN	≥2 x ULN	Initiate intravenous corticosteroids 1-2 mg/kg/day methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent with improvement If no improvement within 48 hours consider addition of immunosuppressive agent Monitor LFTs at least every other day

9.9a Contraception

The treatments used in this study may have adverse effects on a fetus in utero. Furthermore, it is not known if the treatment has transient adverse effects on the composition of sperm.

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

Female patients will be considered of non-reproductive potential if they are (one of the following):

(1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women <45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

(2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

(3) have a congenital or acquired condition that prevents childbearing.

Female and male patients of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 6 months after the last dose of study drug by complying with one of the following:

(1) practice abstinence† from heterosexual activity;

OR

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

Acceptable methods of contraception are‡:
Single method (one of the following is acceptable):
- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of two of the following):
- diaphragm with spermicide (cannot be used in conjunction with cervical

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

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

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

Patients should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study patients of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 5 months after the last dose of trial therapy. If there is any question that a patient of childbearing potential will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

9.9b Use in Pregnancy and Nursing

If a patient inadvertently becomes pregnant while on treatment on this study, the patient will immediately be removed from the study. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Mayo Clinic without delay and within 24 hours to Mayo Clinic 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. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to Mayo Clinic and followed as described above.

Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, patients who are breast-feeding are not eligible for enrollment

9.9c Concomitant Medications

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.

9.9c1 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. Concomitant medications administered after 30 days after the last dose of trial intervention should be recorded for SAEs and ECIs as defined in Section 7.2.

9.9c2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- In patients with creatinine clearances between 45 mL/min and 79 mL/min, modify administration of ibuprofen as follows
  1) Avoid administration of ibuprofen for 2 days before, the day of, and 2 days following administration of pemetrexed
  2) Monitor patients more frequently for myelosuppression, renal, and gastrointestinal toxicity, if concomitant administration of ibuprofen cannot be avoided
- Radiation therapy
  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of 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.

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

10.0 Adverse Event (AE) Monitoring and Reporting

The site principal investigator is responsible for reporting any/all serious adverse events to the sponsor/sponsor-investigator as described within the protocol, regardless of attribution to study agent or treatment procedure.

The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug
- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).

Summary of SAE Reporting for this study
(please read entire section for specific instructions):

WHO:	WHAT form:	WHERE to send:
Mayo Clinic Sites	[redacted]	[redacted]
Mayo Clinic Sites	[redacted]	[redacted]

Reminder: All SAE reports submitted to the FDA must include the batch and lot number of the most recent dose (last dose received) of study drug(s). Check with the pharmacist to obtain this information if needed.

Definitions

Adverse Event
Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction
Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting
Events reported to sponsor within 24 hours, 5 days, or 10 days of study team becoming aware of the event.

Routine Reporting
Events reported to sponsor via case report forms

Events of Interest
Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0 A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site:
[redacted]

a. Identify the grade and severity of the event using the CTCAE version 5.0.
b. Determine whether the event is expected or unexpected (see Section 10.2).
c. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).
d. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).
e. Determine if other reporting is required (see Section 10.5).
f. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Section 10.6).

NOTE: A severe AE is NOT the same as a serious AE, which is defined in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.

An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.

NOTE: *The consent form may contain study specific information at the discretion of the Principal Investigator; it is possible that this information may NOT be included in the protocol or the investigator brochure. Refer to protocol or IB for reporting needs.

10.3 Attribution to agent(s) or procedure

When assessing whether an adverse event (AE) is related to a medical agent(s) medical or procedure, the following attribution categories are utilized:

Definite - The AE *is clearly related* to the agent(s)/procedure.
Probable - The AE *is likely related* to the agent(s)/procedure.
Possible - The AE *may be related* to the agent(s)/procedure.
Unlikely - The AE *is doubtfully related* to the agent(s)/procedure.
Unrelated - The AE *is clearly NOT related* to the agent(s)/procedure.

10.31 AEs Experienced Utilizing Investigational Agents and Commercial Agent(s) on the SAME (Combination) Arm

NOTE: When a commercial agent(s) is (are) used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other investigational therapy under an IND), the **entire combination (arm) is then considered an investigational intervention for reporting.**

- An AE that occurs on a combination study must be assessed in accordance with the guidelines for **investigational** agents/interventions.
- An AE that occurs prior to administration of the investigational agent/intervention must be assessed as specified in the protocol. In general, only Grade 4 and 5 AEs that are unexpected with at least possible attribution to the commercial agent require an expedited report, unless hospitalization is required. Refer to Section 10.4 for specific AE reporting requirements or exceptions.

An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.

- An increased incidence of an expected adverse event (AE) is based on the patients treated for this study at their site. A list of known/expected AEs is reported in the package insert or the literature, including AEs resulting from a drug overdose.

10.32 EXPECTED Serious Adverse Events: Protocol Specific Exceptions to Expedited Reporting

For this protocol only, the following Adverse Events/Grades are expected to occur within this population and do not require Expedited Reporting. These events must still be reported via Routine Reporting (see Section 10.6).*

*Report any clinically important increase in the rate of a serious suspected adverse reaction (at your study site) over that which is listed in the protocol or investigator brochure as an expedited event.

*Report an expected event that is greater in severity or specificity than expected as an expedited event.

*Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event.

CTCAE System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be reported in an expedited manner[1]
Blood and lymphatic system disorders	Anemia	≤Grade 4
General disorders and administration site conditions	Fatigue	≤Grade 3
	Malaise	≤Grade 3
Investigations	Lymphocyte count decreased	≤Grade 4
	Neutrophil count decreased	≤Grade 4
	Platelet count decreased	≤Grade 4
	White blood cell count decreased	≤Grade 4
Skin and subcutaneous tissue disorders	Rash maculopapular	≤Grade 4

[1] These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (*i.e.*, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for elective procedures unrelated to the current disease and/or treatment on this trial
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (*e.g.*, battery replacement) that was in place before study entry
- Hospitalization, or other serious outcomes for signs and symptoms of progression of the cancer.

10.4 Expedited Reporting Requirements for IND Agents

10.41 Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the sponsor within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥24 hrs</td><td colspan="3">7 Calendar Days</td><td rowspan="2">24-Hour 3 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥24 hrs</td><td colspan="2">Not required</td><td>7 Calendar Days</td></tr>
</table>

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

NOTE: Refer to Section 10.32 for exceptions to Expedited Reporting

10.42 General reporting instructions

The Mayo IND and/or MCCC Compliance will assist the sponsor-investigator in the processing of expedited adverse events and forwarding of suspected unexpected serious adverse reactions (SUSARs) to the FDA and IRB.

Use Mayo Expedited Event Report form [redacted] or investigational agents or commercial/investigational agents on the same arm.

10.43 Reporting of re-occurring SAEs

ALL SERIOUS adverse events that meet the criteria outlined in Table 10.41 MUST be immediately reported to the sponsor within the timeframes detailed in the corresponding table. This reporting includes, but is not limited to SAEs that re-occur again after resolution.

10.5 Other Required Reporting

10.51 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS)

Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

Note: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects should not get pregnant/impregnate others, then any pregnancy in a subject/patient or a male patient's partner (spontaneously reported) which occurs during the study or within 120 days of completing the study should be reported as a UPIRTSO.

Mayo Clinic Cancer Center (MCCC) Institutions:

If the event meets the criteria for IRB submission as a Reportable Event/UPIRTSO, provide the appropriate documentation and use the Mayo Clinic Cancer Center Expedited Event Report form [redacted] o submit to

[redacted] The Mayo Clinic Compliance Unit will review and process the submission to the Mayo Clinic IRB and work with the IND Coordinator for submission to FDA.

10.52 Death

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND requires expedited reporting within 24-hours.

Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND requires expedited reporting within 24-hours.

Reportable categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease that cannot be attributed to a CTCAE term associated with Grade 5 should be reported as **Grade 5 "Disease progression"** under the system organ class (SOC) of General disorders and administration site conditions. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.53 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
- All secondary malignancies that occur following treatment with an agent under an IND will be reported. Three options are available to describe the event:
  - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])
  - Myelodysplastic syndrome (MDS)
  - Treatment-related secondary malignancy
- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.54 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is

NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting unless otherwise specified.

10.55 Pregnancy, Lactation, Fetal Death, and Death Neonatal

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

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

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

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

If a female subject (or female partner of a male subject) taking investigational product becomes pregnant, the subject taking should notify the Investigator, and the pregnant female should be advised to call her healthcare provider immediately. The patient should have appropriate follow-up as deemed necessary by her physician. If the baby is born with a birth defect or anomaly, a second expedited report is required.

Prior to obtaining private information about a pregnant woman and her infant, the investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian before any data collection can occur. A consent form will need to be submitted to the IRB for these subjects if a pregnancy occurs. If informed consent is not obtained, no information may be collected.

In cases of fetal death, miscarriage or abortion, the mother is the patient. In cases where the child/fetus experiences a serious adverse event other than fetal death, the child/fetus is the patient.

NOTE: When submitting Mayo Expedited Adverse Event Report reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section. Include any available medical documentation. Include this form: [redacted]

10.551 Pregnancy

Pregnancy should be reported in an expedited manner as **Grade 3 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy)"** under the Pregnancy, puerperium and perinatal conditions SOC. Pregnancy should be followed until the outcome is known.

10.552 Fetal Death

Fetal death is defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation."

Fetal loss at any gestational age should be reported expeditiously, as **Grade 4 "Pregnancy loss" under the SOC of "Pregnancy, puerperium and perinatal conditions""** under the Pregnancy, puerperium and perinatal conditions SOC.

10.553 Death Neonatal

Neonatal death, defined in CTCAE as "Newborn death occurring during the first 30 days after birth" that is felt by the investigator to be at least possibly due to the investigational agent/intervention.

A neonatal death should be reported expeditiously as **Grade 4 "Death neonatal" under the SOC of General disorders and administration site conditions**.

10.56 Other Reporting Required for Merck

10.561 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

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:
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

10.6 Required Routine Reporting

10.61 Baseline and Adverse Events Evaluations

Pretreatment symptoms/conditions to be graded at baseline and adverse events to be graded at each evaluation.
Grading is per CTCAE v5.0 **unless** alternate grading is indicated in the table below:

CTCAE SYSTEM/ORGAN/CLASS	Adverse event/Symptoms	Baseline	Each evaluation
Blood and lymphatic system disorders	Febrile neutropenia	X	X
General disorders and administration site conditions	Fatigue	X	X
Gastrointestinal Disorders	Nausea	X	X
	Vomiting	X	X
	# of Stools	X	
	Diarrhea		X
Investigations	Creatinine increased	X	X
	Neutrophil count decreased	X	X
	Platelet count decreased	X	X
Skin and subcutaneous tissue disorders	Rash, maculo-papular	X	X

10.62 All other AEs including Events of Clinical Interest

Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.6:

10.621 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.622 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.623 Grade 5 AEs (Deaths)

10.6231 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.6232 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly

treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.624 Overdose (Event of Clinical Interest)

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the patient 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 (pembrolizumab), the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

All reports of overdose with and without an adverse event must be reported (as described in Section 10.42) within 24 hours to Mayo Clinic [redacted] and within 2 working days hours to Merck Global Safety. [redacted]

10.625 Elevated Liver Enzymes (Event of Clinical Interest)

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 are to specify a threshold of abnormal hepatic tests that may require additional evaluation for an underlying etiology.

10.7 Late Occurring Adverse Events

Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

10.8 Merck Additional Event Reporting Instructions

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.

10.81 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.

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

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 Section 10.56

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

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

Merck product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by Merck for human use.

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

All AEs, SAEs and other reportable safety events that occur after the consent form is signed but before treatment 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 treatment allocation/randomization through 30 days following cessation of study treatment must be reported by the investigator.
- All AEs meeting serious criteria, from the time of treatment allocation/randomization through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator.

● All pregnancies and exposure during breastfeeding, from the time of treatment allocation/randomization through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the 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 by the investigator if the event is considered to be drug-related.

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study 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 treatment or study participation, the investigator must promptly notify Merck.

10.83 Immediate Reporting of Adverse Events to the Sponsor and to Merck

Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Merck's product that:

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

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

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

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause that occurs to any participant must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside

of the time period specified in the previous paragraph also must be reported immediately to Merck Global Safety.

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

SAE reports and any other relevant safety information are t [redacted]

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

10.84 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

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

11.0 Treatment Evaluation/Measurement of Effect

NOTE: This study uses protocol RECIST v1.1 template dated 2/16/2011. See the footnote for the table regarding measureable disease in Section 11.44, as it pertains to data collection and analysis.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1) [23] Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline.

11.1 Schedule of Evaluations

For the purposes of this study, patients should be reevaluated every 9 weeks (i.e. every 3 cycles). In addition to a baseline scan, confirmatory scans should also be obtained at least 4 weeks following initial documentation of objective response.

11.2 Definitions of Measurable and Non-Measurable Disease

11.21 Measurable Disease

11.211 A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥2.0 cm with chest x-ray, or as ≥1.0 cm with CT scan, CT component of a PET/CT, or MRI.

11.212 A superficial non-nodal lesion is measurable if its longest diameter is ≥1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.213 A malignant lymph node is considered measurable if its short axis is ≥1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

NOTE: Tumor lesions in a previously irradiated area are not considered measurable disease.

11.22 Non-Measurable Disease

All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥1.0 to <1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.

Note: 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis <1.0 cm are considered non-pathological (i.e., normal) and should not be recorded or followed.

11.3 Guidelines for Evaluation of Measurable Disease

11.31 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to

characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.

- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.32 Acceptable Modalities for Measurable Disease:

- Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.
- As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.
- PET-CT: If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.
- FDG-PET: FDG-PET scanning is allowed to complement CT scanning in assessment of progressive disease [PD] and particularly possible 'new' disease. A ‘positive’ FDG-PET scanned lesion is defined as one which is FDG avid with an update greater than twice that of the surrounding tissue on the attenuation corrected image; otherwise, an FDG-PET scanned lesion is considered ‘negative.’ New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  a. Negative FDG-PET at baseline with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  b. No FDG-PET at baseline and a positive FDG-PET at follow-up:
     i. If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
     ii. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT at the same evaluation, additional follow-up CT scans (i.e., additional follow-up scans at least 4 weeks later) are needed to determine if there is truly progression occurring at that site. In this situation, the date of PD will be the date of the initial abnormal PDG-PET scan.
     iii If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, it is not classified as PD.

11.33 Measurement at Follow-up Evaluation:

- A subsequent scan must be obtained at least 4 weeks following initial

documentation of an objective status of either complete response (CR) or partial response (PR).

- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks (see Section 11.44).
- The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.
- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

11.4 Measurement of Effect

11.41 Target Lesions & Target Lymph Nodes

- Measurable lesions (as defined in Section 11.21) up to a maximum of 5 lesions, representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. These lesions can be non-nodal or nodal (as defined in 11.21), where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

  Note: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.
- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.
- Baseline Sum of Dimensions (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.
- Post-Baseline Sum of the Dimensions (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.
- The minimum sum of the dimensions (MSD) is the minimum of the BSD and the PBSD.

11.42 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease (Section 11.22) are classified as non- target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with 11.433.

11.43 Response Criteria

11.431 All target lesions and target lymph nodes followed by CT/MRI/PET-CT/Chest X-ray/physical examination must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

11.432 Evaluation of Target Lesions

Complete Response (CR):	All of the following must be true: a. Disappearance of all target lesions. b. Each target lymph node must have reduction in short axis to <1.0 cm.
Partial Response (PR):	At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (*see* Section 11.41).
Progression (PD):	At least one of the following must be true: a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (<1.0 cm short axis) and increased to ≥1.0 cm short axis during follow-up. b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.41). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD. c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

11.433 Evaluation of Non-Target Lesions & Non-target Lymph Nodes

Complete Response (CR): All of the following must be true:
a. Disappearance of all non-target lesions.
b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.

Non-CR/Non-PD: Persistence of one or more non-target lesions or non-target lymph nodes.

Progression (PD): At least one of the following must be true:
a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (<1.0 cm short axis) and increased to ≥1.0 cm short axis during follow-up.
b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)
c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

11.44 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following table:

Target Lesions & Target Lymph Nodes	**Non-Target Lesions & Non-Target Lymph Nodes**	**New Sites of Disease**	**Overall Objective Status**
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR**
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD

Target Lesions & Target Lymph Nodes	Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

*See Section 11.431

** NOTE: This study uses the protocol RECIST v1.1 template dated 2/16/2011. For data collection and analysis purposes the objective status changed from SD to PR in the NCCTG protocol RECIST v1.1 template as of 2/16/2011 and to match RECIST v1.1 requirements.

11.45 Symptomatic Deterioration

Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration. A patient is classified as having PD due to "symptomatic deterioration" if any of the following occur that are not either related to study treatment or other medical conditions:

- Weight loss >10% of body weight.
- Worsening of tumor-related symptoms.
- Decline in performance status of >1 level on ECOG scale.

12.0 Descriptive Factors

12.1 Prior treatments for this cancer: 1 vs. 2 vs. 3+

12.2 Prior immunotherapy: Yes vs. no vs. unknown

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Continuation of treatment

Patients who are CR, PR, or SD will continue treatment per protocol.

13.2 Progressive disease (PD)

Patients who develop PD while receiving therapy will go to the survival follow-up phase/event monitoring.

13.3 Off protocol treatment

Patients who go off protocol treatment for reasons other than PD will go to the survival follow-up/event-monitoring phase per Section 4.0.

13.4 CNS PD

Patients who develop PD in the CNS only should receive clinically appropriate radiotherapy, and may resume treatment on study after completion, if clinically appropriate.

13.5 Ineligible

A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. If the patient received treatment, the patient may continue treatment at the discretion of the physician as long as there are not safety concerns. The patient will continue in the Active Monitoring/Treatment phase of the study, per Section 4.0 of the protocol.

- If the patient never received treatment, on-study material and the End of Protocol Treatment Form must be submitted. No further data submission is necessary and no further follow-up required.

13.6 Major violation

A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. If the patient received treatment, the patient may continue treatment at the discretion of the physician as long as there are not safety concerns. The patient will continue in the Active Monitoring/Treatment phase of the study, per Section 4.0 of the protocol.

13.7 Cancel

A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Protocol Treatment Form must be submitted. No further data submission is necessary.

13.8 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a participant initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the participant will move into survival follow-up/event monitoring per Section 4.0.

14.0 Body Fluid Biospecimens

14.1 Summary Table of Research Blood and Body Fluid Specimens to be Collected for this Protocol

Research	Specimen Purpose (check all that apply)	Mandatory or Optional	Blood or Body Fluid being Collected	Type of Collection Tube (color of tube top)	Volume to collect per tube (# of tubes to be collected)	Baseline prior to treatment	End of every third cycle[2]	End of treatment for any reason[1]	Process at site? (Yes or No)	Temperature Conditions for Storage /Shipping
Immune profiling	☒ Correlative	Mandatory	Whole blood	NaHep (green)	10 ml (1)	X	X	X	No	Ship refrigerated
cfDNA	☒ Correlative	Mandatory	Whole blood	Streck	10 ml (2)	X	X	X	No	Ship ambient
DNA, buffy coat, plasma	☒ Banking	Mandatory	Whole blood	EDTA (lavender)	10 ml (1)	X			No	Ship refrigerated
PSMA EV Cohort A1 (Rochester only)	Correlative	Mandatory	Whole blood	EDTA	10 mL	X	X	X	Yes	BAP to process per 14.23

[1]Samples at end of treatment are requested, and if patient refuses, there is no protocol deviation.

[2]Samples should be obtained at time of imaging at end of every third cycle

NOTE: All specimens collected outside of Rochester, MN, will be shipped overnight to BAP in Rochester for processing and storage.

14.2 Collection and Processing

14.21 Collection

14.212 Mayo Clinic Rochester Campus: Samples may be collected Monday-Friday. Internal transport of specimens will be at room temperature.

14.213 AZ/FL Sample collection should be restricted to **Monday – Thursday**. However, if the subject can only be seen on a Friday, please contact the Biospecimen Resource Manager for additional instructions (see Protocol Resources for contact information).

14.22 Specimen tube(s) must be labeled with the protocol number, study patient ID number, and the time and date of the blood draw.

14.23 Blood/blood products must be collected and shipped according to specific instructions provided in the kit and the table above.

14.21 Immune profiling

Using the kit provided by BAP at each site, AZ and FL sites will ship whole blood refrigerated overnight to BAP at Mayo Clinic in Rochester, MN for future processing.

14.22 Banking

Using the kit provided by BAP at each site, AZ and FL sites will ship whole blood ambient overnight to Mayo Clinic in Rochester, MN.

Send to:

14.23 PSMA EVs (Rochester only)

Samples will be processed through BAP according to Urology Research RLIMS instructions:

M-PPP

EXPDT. Ambient Centrifuge at 2500xg for 15 min

Aliquot 4.5 mL of plasma into (1) intermediate vial.

Ambient Centrifuge intermediate at 2500xg for 15 min to create PPP.

Aliquot PPP into the following:

- 4: 1mL

Freeze -80C

Contact [redacted] for DOC frozen pickup.

(1 Intermediate - 4 PPP children per parent tube)

14.3 Shipping and Handling

Mayo Clinic Arizona/Florida Campus: Ship on same day drawn **Monday-Thursday** for arrival Tuesday-Friday in Rochester

14.31 Kits will be used for this study for sites outside of Rochester, MN.

14.311 Kits will be supplied by the Biospecimen Accessioning and Processing Shared Resource (BAP) at each site.

14.312 The kit contains supplies and instructions for collecting, processing and shipping specimens.

14.313 Participating institutions may obtain kits byordering them directly from BAP. Because we are charged for all outgoing kits, a small, but sufficient, supply of the specimen collection kits should be ordered prior to patient entry.

14.314 Kits will be sent via Fed Ex® Ground at no additional cost to the participating institutions. **Allow at least two weeks to receive the kits.**

14.315 Kits will not be sent via rush delivery service unless the participating institution provides their own Fed Ex® account number or alternate billing number for express mail. **Cost for rush delivery of kits will not be covered by the study.**

14.316 All specimens must be collected and shipped Monday – Thursday ONLY.

14.32 Shipping Specimens

14.321 Mayo Clinic Rochester samples will be routed through BAP for lab pickup.

14.322 All other sites will use kits as described in Section 14.31, shipped to BAP Mayo Clinic in Rochester

Specimens collected at sites other than Rochester, MN, will be stored at 4°C after acquisition until packaged for shipping.

Specimens will be shipped the same day as they are acquired.

For packaging, blood collection tubes will be placed in a plastic bag, then packed in a Styrofoam box containing dry ice.

14.33 Handling Specimens (once received in destination laboratory)

NOTE: BAP Shared Resource (MN) will process the specimens including prepping PBMCs for immune profiling (Immune Monitoring Core – Jolaine Hines/Kevin Pavelko PhD)

14.361 PBMC Handling and Isolation
Patient donors will provide 10 mL of whole blood drawn into a green top heparin tube. The whole blood sample will be layered over Ficoll-Paque for enrichment of peripheral blood mononuclear cells (PBMC). After centrifugation of the sample at 1500g, the enriched PBMC cells are washed with RPMI media. After washing with PBS cells are counted and prepared for cryopreservation. Cells are resuspended in cryopreservation media (10% DMSO in RPMI supplemented with fetal bovine serum and a penicillin streptomycin glutamine cocktail). Controlled rate freezing methods are then used to freeze the samples prior to storage in liquid nitrogen.

14.362 Sample Thawing and Preparation for Mass Cytometry

Cells will be thawed and resuspended in complete media (RPMI supplemented with fetal bovine serum) containing 2.5 units/mL of Benzonase Nuclease (Sigma-Aldrich). After washing, cells are rested for 1 hour in complete media at 37°C before staining. After resting $4x10^6$ cells are resuspended in 1 mL of CSB. FcR-block will be added to block non-specific staining due to Fc receptor antibody interactions. Each sample will then be incubated for 5 minutes with 0.5 μm Cisplatin solution in PBS. Cells are then transferred to the 5 mL tubes containing the dry antibody pellet cocktail (Table 1). Samples are then incubated at room temperature for 30 minutes. After washing twice with CSB, samples are then fixed with 2% PFA in PBS. After fixation and wash, samples are resuspended in 30 nM intercalation solution and incubated overnight at 4°C. On the following morning cells are washed with PBS and pooled prior to resuspension in a 1:10 solution of calibration beads and cell acquisition solution at a concentration of $0.5x10^6$ cells/mL. Prior to data acquisition samples were filtered through a 35 μm blue cap tube (Falcon).

14.363 Mass Cytometry and Data Acquisition
The prepared samples are loaded onto a Helios CyTOF® system (Fluidigm) using an attached autosampler and cellular events are acquired at a rate of 200-400 events per second. Data are collected as .FCS files using the Cytof software (Version 6.7.1014). After acquisition intrafile signal drift is normalized to the acquired calibration bead signal using the Cytof software. File cleanup and analysis will be performed using the Pathsetter software (Verity Software House) cleanup protocol.

14.364 PSMA

Our study will collect blood for platelet-free plasma (PPP). Plasma will be aliquoted (0.5 ml) and frozen, then transferred to Urology Research and stored in a -80ºC freezer with access card lock.

14.37 Double spun, platelet poor plasma will be derived from the Streck cfDNA BCT tubes using established laboratory processes, and stored at ≤-65ºC by BAP.

14.38 For banking: DNA will be extracted from whole blood, and white blood cells and plasma will be derived from remaining blood from the EDTA tubes, divided into aliquots, and stored at ≤-65ºC by BAP according to patient consent information.

14.39a As part of ongoing research at the Mayo Clinic, we will retain residual whole blood, white blood cells, CTCs, DNA, and plasma for future research studies, according to patient consent information. Samples will be stored until specific analyses are identified and may be used for exploratory biomarker analyses, validation studies, or potential diagnostic development. As protocols are developed, they will be presented for IRB review and approval.

14.4 Background and Methodology

Each potential biomarker will be evaluated in consideration of the observed clinical responses.

14.41 Immune Profiling

14.411 Mass Cytometry (CyTOF)

Maxpar ® Direct Immune Profiling System provides a comprehensive evaluation and analysis tool for assessing the abundance and phenotypic characteristics of peripheral mononuclear cells (PBMC). This system is designed using industry-proven antibody clones that can analyze 37 immune cell types from PBMC or whole blood with an optimized 30-marker panel (see table in appendix II)

Whole blood (10 ml) is collected in a heparinized green top tube. PBMC are isolated from whole blood samples using Ficoll-Hypaque at the Biospecimens Accessioning and Processing laboratory (BAP) prior to cryopreservation. Cryopreserved samples are sent in batches to the Mayo Clinic Immune Monitoring Core for analysis by mass cytometry. A concentration of 6 X 10^7 viable cells/mL is prepared from the cryopreserved sample in Maxpar Cell Staining Buffer (Fluidigm). Fc receptors are blocked by adding Human TruStain FcX (BioLegend) to 4X10 ^6 cells in 50 µL followed by incubation for 10 minutes at room temperature. PBMC are added directly to the ready to assay tubes containing 30 lyophilized metal-conjugated antibodies. After a 45-minute incubation, the cells are washed, and then fixed in 2% paraformaldehyde. The fixed cells are spun to a pellet, fixative is removed, followed by resuspension in 1 mL of the 125 nM cell-ID Intercalator-Ir (Fluidigm) and incubated overnight at 4°C. Following the overnight incubation, PBMC are resuspended in MaxPar Cell Acquisition Solution (Fluidigm) at 0.5x10 ^6 cells/mL with 0.1X EQ™ Four Element Calibration Beads (Fluidigm). 300,000 events are acquired per sample at an acquisition rate of 250–500 events/second using the Fluidigm Helios mass cytometry platform. Data will be normalized for intra-sample signal drift using EQ™ Four Element Calibration Beads as a calibrator with the CyTOF Software v.6.7.1016. FCS files generated by the Helios are analyzed by Maxpar Pathsetter, an automated analysis system based on GemStoneTM 2.0.41 (Verity Software House, Topsham, ME). The results are reported as numbers of cells exhibiting distinct phenotypes. See Appendix II.

14.42 **Enumeration of PSMA-Positive Extracellular Vesicles by Nanoscale Flow Cytometry**

Plasma will be thawed at 37° C and each sample will be incubated with fluorescent antibody-matched isotypes or antibodies against PSMA.

Samples will be subsequently analyzed by nanoscale flow cytometry. Positive counts in the isotype controls will be subtracted from the counts observed in corresponding samples incubated with antibodies of interest in order to correct for the level of non-specific binding.

14.5 Future studies

As part of ongoing Mayo Clinic Cancer Center research, we will collect serum/platelet poor plasma, buffy coat and DNA for future research studies on molecular determinants of efficacy and tolerability. Serum/platelet poor plasma and DNA samples will be collected at timepoints indicated in Section 14.2 and stored frozen by BAP until specific analyses are identified. As protocols are developed, they will be presented for IRB review and approval.

14.6 Return of Genetic Testing Research Results

For this study, DNA and/or RNA specimens are only being banked and no specific genetic testing is being performed. If, at any time, genetic results are obtained that may have clinical relevance, IRB review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

15.0 Drug Information

15.1 Pembrolizumab (MK-3475, SCH 900475, Keytruda®)

15.11 Background

Pembrolizumab is a potent humanized IgG4 monoclonal antibody with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical *in vitro* data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1.

15.12 Formulation

Pembrolizumab is available as a liquid 25 mg/mL, 100 mg/vial.

15.13 Preparation and storage

Vials should be stored in the refrigerator at temperatures between 2-8°C.

Drug concentrate is further diluted with normal saline (or 5% dextrose in the concentration range of 1 to 10 mg/mL) in IV containers made of polyvinyl chloride (PVC) or non-PVC material. The infusion solution in the IV bag should be immediately administered. Diluted pembrolizumab solutions may be stored at room temperature for a cumulative period of up to 4 hours. This includes room temperature storage of admixture solutions in the IV bags and the duration of infusion. In addition, IV bags may be stored at 2-8°C for up to a cumulative time of 20 hours. This 24-hour total hold time from dilution may include up to 6 hours at room temperature

15.14 Administration

Pembrolizumab is administered by intravenous infusion over 30 minutes via a 0.22 micron in-line filter. The final infusion volume must be between 1 and 10 mg/mL. Maximum rate of infusion should not exceed 6.7 mL/minute through a peripheral or indwelling catheter. Flush the line with 0.9% NaCL following the completion of the infusion.

15.15 Pharmacokinetic information

a) Absorption – Because pembrolizumab is administered intravenously, it is immediately and completely bioavailable. Steady-state concentrations of pembrolizumab are reached by16 weeks of repeated dosing with a Q3W regimen, and the systemic accumulation is 2.1-fold. The peak concentration, trough concentration, and area under the plasma concentration versus time curve at steady state of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg Q3W.
b) Distribution – Pembrolizumab has a limited volume of distribution.
c) Excretion – CL is approximately 23% lower after achieving maximal change at steady state compared with the first dose. The terminal elimination half-life (t½) is estimated to be 22 days at steady state.
d) Metabolism - Pembrolizumab is catabolized through non-specific pathways; metabolism does not contribute to its CL.

15.16 Potential Drug Interactions

There are no known significant drug interactions.

15.17 Known potential adverse events:

Very common known potential adverse events, ≥10%:
Skin and subcutaneous tissue disorders: Pruritus, skin rash
Gastrointestinal disorders: Diarrhea, nausea, abdominal pain
General disorders and administration site conditions: fatigue

Common known potential adverse events, >10%:
Blood and lymphatic system disorders: anemia
Immune system disorders: infusion related reaction
Endocrine disorders: hyperthyroidism, hypothyroidism
Metabolism and nutrition disorders: decreased appetite
Nervous system disorders: headache, dizziness, dysgeusia
Respiratory, thoracic, and mediastinal disorders: pneumonitis, dyspnea, cough
Gastrointestinal disorders: colitis, vomiting, constipation, dry mouth
Skin and subcutaneous tissue disorders: severe skin reactions, vitiligo, dry skin, erythema
Musculoskeletal and connective tissue disorders: arthralgia, myositis, musculoskeletal pain, arthritis, pain in extremity
General disorders and administration site conditions: asthenia, edema, pyrexia, influenza like illness, chills
Investigations: alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatinine increased

Uncommon known potential adverse events, 1% - 10%:
Infusion related reactions
Blood and lymphatic system disorders: neutropenia, thrombocytopenia, leukopenia, lymphopenia, eosinophilia
Endocrine disorders: hypophysitis, adrenal insufficiency, thyroiditis, hypopituitarism
Metabolism and nutrition disorders: type I diabetes mellitus, hyponatremia, hypokalemia, hypocalcemia
Psychiatric disorders: insomnia, confusional state
Nervous system disorders: epilepsy, lethargy, peripheral neuropathy
Eye disorders: uveitis, dry eye
Cardiac disorders: myocarditis, atrial fibrillation
Vascular disorders: hypertension
Gastrointestinal disorders: pancreatitis
Hepatobiliary disorders: hepatitis
Skin and subcutaneous tissue disorders: lichenoid keratosis, psoriasis, alopecia, dermatitis, dermatitis acneiform, eczema, hair color changes, papule
Musculoskeletal and connective tissue disorders: tenosynovitis
Renal and urinary disorders: nephritis, acute kidney injury
Investigations: blood bilirubin increased, amylase increased, hypercalcemia

Rare known potential adverse events, <1% (Limited to important or life-threatening):
Blood and lymphatic system disorders: immune thrombocytopenic purpura, hemolytic anemia
Immune system disorders: sarcoidosis
Nervous system disorders: Guillain-Barre syndrome, myasthenic syndrome
Gastrointestinal disorders: small intestinal perforation

Skin and subcutaneous tissue disorders: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema nodosum

The risk profile for pembrolizumab also includes two important potential risks: a) myasthenic syndrome, and b) an increased risk of severe complications (such as early severe graft versus host disease and veno-occlusive disease) of allogeneic transplant in patients with hematologic malignancies who have previously been treated with PD-1 inhibitors.

15.18 Drug procurement

Pembrolizumab will be provided free of charge to study participants by Merck.

15.19 Nursing Guidelines

15.191 Pembrolizumab side effects vary greatly from those of traditional chemotherapy and can vary in severity from mild to life threatening. Instruct patients to report any side effects to the study team immediately. Side effects may be immediate or delayed up to months after discontinuation of therapy. Most side effects are reversible with prompt intervention of corticosteroids.

15.192 Diarrhea can be seen, however is less common than that seen with anti-CTLA-4 agents. However it can be severe, leading to colonic perforation. Instruct patients to report ANY increase in the number of stools and/or change in baseline, blood in the stool, abdominal pain to the study team immediately.

15.193 Rash/pruritis/dermatitis is seen. Patients should report any rash to the study team. Treat per section 9.0 and monitor for effectiveness.

15.194 Monitor LFTs closely as elevations in these levels could indicate early onset autoimmune hepatitis. Patients should also be instructed to report any jaundice, or right upper quadrant pain to the study team immediately.

15.195 Pneumonitis can be seen and may be mild (only seen on imaging) to severe. Patients should be instructed to report any SOB, dyspnea, cough, chest pain, etc. to the study team immediately. Patients reporting these symptoms should have a pulse ox checked and consider immediate imaging per the treating MD.

15.196 Endocrinopathies (including hypopituitarism, hypothyroidism, hypophysitis, and adrenal insufficiency) are seen with this agent. Patients may present only with the vague sense of fatigue and “not feeling well.” Additional symptoms may be that of nausea, sweating and decreased activity tolerance. Instruct patients to report these signs or symptoms immediately and obtain appropriate labs as ordered by MD.

15.197 Patients who are started on steroid therapy for any side effects of pembrolizumab toxicity should be instructed to take the steroids as ordered, and not to discontinue abruptly as symptoms may return and be severe. Patients may be on steroid therapy for weeks. Instruct patients to report any increase or change in side effects with any dosage decrease as patients may need a slower taper.

15.198 Fatigue is common and may or may not be associated with immune related side effects. Assess patient's fatigue level prior to each cycle of therapy and report any changes to the study team.

15.199a Patients should avoid receiving live vaccines within 30 days of study drug administration or per other study guidelines.

15.199b Patients who have undergone an allogenic bone marrow transplant, have an increased risk of severe complications including early GVHD, and veno-occlusive disease, if they have previously been treated with pembrolizumab

15.199c Myocarditis has been reported and associated with pembrolizumab. Instruct patients to report chest pain, SOB, or dyspnea to study team immediately and/or seek emergency medical attention.

15.199d Autoimmune hematologic disorders including ITP and hemolytic anemia have been reported. Monitor blood counts closely and report any abnormalities to the study team.

15.199e Rare neurologic disorders including Guillain-Barre syndrome and myasthenia gravis have been reported. Instruct patients to report any neurologic symptoms including weakness, paresthesias or numbness, tingling to the study team immediately.

15.2 Pemetrexed (Alimta)

15.21 Background

Pemetrexed is a multitargeted antifolate (MTA). Pemetrexed inhibits thymidylate synthase, dihydrofolate reductase, glycinamide ribonucleotide formyltransferase, and aminoimidazole carboxamide ribonucleotide formyltransferase, the enzymes involved in folate metabolism and DNA synthesis, resulting in inhibition of purine and thymidine nucleotide and protein synthesis.

15.22 Formulation

Commercially available as a sterile lyophilized powder for intravenous infusion available in single-dose 100 and 500 mg vials.

15.23 Preparation, storage, and stability

Store unopened vials at 15ºC to 30ºC. Add 20 mL of 0.9% NaCl to make a 25 mg/mL solution. Gently swirl. Solution may be colorless to green-yellow. Reconstituted and infusion solutions are stable for 24 hours when refrigerated at 2ºC to 8ºC or stored at room temperature of 15ºC to 30ºC. Concentrations at 25 mg/mL are stable in polypropylene syringes for 2 days at room temperature (23ºC).

15.24 Administration

Administer IV over 10 minutes in 100 mL 0.9% NaCl. Start vitamin supplements 1 week before initial dose of pemetrexed. Folic acid 350-1000 mcg/day orally (continue for 21 days after last dose of pemetrexed) and vitamin B12 1000 mcg I.M. every 9 weeks. Dexamethasone 4 mg orally twice daily can be started the day before therapy, and continued the day of and the day after to minimize cutaneous reactions.

15.25 Pharmacokinetic information:

Distribution: Vdss: 16.1 L

Protein Binding: ~73% to 81%
Metabolism: Pemetrexed undergoes limited hepatic metabolism. Unchanged pemetrexed accounts for the majority of the drug-related material in urine.
Half-life elimination: Normal renal function: 3.5 hours; Clcr 40-59 mL/minute: 5.3-5.8 hours
Excretion: Urine (70% to 90% as unchanged drug)

15.26 Potential Drug Interactions:

Increased Effect/Toxicity: The administration of ibuprofen 400 mg every 6 hours to patients resulted in a 22% increase in AUC and a 16% increase in CMAX. These alterations are no greater than those observed in patients with moderate renal impairment (CrCl 45 mL/min) and do not fall outside of what is considered an acceptable increase in exposure. Therefore, ibuprofen (400 mg every 6 hours) can be given concurrently with pemetrexed in patients with normal renal function (CrCl greater than or equal to 80 mL/min).
Ethanol/Nutrition/Herb Interactions: Lower ANC nadirs occur in patients with elevated baseline cystathionine or homocysteine concentrations. Levels of these substances can be reduced by folic acid and vitamin B12 supplementation.

15.27 Known potential adverse events:

Consult the package insert for the most current and complete information. Percentages reported with single-agent therapy (in patients who received folate and B12 supplementation); dose limiting toxicities include myelosuppression (neutropenia, thrombocytopenia); fatigue and dermatitis.

Common known potential adverse events, > 10%:
Cardiovascular: Chest pain, edema, hypertension
Central nervous system: Fatigue, fever, depression
Dermatologic: Rash/desquamation, alopecia
Gastrointestinal: Anorexia, nausea, constipation, vomiting, diarrhea, stomatitis
Hematologic: Anemia, leukopenia, neutropenia
Neuromuscular & skeletal: Neuropathy
Respiratory: Dyspnea, pharyngitis
Miscellaneous: Infection

Less common known potential adverse events, 1% - 10%:
Cardiovascular: Thrombosis/embolism, cardiac ischemia
Endocrine & metabolic: Dehydration
Gastrointestinal: Dysphagia/esophagitis/odynophagia
Hematologic: Thrombocytopenia, febrile neutropenia
Hepatic: ALT increased, AST increased
Neuromuscular & skeletal: Arthralgia
Renal: Creatinine clearance decreased, serum creatinine increased
Miscellaneous: Allergic reaction/hypersensitivity

Rare known potential adverse events, <1% (Limited to important or life-threatening):
Colitis, renal failure

15.28 Drug procurement

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.29 Nursing Guidelines

15.291 Monitor blood counts. Instruct patient to report fevers >101°F (38.3°C), excessive fatigue, bruising, or unusual bleeding.

15.292 Advise patient about possible rash, pruritus and the need to report these problems, which can be treated by steroids.

15.293 Supply warm packs to injection site if arm becomes inflamed.

15.294 Administer antiemetics and antidiarrheals as ordered.

15.295 Instruct patient that adequate hydration is important. Patient should report inability to maintain hydration.

15.296 Instruct patient in energy-conserving techniques.

15.297 Advise patient about possible hair loss.

15.298 Monitor liver and renal function tests.

15.299a Advise patient that urinary tract infections (UTIs) are possible, instruct in the signs and symptoms of a UTI and tell patients to report any of these to the health care team immediately.

15.299b Advise patient about possibility of mouth sores. Emphasize good oral care.

15.299c Advise patient that he/she should contact his/her physician in the event of trouble swallowing folic acid pills.

16.0 Statistical Considerations and Methodology

This study will be a single arm phase II trial of the combination of pembrolizumab and pemetrexed with enrollment into two separate cohorts. Cohort A will be for adenoid cystic carcinoma (ACC), and Cohort B for non-ACC. Given the heterogeneity of salivary gland tumors and the increased likelihood of response with non-ACC histologies, two cohorts are needed for accurate initial assessment of anti-cancer activity. Although patients will be analyzed by cohort, the treatment will be the same for both Cohort A and Cohort B.

NOTE: Cohort A (ACC) was closed as of 06Apr2022. Cohort A1 (ACC) will re-open using a new clinical benefit rate (CBR) primary endpoint effective with MCCCC Amendment 3.

16.1 Primary Endpoint (original design)

The primary endpoint for this study will assess the confirmed response rate (by RECIST 1.1) of pembrolizumab and pemetrexed done by cohort. Any confirmed response that occurs during the first 8 cycles of treatment will count as a success (24 weeks), where late responses will still be counted and reported as well, but just not part of the primary analysis decision rules. Per RECIST 1.1, responses need to be confirmed (2 consecutive responses at least 4 weeks apart) to count as a response (see Section 11.0). All eligible patients who are registered and start treatment will be evaluable for response. Patients treated, but with no follow-up disease assessment for any reason will be classified as non-responders. A Simon's optimal two-stage design was utilized (see below) for each cohort separately for the original design. For the new design for Cohort A (Cohort A1) described in Section 16.12 below, the clinical benefit rate (CBR) is the new primary endpoint. Clinical benefit rate is the rate of patients with SD, PR, or CR as their best response during treatment. See below for details of the original and new design for Cohort A, along with the design for Cohort B as well.

16.11 Cohort A (original design)

This design has 80% power to detect an improvement in the confirmed response rate from 10% to 30%, with a significance level of 0.10. See design details below:

- Interim Analysis: Enroll 7 eligible patients. If at least 1 confirmed response is observed in the first 7 eligible patients, we will continue to a full accrual of 18 eligible patients. Otherwise, the cohort will be permanently closed due to lack of efficacy. The study will continue to enroll during the interim analysis phase, due to the slow expected accrual rate for this study.
- Final Analysis: If the trial is a success during the interim analysis, we will enroll another 11 eligible patients to the second stage (18 eligible total). If at least 4 confirmed responses are observed in the first 18 eligible patients (22%), the treatment will be considered worthy of further investigation. Otherwise, the study will be permanently closed due to lack of efficacy.

16.12 Cohort A1

Due to negative results for response, but promising data in support of the treatment, it was decided to re-open Cohort A with a new design using the clinical benefit rate as the primary endpoint, where currently enrolled patients to cohort A would still be included as part of this new design (cohort A + cohort A1 patients). Under the original design, which was negative for the primary endpoint at the interim analysis, we enrolled 11 ACC patients, so with the new design we only need an additional 9 patients enrolled (Cohort A1) to reach 20 total. This new design has 80% power to detect an improvement in the clinical benefit rate (i.e.

rate of patients with SD, PR, or CR as their best response during treatment) from 50% to 75%, with a significance level of 0.10. See 1-stage design details below:

- Final Analysis: Enroll 19 eligible patients to this cohort (Cohort A + Cohort A1). If at least 13 patients have stable disease or better (SD or PR or CR) for their best response during treatment in the first 19 eligible patients (68%), the treatment will be considered worthy of further investigation. Otherwise, the study will be permanently closed due to lack of efficacy.

16.13 Cohort B

This design has 80% power to detect an improvement in the confirmed response rate from 15% to 35%, with a significance level of 0.10. See design details below:

- Interim Analysis: Enroll 9 eligible patients. If at least 2 confirmed responses are observed in the first 9 eligible patients, we will continue to a full accrual of 23 eligible patients. Otherwise, the cohort will be permanently closed due to lack of efficacy. The study will continue to enroll during the interim analysis phase, due to the slow expected accrual rate for this study.
- Final Analysis: If the trial is a success during the interim analysis, we will enroll another 14 eligible patients to the second stage (23 eligible total). If at least 6 confirmed responses are observed in the first 23 eligible patients (26%), the treatment will be considered worthy of further investigation. Otherwise, the study will be permanently closed due to lack of efficacy.

16.2 Total sample size, expected accrual, etc.

A maximum of 42 evaluable patients (19-Cohort A + A1 and 23-Cohort B) will be accrued onto this phase II study unless the study is closed early for excessive toxicity or lack of efficacy. We anticipate accruing an additional 7% of patients to account for ineligibility, cancellation, major treatment violation, or other reasons. Therefore, maximum accrual is 45 patients (20-Cohort A + A1, 25-Cohort B).

The expected accrual rate is about 2 patients per month. With this accrual rate, we expect to finish accrual within about 2 years, assuming we accrue 45 total patients.

We anticipate that the study will take approximately 4 years to complete. This allows a 12-month follow-up for the final patient enrolled, along with data entry, data clean-up, and analysis.

16.3 Analysis Plan for Secondary Endpoints (done by cohort)

The following secondary endpoints will be assessed as well: overall survival, progression-free survival, response rate (ACC cohorts), CBR (non-ACC cohort), and adverse events.

Overall Survival: Overall Survival (OS) is defined as the time from study entry to death from any cause, where patients alive at last follow-up will be censored. OS will be estimating using the Kaplan-Meier method.

Progression-Free Survival: Progression-free survival (PFS) is defined as the time from study entry to the first of either disease progression or death from any cause, where disease progression will be determined based on RECIST 1.1 criteria. Patients that are alive and progression-free will be censored on their last tumor assessment date. PFS will be estimated using the Kaplan-Meier method.

Response rate: For Cohort A + A1 (ACC cohorts), we'll assess the response rate per standard RECIST 1.1 criteria. The data will be reported descriptively, with frequencies and percentages.

Clinical benefit rate (CBR): For Cohort B, we'll assess the CBR rate as a secondary endpoint. The data will be reported descriptively, with frequencies and percentages.

Adverse events: The maximum grade for each type of adverse event will be summarized using CTCAE version 5.0. The frequency and percentage of Grade 3+ adverse events will be estimated.

16.4 Analysis Plan for Correlative studies (done by cohorts)

To investigate the frequency of MTAP loss by immunohistochemistry in R/M SGC and whether it correlates with enhanced response to pemetrexed. To measure the degree of PDL1 expression using formalin-fixed tumor samples, and determine the extent of PDL1 expression correlates with response to study treatment. To investigate expression of thymidylate synthase by immunohistochemistry in R/M SGC and whether it correlates with enhanced response to pemetrexed. The associations of these markers with response will be done via Chi-square or Fisher's exact tests by cohort for categorical biomarkers and done via 2-sample t-tests (or the Wilcoxon Rank-Sum test) by cohort for continuous biomarker data. Descriptive statistics and tables will be reported.

16.5 Data & Safety Monitoring

16.51 Safety review

The principal investigator(s) and the study statistician will review the study monthly to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least biannually, based on reports provided by the MCCC Statistical Office.

16.52 Adverse Event Stopping Rules

The stopping rule specified below is based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual after any temporary suspension or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may also choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e., an adverse event with attribute specified as "possible", "probable", or "definite") that satisfy any of the following criteria for each cohort separately:

- If at any time, 4 of the initial 10 treated patients or 40% or more of all patients (i.e., when accrual is greater than 10 patients) have experienced a Grade 4 adverse event.
- If at any time, 2 patients have experienced a Grade 5 adverse event (non–progressive disease).

16.6 Subset Analyses for Minorities

16.61 Study availability

This study will be available to all eligible patients, regardless of gender, race or ethnic origin.

16.62 Statistical analysis by subset

There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analyses will look for differences in treatment effect based on racial groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.63 Regional population

The geographical region served by MCCC has a population which includes approximately 5% minorities. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Targets			
	Sex/Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	1	1	2
Not Hispanic or Latino	21	22	43
Ethnic Category: Total of all subjects	**22**	**23**	**45**
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	0	1	1
Black or African American	1	1	2
Native Hawaiian or other Pacific Islander	0	0	0
White	21	21	42
Racial Category: Total of all subjects	**22**	**23**	**45**

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa.

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens

17.1 Summary Table of Research Tissue Specimens to be Collected for this Protocol

Research Study	Specimen Purpose	Mandatory or Optional	Type of Tissue to Collect	Block, Slides, Core, etc. (# of each to submit)	Prior to end of Cycle 3[16]	Process at site? (Yes or No)	Temperature Conditions for Storage /Shipping
PD-L1, RNA and/or DNA seq	☒ Correlative	Mandatory	Formalin Fixed, Paraffin Embedded (FFPE)	1 H&E slide 5-10 unstained slides	X	Cut slides at each site	ambient

[16] Archived tissue from surgery/biopsy prior to C1D1; if none available, patient is still eligible for treatment on this study

17.2 Diagnostic Slides from Original and /or Recurrent Tissue

Study coordinator will request blocks from Tissue Registry to give to pathologist to determine best option for study use. Pathologist will request a minimum of 4 slides cut at 4 microns including one H&E. These slides will be used for PD-L1, and, if sufficient tissue is available, RNA and/or DNA sequencing.

Along with original diagnostic slides, include pathology reporting form, surgical pathology report and operative report.

17.3 Correlative Tissue Collection

17.31 Tissue Kits will not be provided for this protocol.

17.32 Paraffin Embedded Tissue

17.321 Requirements

The following will be required: 1 H&E slide for confirmation of diagnosis, and 5-10 unstained slides for correlative studies.

Slides should be 4-µm-thick formalin-fixed, paraffin-embedded (FFPE) tumor samples.

The H&E slide for confirmation of diagnosis (if patient was treated at an outside institution) will be required prior to initiating treatment.

The unstained slides can be collected at any point the patient is on study or in follow-up and are not mandatory to have before initiating study treatment

17.322 Rochester

Coordinator will route tissue samples for formalin fixing/paraffin embedding (block creation and cut one IHC per block) if needed, or call existing blocks/slides.

Once blocks and slides are created, coordinator will route to Study Pathologist for review.

Once pathologist has reviewed, chosen blocks/slides can be routed to Principal Investigator for storage.

Be sure to include the pathology report and the completed MC200708 Tissue Specimen Submission Form with patient ID/protocol #, collection date, tissue submitted, and a contact person for questions

17.322 Arizona and Florida

AZ and FL will ship FFPE slides with accompanying H&E to Rochester, MN, at the address below and include the completed MC200708 Tissue Specimen Submission Form with patient ID/protocol #, collection date, list of tissue blocks submitted, and a contact person for questions.

NOTE: Please include room temperature cool pack if weather conditions are hot in either shipping or receiving location.

Send blocks/slides and forms to:

17.324 All tissue will be stored in Rochester until the end of the study.

17.4 Background and Methodology

17.41 Methylthioadenosine phosphorylase (MTAP) loss

MTAP loss has been reported in salivary cancer but the prevalence has not been prospectively characterized. MTAP loss has been shown in other tumor types such as bladder cancer to correlate with response to anti-folate chemotherapy. Given the heterogeneity of R/M SGCs, identifying a biomarker of response is important. This study will investigate the frequency of MTAP loss by immunohistochemistry (IHC) and whether it correlates with response to pemetrexed.

Methodology: IHC will be performed on formalin-fixed, paraffin-embedded (FFPE), 4-µm-thick tissue sections of archived tissue using anti-MTAP rabbit monoclonal (Abcam; 1:500; RT, 1 h) antibodies. Immunoreacted cells will be visualized with 3, 3′-diaminobenzidine, and the nuclei counterstained with hematoxylin. Staining for MTAP will be carried out with the Dako Omnis (Agilent Technologies Company, Glostrup, Denmark).

17.42 Programmed death ligand-1(PDL1)

PDL1 expression has been shown to correlate with response to checkpoint inhibitor therapy in multiple tumor types. The only published study of pembrolizumab in R/M SGC was a phase 1b study in patients whose tumors expressed PDL1. This study will treat patients irrespective of the PDL1 status which will allow exploration of whether PDL1 expression is necessary for a response to the combination of pembrolizumab and pemetrexed.

Methodology: PDL1 expression will be determined using the PDL1 IHC 22C3 pharmDx assay *per standard clinical practice* using FFPE tumor samples and the degree of expression will be correlated with response.

17.43 Thymidylate synthase (TS)

A high level of TS expression in malignant tumors has been hypothesized to result in reduced sensitivity to pemetrexed but this has not been explored in SGC. This study will investigate the degree of expression of TS and whether it correlates with response to pemetrexed.

Methodology: FFPE tissue using 4-µm-thick tissue sections will be deparaffinized in xylene, rehydrated through graded alcohols, and washed in phosphate-buffered saline. The TS 106 monoclonal antibody will be applied using the avidin-biotin complex IHC technique.

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Data submission instructions for this study can be found in the Data Submission Schedule.

18.2 Survival Follow-up

See Section 4.

18.3 CRF completion

This study will use Medidata Rave® for remote data capture (rdc) of all study data. Data collection for this study will be done exclusively through the Medidata Rave® clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active account and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on the organization roster at the enrolling site.

18.4 Site responsibilities

Each site will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.5 Supporting documentation

This study requires supporting documentation for diagnosis and progression prior to study entry as well as for evidence of response to study therapy and progression after study therapy. These documents should be submitted within 14 days of registration (for prior to study entry materials) or within 14 days after the visit at which response or progression is determined.

If clinical genetic testing results such as next generation sequencing (NGS) data are available, they may be uploaded at any time during the study.

Clinical PD-L1 testing may be uploaded at any time during the study.

18.6 Labeling of materials

Each site will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.7 Overdue lists

A list of overdue forms and outstanding queries will be available in Rave through the Rave Task Summary. In addition to this, the Overdue Materials report is available on the Cancer Center Systems homepage.

19.0 Budget

19.1 Costs charged to patient:

Routine clinical care including costs of pemetrexed and its administration
PD-L1 testing on tissue

19.2 Tests to be research funded:

Research testing on blood and tissue specimens

19.3 Other budget concerns:

Merck & Co. will provide Mayo Clinic with funding to support the costs of running this study.

Merck & Co. will provide study drug pembrolizumab for use in this study.

20.0 References

1) Barnes L, Everson JW, Reichart P, Sidransky D, editors. World Health Organization Classification of Tumors. Lyon: IARC Press; 2005.

2) Laurie SA, Licitra L. Systemic therapy in the palliative management of advanced salivary gland cancers. J Clin Oncol. 2006;24(17):2673–8.

3) Gilbert J, Li Y, Pinto HA, et al. Phase II trial of taxol in salivary gland malignancies (E1394): a trial of the eastern cooperative oncology group. *Head Neck*. 2006; 28(3): 197- 204.

4) Airoldi M, GarzaroM PF, et al. Cisplatin + vinorelbine treatment of recurrent or metastatic salivary gland malignancies (RMSGM): a final report on 60 cases. *Am J Clin Oncol*. 2017; 40: 86- 90.

5) Licitra L, Cavina R, Grandi C, Palma SD, Guzzo M, Demicheli R, Molinari R. Cisplatin, doxorubicin and cyclophosphamide in advanced salivary gland carcinoma. A phase II trial of 22 patients. Ann Oncol. 1996;7(6):640–2.

6) Dreyfuss AI, Clark JR, Fallon BG, Posner MR, Norris Jr CM, Miller D. Cyclophosphamide, doxorubicin, and cisplatin combination chemotherapy for advanced carcinomas of salivary gland origin. Cancer. 1987;60(12):2869–72.

7) Viscuse P and Price K. Marked responses to pemetrexed chemotherapy for metastatic adenocarcinoma of the parotid gland: Case series Head Neck . 2019 Jun;41(6):E99-E103.

8) Cohen et al. Pembrolizumab for the Treatment of Advanced Salivary Gland Carcinoma: Findings of the Phase 1b KEYNOTE-028 Study American Journal of Clinical Oncology: November 2018 - Volume 41 - Issue 11 - p 1083-1088.

9) Gandhi et al. Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer N Engl J Med 2018; 378:2078-2092.

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

11) 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.

12) 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.

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

14) 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.

15) 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.

16) 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.

17) 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.

18) Riley JL. PD-1 signaling in primary T cells. Immunol Rev 2009;229:114-25.

19) 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.

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

21) 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.

22) Alhalabi et al. J Clin Oncol 37, 2019 (suppl; abstr 4521).

23) Eisenhauer EA, Therasse P, Bogaert J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 45(2): 228-247, 2009.

Johnston PG, Fisher ER, Rockette HE, Fisher B, Wolmark N, Drake JC, Chabner BA, Allegra CJ (1994) The role of thymidylate synthase expression in prognosis and outcome of adjuvant chemotherapy in patients with rectal cancer. *J Clin Oncol* **12**: 2640–2647

Pestalozzi BC, Peterson HF, Gelber RD, Goldhirsch A, Gusterson BA, Trihia H, Lindtner J, Cortes-Funes H, Simmoncini E, Byrne MJ, Golouh R, Rudenstam CM, Castiglione-Gertsch M, Allegra CJ, Johnston PG (1997) Prognostic importance of thymidylate synthase expression in early breast cancer. *J Clin Oncol* **15**: 1923–1931

MCCC Amendment 3

Klein Nulent, T. J. W., M. H. Valstar, L. A. Smit, L. E. Smeele, N. P. A. Zuithoff, B. de Keizer, R. de Bree, R. J. J. van Es, and S. M. Willems. 2020. "Prostate-specific membrane antigen (PSMA) expression in adenoid cystic carcinoma of the head and neck." *BMC Cancer* 20 (1):519. doi: 10.1186/s12885-020-06847-9.

Klein Nulent, T. J. W., R. J. J. van Es, G. C. Krijger, R. de Bree, S. M. Willems, and B. de Keizer. 2017. "Prostate-specific membrane antigen PET imaging and immunohistochemistry in adenoid cystic carcinoma-a preliminary analysis." *Eur J Nucl Med Mol Imaging* 44 (10):1614-1621. doi: 10.1007/s00259-017-3737-x.

Tan, B. F., W. C. C. Tan, F. Q. Wang, M. Lechner, V. H. Schartinger, D. S. W. Tan, K. S. H. Loke, and W. L. Nei. 2022. "PSMA PET Imaging and Therapy in Adenoid Cystic Carcinoma and Other Salivary Gland Cancers: A Systematic Review." *Cancers (Basel)* 14 (15). doi: 10.3390/cancers14153585.

van Boxtel, W., S. Lütje, I. C. H. van Engen-van Grunsven, G. W. Verhaegh, J. A. Schalken, M. A. Jonker, J. Nagarajah, M. Gotthardt, and C. M. L. van Herpen. 2020. "(68)Ga-PSMA-HBED-CC PET/CT imaging for adenoid cystic carcinoma and salivary duct carcinoma: a phase 2 imaging study." *Theranostics* 10 (5):2273-2283. doi: 10.7150/thno.38501.

Appendix I ECOG Performance Status

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. 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 ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

From [redacted]