SARC Protocol #: 028

TITLE: SARC028: A Phase II Study of the Anti-PD1 Antibody Pembrolizumab (MK-3475) in Patients with Advanced Sarcomas

Sponsor: SARC (Sarcoma Alliance for Research through Collaboration)

Supporter: Merck Inc.

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Principal Investigator: Hussein Tawbi, MD, PhD
Associate Professor
Department of Melanoma Medical Oncology
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
1400 Holcombe Blvd.
Houston, TX 77030
Phone: 713-792-6111
Fax: 713-745-1046
Email: HTawbi@mdanderson.org

Statistician: John Crowley, PhD
Cancer Research and Biostatistics (CRAB)
1730 Minor Ave, Suite 1900
Seattle, WA 98101-1468
Phone: (206) 652-9711
Fax: (206) 652-4612
Email: johnc@crab.org

SARC Operations Office: 24 Frank Lloyd Wright Drive
Lobby A, Suite 3100; PO Box 406
Ann Arbor, MI 48105
Telephone: (734) 930-7600
Fax: (734) 930-7557
Email: sarc@sarctrials.org

GLOSSARY OF ABBREVIATIONS

ALP	Alkaline phosphatase
ALT (SGPT)	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated Partial Thromboplastin Time
ASCO	American Society of Clinical Oncology
AST (SGOT)	Aspartate aminotransferase
Ca	Calcium
CBC	Complete Blood Count
CI	Confidence interval
CR	Complete Response
Cr	Creatinine
DLT	Dose Limiting Toxicity
ECOG	Eastern Cooperative Oncology Group
FISH	Fluorescence in situ hybridization
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
Hgb	Hemoglobin
IHC	Immunohistochemistry
irAE	Immune Related Adverse Events
irECL	Immune Related Events of Clinical Interests
irRC	Immune Related Response Criteria
K	Potassium
INR	International Normalized Ratio
LLN	Lower limit of normal
ITP	Idiopathic thrombocytopenic purpura
LVEF	Left Ventricular Ejection Fraction
MDSCs	Myeloid-derived suppressor cells
MUGA	Multiple Gated Acquisition scan
NCI	National Cancer Institute

NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NSCLC	Non-small-cell lung carcinoma
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death-ligand 1
PFS	Progression free survival
PLT	Platelets
PS	Performance Status
PR	Partial Response
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RECIST	Response Evaluation Criteria in Solid Tumors
SD	Stable Disease
SF	Shortening Fraction
STS	Soft Tissue Sarcoma
T3	Tri-iodothyronine
T4	Thyroxine
TILs	Tumor-infiltrating lymphocytes
TNM	TNM Classification of Malignant Tumors (tumor/nodes/metastasis)
TSH	Thyroid-Stimulating Hormone
TTP	Time to Tumor Progression
T_{regs}	Regulatory T cells
ULN	Upper Limit of Normal
VEGF	Vascular endothelial growth factor
WBC	White Blood Cells

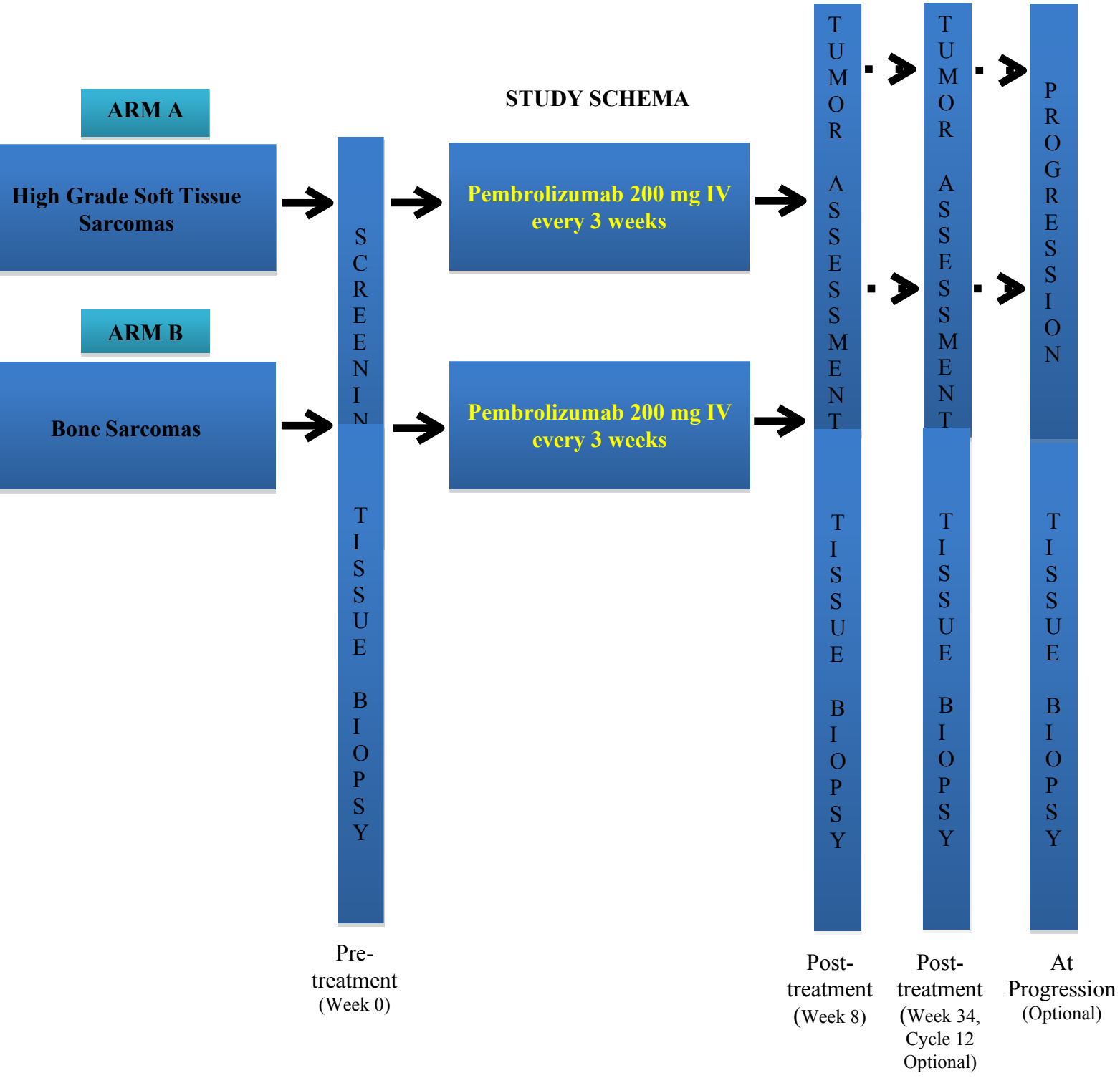
Roles and Responsibilities of Study Personnel:

Hussein Tawbi, MD, PhD: Principal Investigator of the study

Denise Reinke, MS, NP, MBA: President and CEO, SARC

Erin Peregrine Antalis, MPH, PhD, Research Manager

John Crowley, PhD: Study Statistician



STUDY SYNOPSIS

Primary Objective

1. To determine the efficacy of pembrolizumab (MK-3475, SCH 900475) in patients with advanced sarcomas as measured by Objective Response Rate (ORR) using RECIST 1.1

Secondary Objectives

1. To determine the safety and tolerability of pembrolizumab in this patient population
2. To determine the Progression-Free Survival (PFS) by RECIST 1.1 and Overall Survival (OS) in this patient population
3. To determine the response rate as measured by the immune-related Response Criteria (ir-RC)

Exploratory Objectives

1. To determine the effect of pre-treatment PD-L1 expression levels on response rates and the role of PD-L1 expression as a predictive biomarker for clinical benefit
2. To determine the association of circulating regulatory T cells (Tregs) and Myeloid-Derived Suppressor Cells (MDSCs) at baseline and their changes while on therapy with clinical benefit
3. To perform immune monitoring in the circulation and in the tumor microenvironment while on therapy with pembrolizumab – specifically, the frequency of circulating T cell populations, including NY-ESO-1 specific cytotoxic T cells, as well as T cell infiltration in available pre- and post- therapy tumor tissues will be assessed.

Trial Design

This is an open-label phase II study of pembrolizumab given at 200 mg IV every 3 weeks in patients with locally advanced or metastatic bone and soft tissue sarcomas.

Maximum Total Number of Patients

Initial enrollment was 86 patients: patients with soft tissue sarcomas and patients with bone sarcomas

In an expansion study, there will be an additional 60 patients enrolled to the soft tissue cohort: 30 patients with undifferentiated pleomorphic sarcoma and 30 patients with dedifferentiated or other high grade liposarcoma

Target Population

Patients with advanced refractory soft tissue or bone sarcomas

Efficacy Evaluations

Tumor measurements by CT/MRI imaging will be performed initially at 8 weeks and every 12 weeks subsequently - RECIST 1.1 will be the primary outcome measure and immune-related Response Criteria (ir-RC) will be a secondary outcome.

Duration of Participation

Each patient will participate in the trial from the time of Informed Consent Form (ICF) is signed through final protocol-specified contact. After a screening phase for eligibility, patients will receive pembrolizumab every 3 weeks. Treatment for patients that achieve stable disease (SD), a partial response (PR), or a complete response (CR) can continue for a maximum of 2 years total duration of treatment. At the discretion of the investigator, patients who have progressive disease (PD) but continue to achieve clinical benefit, may also continue on therapy for a maximum of 35 cyclestotal duration of treatment.

Safety Evaluations/ Concerns

Safety evaluations will be done according to CTCAE version 4.0 with special emphasis on immune-related adverse events (ir-AEs).

Correlative Studies

Blood for research studies will be collected prior to first study drug administration, at week 8, week 20 and week 32 and flow cytometry analyses will be performed to determine the presence of PD-1 expressing T cells, as well as the proportion of circulating Treg cells and MDSCs.

In the initial enrollment and in the first 20 patients of the expansion cohorts (UPS and LPS), pre- and post-treatment biopsies at week 0 and week 8 are mandatory. Biopsies at cycle 12 (week 34) and at progression are optional. PD-L1 expression, T cell infiltration, as well as suppressor sub-populations will be compared between pre and post-treatment biopsies.

Brief Statistical Design

In the initial enrollment of the study we tested the hypothesis that pembrolizumab has clinical activity in patients with advanced sarcoma. A patient will be classified as a treatment success if he/she achieves a Partial Response (PR) or better by RECIST 1.1. For each arm, an ORR of 25% will be considered clinically meaningful and a response rate less than 10% will be considered ineffective. In this study with a single stage design, we will accrue 40 patients in each arm. The treatment will be considered a success if 8 or more of 40 enrolled patients have a PR or better by RECIST 1.1. This design has a one-sided type I error of 4.2% and a power of 82% to detect a difference between 10 and 25% response rates. This design will also have 87% power to detect an improvement in the 4-months PFS rate from 20% to 40% with a one-sided type I error of 4%.

In the original 86 patient group, 80 patients were evaluable for objective response rate by

RECIST 1.1. Among 40 evaluable patients in the STS cohort, there were 7 partial responses with an ORR of 18%. Four partial responses were seen among 10 patients with undifferentiated pleomorphic sarcoma for an ORR of 40%. Two additional PRs were observed in the dedifferentiated/high grade liposarcoma cohort (2 out of 10) for an ORR of 20%. There was an additional PR seen in the synovial sarcoma cohort. Among 40 evaluable patients in the bone sarcoma cohort, there were 2 partial responses with an ORR of 5%. 1 PR was seen each in the dedifferentiated/high grade chondrosarcoma and osteosarcoma cohorts. Given the observed PRs in the UPS and dedifferentiated/high grade liposarcoma cohorts, we will enroll patients to expansion cohorts to include an additional 30 patients each (UPS and LPS) to further explore and confirm the activity of pembrolizumab.

In the study expansion, the response rates for undifferentiated pleomorphic sarcoma cohort and the poorly differentiated/dedifferentiated liposarcoma cohort will be analyzed separately. In each subtype cohort, we will analyze a total of 40 patients (10 from part 1 of the study and 30 from the expansion cohort). An objective response rate of 25% will be considered clinically meaningful and a response rate less than 10% will be considered lack of efficacy. The treatment will be considered a success if 8 or more of 40 enrolled patients have a PR or better by RECIST 1.1. This design has a one-sided type I error of 4.2% and a power of 82% to detect a difference between 10 and 25%.

At least 20 patients in each of the undifferentiated pleomorphic sarcoma and poorly differentiated/dedifferentiated expansion cohorts will have mandated biopsies for correlative analysis. The remaining 10 patients in each of the cohorts will not be required to obtain baseline and 8-week tumor biopsies, although archival tissue will be required for PD-L1 testing.

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1. OBJECTIVES

1.1 Primary Objective

1. To determine the efficacy of pembrolizumab (MK-3475, SCH 900475) in patients with advanced sarcomas as measured by Objective Response Rate (ORR) using RECIST 1.1

1.2. Secondary Objectives

1. To determine the safety and tolerability of pembrolizumab in this patient population
2. To determine the Progression-Free Survival (PFS) by RECIST 1.1 and Overall Survival (OS) in this patient population
3. To determine the response rate as measured by the immune-related Response Criteria (ir-RC)

1.3. Exploratory Objectives

- To determine the effect of pre-treatment PD-L1 expression levels on response rates and the role of PD-L1 expression as a predictive biomarker for clinical benefit
- To determine the association of circulating regulatory T cells (Tregs) and Myeloid-Derived Suppressor Cells (MDSCs) at baseline and their changes while on therapy with clinical benefit
- To perform immune monitoring in the circulation and in the tumor microenvironment while on therapy with pembrolizumab – specifically, the frequency of circulating T cell populations, including NY-ESO-1 specific cytotoxic T cells, as well as T cell infiltration in available pre- and post- therapy tumor tissues will be assessed.

2. BACKGROUND

[redacted]

2.2 Study Agent - Pembrolizumab

Pembrolizumab formerly known as MK-3475 and SCH 900475 is a potent humanized IgG4 mAb with high specificity for binding to the PD-1 receptor, and 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. Overall, as of 03-Mar-2018, approximately 25,519 patients have been treated with pembrolizumab in clinical studies. Pembrolizumab has an acceptable preclinical safety profile and is FDA approved for the treatment of advanced melanoma, non-small cell lung cancer, squamous cell head and neck cancer, urothelial cancer, classical Hodgkin lymphoma, MSI-H or mismatch repair deficient colon cancer or solid tumors, and gastric/gastroesophageal junction adenocarcinoma.

2.3 Background

[redacted]

[redacted]

[redacted]

2.5 General Investigational Approach

Refer to current Investigator's Brochure for information on General Investigational Approach.

2.6 Chemical Properties

[redacted]

[redacted]

2.7 Structure

[redacted]

2.8 Physico-Chemical Properties

Refer to current Investigator's Brochure for Physico-Chemical Properties

2.9 Pharmaceutical Formulation

Refer to current Investigator's Brochure for information on Pharmaceutical Formulation

2.10 Nonclinical Pharmacology

[redacted]

[redacted]

[redacted].

2.11 Affinity and Ligand Blockade of Pembrolizumab

[redacted]

2.12 *In Vivo* Efficacy of Analog Anti-Mouse PD-1 Antibody (as a Monotherapy) in Syngeneic Tumor Models

[redacted]

Figure 1

Figure 1: Effect of Anti-PD-1 Monoclonal Antibody Monotherapy on Growth of MC38 Tumor

[Redacted]

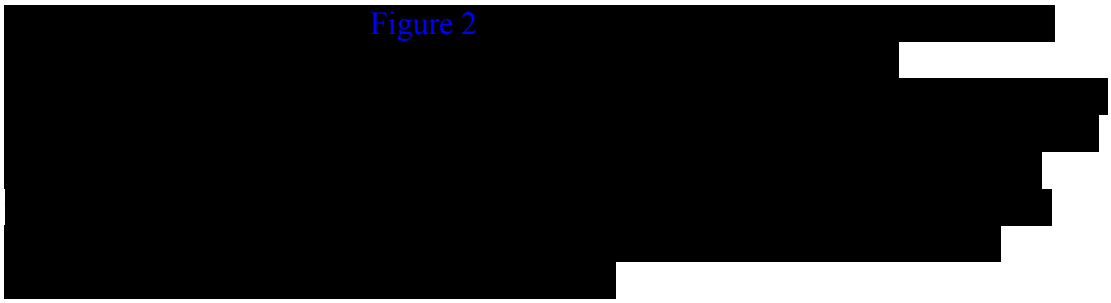

Figure 2: Effects of Anti-PD-1 Monoclonal Antibody Monotherapy on Survival in MC38 Tumor Model

[redacted]

Non

2.14 Clinical Summary of Results

[redacted]

2.15 Preclinical and Clinical Trial Data

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

2.16 Rationale for the Trial and Selected Patient Population

[redacted]

This study is therefore a Phase II clinical trial to determine the preliminary clinical

efficacy of the anti-PD1 antibody pembrolizumab in patients with advanced sarcomas. Given the heterogeneity of advanced sarcomas, the study will have two separate arms that each encompasses sarcoma subtypes with similar anatomic primary sites and patterns of progression.

In the original 86 patient group, 80 patients were evaluable for objective response rate by RECIST 1.1. Among 40 evaluable patients in the STS cohort, there were 7 partial responses with an ORR of 18%. Four partial responses were seen among 10 patients with undifferentiated pleomorphic sarcoma for an ORR of 40%. Two additional PRs were observed in the dedifferentiated/high grade liposarcoma cohort (2 out of 10) for an ORR of 20%. There was an additional PR seen in the synovial sarcoma cohort. Among 40 evaluable patients in the bone sarcoma cohort, there were 2 partial responses with an ORR of 5%. 1 PR was seen each in the dedifferentiated/high grade chondrosarcoma and osteosarcoma cohorts.

Given the observed PRs in the UPS and dedifferentiated/high grade liposarcoma cohorts, we will enroll patients to expansion of both cohorts to include an additional 30 patients each (UPS and LPS) to further explore and confirm the activity of pembrolizumab.

2.17 Study Design

This is an open-label, Phase II study of pembrolizumab for patients ≥18 years of age with locally advanced, unresectable, recurrent, and/or metastatic soft tissue sarcomas, or ≥12 years of age for bone sarcomas. Patients will be assigned to one of 2 arms based on the sarcoma histologic subtypes: high grade aggressive soft tissue sarcomas (specifically leiomyosarcoma, poorly differentiated/de-differentiated liposarcoma, high grade pleomorphic undifferentiated sarcoma/MFH, MPNST and synovial sarcoma), and bone sarcomas (Ewing Sarcoma, osteosarcoma, and chondrosarcoma [de-differentiated or mesenchymal]). The patient population must meet all eligibility criteria specified in Section 3. A total of up to 80 patients will be included in the study. Patients will undergo screening evaluations to determine eligibility within 30 days of the first dose. Each 21 day dosing period will constitute a cycle.

Pembrolizumab is a potent humanized IgG4 anti-PD-1 mAb with high specificity of binding to the PD-1 receptor, thus perpetuates inhibition of PD-L1 and PD-L2 interaction. Based on preclinical *in vitro* data, pembrolizumab has higher affinity and receptor-blocking activity compared to other anti-PD-1 products in development. Pembrolizumab has an acceptable preclinical safety profile and is being advanced for clinical development as an IV immunotherapy for advanced malignancies. Pembrolizumab has been evaluated at 2 and 10 mg/kg every 3 weeks but a flat dose of 200 mg IV every 3 weeks will be utilized for further development.

Patients will be assessed for response (RECIST 1.1) by CT or MRI beginning 8 weeks (± 1 week) after treatment initiation and then every 12 weeks (± 1 week) until progression or treatment discontinuation, whichever occurs first. Treated patients will

be allowed to continue study therapy after initial RECIST 1.1 defined progression if they are assessed by treating physician to be deriving clinical benefit and tolerating study drug. Treating physician may consult with overall study PI as needed for help with assessing patient. Such patients should discontinue study therapy upon further evidence of progression.

In the initial enrollment and in the first 20 patients enrolled in each of the UPS and LPS cohorts, mandatory biopsies will be obtained during screening prior to initiation of therapy (week 0) and at 8 weeks (± 1 week) to coincide with radiologic disease assessment Additional tumor biopsies (optional) at cycle 12 (week 34) and at time of progression may be collected for easily accessible tumors. Surgical excisional biopsies or core biopsies are acceptable.

2.18 Correlative Studies

In part 1 of the study and in up to 20 patients enrolled in each of the UPS and LPS cohorts, pre- and post-treatment biopsies (week 0, 8) will be required and biopsies at cycle 12 (week 34) and at progression are optional. T cell infiltration as well as suppressor subpopulations will be compared between pre- and post-treatment biopsies.

Blood for research studies will be collected prior to first study drug administration, at week 8, week 20 and week 32 and flow cytometry analyses will be performed to determine the presence of PD-1 expressing T cells, as well as, the proportion of circulating regulatory T cells (T_{regs}) and myeloid-derived suppressor cells (MDSCs).

3. PATIENT SELECTION

3.1 Eligibility Criteria

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion / exclusion criteria. Results of all baseline evaluations, which assure that all inclusion and exclusion criteria have been satisfied must be reviewed by the Principal Investigator or his/her designee prior to enrollment of the patient. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

3.2 Inclusion Criteria

3.2.1 Age ≥ 18 years (Age ≥ 12 years for patients with bone sarcomas).

3.2.2 Histologically confirmed diagnosis of unresectable, recurrent, and/or metastatic high grade soft-tissue or bone sarcoma of one of the following subtypes: soft

tissue sarcomas (leiomyosarcoma, poorly differentiated/de-differentiated liposarcoma, high grade pleomorphic undifferentiated sarcoma/MFH and synovial sarcoma), and bone sarcomas (Ewing sarcoma, osteosarcoma, and chondrosarcoma [de-differentiated or mesenchymal]).

3.2.3 ECOG Performance Status of 0 or 1.

3.2.4 At least one site of measurable disease on CT/MRI scans as defined by RECIST 1.1. Baseline imaging must be performed within 30 days of dosing.

3.2.5 At least one site of accessible disease for pre- and post-treatment core biopsies for at least 20 patients per arm on the expansion cohorts.

3.2.6 Patients may have received 1-3 prior systemic therapies in the metastatic setting.

3.2.7 Adequate organ function within 14 days of dosing defined as:

3.2.7.1 Absolute Neutrophil Count (ANC) ≥ 1000/μL

3.2.7.2 Platelets ≥ 100,000/μL (transfusion independent)

3.2.7.3 Hemoglobin ≥ 9 g/dL or ≥ 5.6 mmol/L

3.2.7.4 ALT and AST ≤ 2.5 x institutional upper limit of normal (ULN) or ≤ 5.0 x institutional ULN if considered due to tumor

3.2.7.5 Alkaline phosphatase ≤ 2.5 x institutional ULN unless considered due to tumor

3.2.7.6 Serum bilirubin ≤ 1.5 x institutional ULN. **NOTE**: Patients with elevated bilirubin secondary to Gilbert's disease are eligible to participate in the study

3.2.7.7 Serum creatinine ≤ 1.5 x institutional ULN or 24-hour creatinine clearance ≥ 50 ml/min (calculated creatinine clearance using Cockroft-Gault formula is acceptable)

3.2.8 Must be willing to provide and have available archival tissue for PD-L1 testing.

3.2.9 Written, voluntary informed consent.

3.2.10 Fertile men and women of childbearing potential must agree to use an effective method of birth control from providing signed consent and for 120 days after last study drug administration. Women of childbearing potential include pre-menopausal women and women within the first 2 years of the onset of menopause. Women of childbearing potential must have a negative pregnancy

test ≤ 72 hours prior to Day 1 of study.

Effective methods of birth control include: surgically sterile, barrier device (condom, diaphragm), contraceptive coil, intrauterine device (IUD), and abstinence.

3.2.11 Life expectancy of >12 weeks.

3.2.12 Patients with central nervous system disease are eligible for enrollment if they have received prior radiotherapy or surgery to sites of CNS metastatic disease and are without evidence of clinical progression for at least 4 weeks prior to screening, have no evidence of new or enlarging brain metastases, and are off steroids for at least 7 days before first dose of pembrolizumab.

3.3 Exclusion Criteria

3.3.1 Prior systemic therapy targeting PD-1: PD-L1 axis.

3.3.2 Patients who are curable by conventional multidisciplinary management.

3.3.3 Patients with severe and/or uncontrolled concurrent medical disease that in the opinion of the investigator could cause unacceptable safety risks or compromise compliance with the protocol.

3.3.4 Patients who have received wide field radiotherapy ≤ 4 weeks or limited field radiation for palliation < 2 weeks prior to screening or who have not recovered adequately from side effects of such therapy.

3.3.5 Patients who have active infections requiring therapy.

3.3.6 Patients that are known to be positive for Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies), active Hepatitis B (HBsAg reactive), or Hepatitis C (HCV RNA [qualitative] is detected); patients with negative Hepatitis C antibody testing may not need RNA testing.

3.3.7 Patients that have a known psychiatric or substance abuse disorder that would interfere with cooperation with the requirements of the trial.

3.3.8 Patients who received systemic anti-cancer treatment prior to the first dose of study drug within the following time frames:

- Patients who have received cyclical chemotherapy within a period of time that is shorter than the cycle length used for that treatment (e.g., 6 weeks for nitrosourea, mitomycin-C) prior to starting study drug.
- Patients who have received biologic therapy (e.g., antibodies) within a period of time that is ≤ 5 $t_{1/2}$ or ≤ 4 weeks (whichever is shorter) prior to starting

study drug.

- Patients who have been treated with a continuous or intermittent small molecule therapeutics within a period of time that is ≤ 5 $t_{1/2}$ or ≤ 4 weeks (whichever is shorter) prior to starting study drug.
- Patients who have received any other investigational agents within a period of time that is ≤ 5 $t_{1/2}$ or less than the cycle length used for that treatment or ≤ 4 weeks (whichever is shorter) prior to starting study drug.
- Patients who have received wide field radiotherapy (including therapeutic radioisotopes such as strontium 89) ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to starting study drug.
- Patients who have undergone surgery ≤ 2 weeks prior to starting study drug (minor surgical procedures may be allowed).

3.3.9 Patients with active autoimmune disease or a documented history of autoimmune disease or syndrome that requires systemic steroids or immunosuppressive agents. Patients with vitiligo or resolved childhood asthma/atopy would be exception to this rule. Patients that require inhaled steroids or local steroid injections would not be excluded from the study. Patients with hypothyroidism not from autoimmune disease that is stable on hormone replacement will not be excluded from the study.

3.3.10 Women who are pregnant or nursing/breastfeeding.

3.3.11 Known hypersensitivity to pembrolizumab or another mAb (another PD-1 monoclonal antibody). This is only in the case of pembrolizumab or related mABs hypersensitivity

3.3.12 Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.

3.3.13 Patients with untreated central nervous system disease. Patients with controlled treated CNS lesions who have undergone surgery or stereotactic radiosurgery and stable for 4 weeks are eligible.

3.3.14 Inability to comply with protocol required procedures.

3.3.15 Patients with medical conditions that require chronic systemic corticosteroid therapy or require any other form of immunosuppressive medication. However, patients using physiologic replacement doses of hydrocortisone, or its equivalent, will be considered eligible for this study: up to 20 mg hydrocortisone (or 5 mg of prednisone) in the morning and 10 mg hydrocortisone (or 2.5 mg prednisone) in the evening.

3.3.16 Patients with the risk factors for bowel obstruction or bowel perforation (examples include but not limited to a history of acute diverticulitis, intra-

abdominal abscess, abdominal carcinomatosis).

3.3.17 Patients who have received a live vaccine within 30 days prior to the first dose of trial treatment.

3.3.18 Patients who have had allogeneic SCT/solid organ transplant

3.4 Inclusion of Women and Minorities

Men, women, children (age ≥12 for bone sarcomas only), and members of all ethnic and racial groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines

After obtaining informed consent, only eligible patients will be enrolled in this trial. Eligible patients will be registered by local sites through an electronic database, and will be issued a subject unique identifying number. An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each patient treated with the study drug in the study or registered to the study. SARC may request faxed copies of selected source documents with PHI redacted for verification of records, accuracy of electronic submissions and review of data.

While all study evaluations must be performed by the Investigator, as described in Section 10 (Study Evaluations and Study Calendar), only data related to the primary and secondary endpoints, as well as safety data, will be captured in the eCRFs.

4.2 Registration Process

This study uses a web based data capture system. All patient registration and Case Report Forms (CRFs) will be submitted electronically via a web-based electronic database. All patients must be registered on the study website prior to start of treatment. Data Managers and other authorized users will be provided with a unique user identification number and password to access the site. All study case report forms may be accessed online through the study website. In case there are problems accessing the website, please contact the SARC office directly by phone: 734-930-7600 or by fax: 734-930-7557.

5. TREATMENT PLAN

5.1 Agent Administration

Pembrolizumab will be administered at 200 mg intravenously every 3 weeks. The pharmacist will prepare pembrolizumab for administration. The Pharmacy Manual that contains specific instructions for pembrolizumab dose calculation, reconstitution,

preparation and administration of the infusion fluid will be provided by Merck. The treatment dosing schedule for this trial is outlined below in Table 1.

Table 1: Treatment Dosing Schedule

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	every 3 weeks	IV infusion	30 minutes (-5/+10)	Experimental

The pembrolizumab dosing interval may be increased due to toxicity as described in Section 6.2. Pre medications will not be administered prior to study drug.

5.2 Time of Drug Administration

Study drug should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Study Calendar (Section 10). After the first cycle, trial treatment may be administered ± 3 days to the scheduled Day 1 of each cycle.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab will be administered as a 30 minute IV infusion (treatment cycle intervals may be increased due to toxicity as described in Section 6.2). Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., allowed infusion time is between 25 and 40 minutes).

5.3 Trial Blinding/Masking

This is an open-label trial; therefore, the Sponsor, site Investigator and patient will know the treatment to be administered. All enrolled patients will receive pembrolizumab.

5.4 General Concomitant Medication and Supportive Care Guidelines

5.4.1 Concomitant Medications/Vaccinations

Any concomitant medications that the patient is taking that leads to an Adverse Event (AE) grade 1 or greater based on CTCAE v 4.0 will be recorded. This data will be captured on the Adverse Events eCRF.

Also, any concomitant medication abnormality fulfilling the criteria for a Serious Adverse Event (SAE) should be reported as such, in addition to being recorded as an adverse event in the eCRF.

5.4.1.1 Prohibited Concomitant Medications

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

- Anti-cancer systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with Sponsor.
- Live vaccines within 30 days prior to the first dose of study drug and while on study. Examples of live vaccines include, but are not limited to the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Glucocorticoids for any purpose other than to treat or prevent any AE, or to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic dose of corticosteroids is allowed.

Patients who require the use of any of the aforementioned treatments for clinical management, per the site Investigator's assessment should be removed from the trial. Patients may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria describes other medications which are prohibited in this trial.

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

5.4.2 Rescue Medications & Supportive Care

5.4.2.1 Supportive Care Guidelines

Patients should receive appropriate supportive care measures as deemed necessary by the treating site Investigator including but not limited to the items outlined below:

Pneumonitis:

- For **Grade 2 events**, treat with systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent).

- For **Grade 3-4 events**, bronchoscopy should be performed to exclude infectious etiologies before starting immunosuppression. Once infectious etiologies are excluded, immediately treat with intravenous steroids (1-2 mg/kg/day of prednisone or equivalent). If symptoms persist for more than 3-5 days, then begin infliximab 5 mg/kg. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Permanently discontinue pembrolizumab.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Permanently discontinue pembrolizumab.
- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

Diarrhea/Colitis:

Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

- All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
- For **Grade 2 diarrhea/colitis,** administer oral corticosteroids (1-2 mg/kg/day prednisone or equivalent).
- For **Grade 3 or 4 diarrhea/colitis,** treat with intravenous steroids (1-2 mg/kg/day prednisone or equivalent) followed by high dose oral steroids. If grade 3-4 diarrhea persists for more than 3-5 days, then begin infliximab 5 mg/kg.
  - For grade 4 diarrhea/colitis, permanently discontinue pembrolizumab.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)

- For **T1DM** or **Grade 3-4** Hyperglycemia
  - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with

metabolic acidosis or ketonuria.

- Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

Hypophysitis:

- For **Grade 2** events, treat with corticosteroids (1-2 mg/kg/day prednisone or equivalent). When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

Hyperthyroidism or Hypothyroidism:

Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

- **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
  - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
  - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.
- **Grade 3-4** hyperthyroidism
  - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids (1-2 mg/kg/day prednisone or equivalent). When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - Permanently discontinue pembrolizumab for **Grade 4** hyperthyroidism.

Hepatic Adverse Events:

- For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
  - Treat with IV or oral corticosteroids (0.5-1 mg/kg/day prednisone or equivalent)
- For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to

48 hours (1-2 mg/kg/day prednisone or equivalent. If grade 3-4 hepatitis persists for more than 3-5 days, then begin mycophenolate 1 g twice daily. Permanently discontinue pembrolizumab for AST or ALT > 5x ULN or total bilirubin >3x ULN.

- When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

- **Renal Failure or Nephritis**:For **Grade 2** events, treat with corticosteroids (1-2 mg/kg/day prednisone or equivalent).
- For **Grade 3-4** events, treat with systemic corticosteroids (1-2 mg/kg/day prednisone or equivalent). Permanently discontinue pembrolizumab.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. For **Grade 3-4** events, stop infusion and permanently discontinue pembrolizumab.

Table 2 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 2: Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg
NCI CTCAE Grade	**Treatment**	**Premedication at subsequent dosing**

	Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

- **Steven Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)**:
  - **For signs or symptoms of SJS or TEN, withhold pembrolizumab and refer the patient for specialized care for assessment and treatment**.
  - **If SJS or TEN is confirmed, permanently discontinue pembrolizumab**.
- **Immune-mediated myocarditis management**
  - **For suspected immune-mediated myocarditis, ensure adequate evaluation to exclude other etiologies, and administer corticosteroids as appropriate.**

5.5 Diet/Activity/Other Considerations

5.5.1 Diet

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

5.5.2 Contraception

Pembrolizumab may have adverse effects on a fetus *in utero*. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. Men and non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive women are defined as: 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥ 45 years of age and has not had menses for more than 1 year), or 3) not heterosexually active for the duration of the study. The two birth control methods can either be two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Patients should start using birth control from study visit 1 throughout the study period up to 120 days after the last dose of study therapy.

The following are considered adequate barrier methods of contraception: diaphragm, condom, copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including subcutaneous, intrauterine, or intramuscular agents).

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 they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 7.2.4. If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

5.5.3 Use in Pregnancy

If a patient inadvertently becomes pregnant while on treatment with pembrolizumab, 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 site will report the outcome of the pregnancy to SARC without delay and **within 24 hours** 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 site

investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to SARC. If a male patient impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to SARC and followed as described above and in Section 7.2.4.

5.5.4 Use in Nursing Women

It is unknown whether pembrolizumab is excreted in human milk. Since many

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

5.6 Duration of Therapy

Treatment may continue until one of the following criteria applies:

- Patient achieves SD, PR, or CR and completes 35 cycles of treatment without unacceptable adverse event(s) (Section 6.1).
- Clinical or radiographic disease progression as defined by RECIST 1.1. Patient may be allowed to continue treatment after progression for a maximum of 35 cycles of treatment if they are deriving clinical benefit (refer to section 2.17).
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the site investigator
- Unacceptable adverse event(s) (Section 6.1)
- Need for > 2 dose delays due to toxicity
- Pregnancy in patient
- Patient is lost to follow-up.

5.6.1 Duration of Participation

Each patient will participate in the trial from the time of Informed Consent Form (ICF) is signed through final protocol-specified contact. After a screening phase for eligibility, patients will receive pembrolizumab every 3 weeks. Treatment for patients that achieve SD, a PR, or a CR can continue for a maximum of 2 years. At the discretion of the investigator, patients who have progressive disease (PD) but continue to achieve clinical benefit, may also continue on therapy for a maximum total duration of treatment of ***35cycles***.

5.7 Duration of Follow Up

Patients will be followed for 30 days +/- 14 days after termination of study treatment or until death, whichever occurs first. Patients removed from study for adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.8 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 5.6 applies. The reason for study removal and the date the patient was removed must be documented in the eCRF including death or lost to follow up.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose reduction of pembrolizumab will not be permitted in individual patients.

6.1 Discontinuation of Therapy:

Therapy with pembrolizumab will be permanently discontinued for any of the following:

a. Severe or life-threatening adverse reactions, including, but not limited to, any of the following (SARC must be notified in the event of these AEs and final decision regarding treatment will be made after a discussion):

- Drug related grade 4 toxicity (non-hematologic or hematologic)
- Diarrhea with abdominal pain, fever, ileus, or peritoneal signs; increase in stool frequency (7 or more bowel movements over baseline), stool incontinence, need for intravenous hydration for more than 24 hours, gastrointestinal hemorrhage, and gastrointestinal perforation
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5 times upper limit of normal. For patients with liver metastasis who entered the study with grade 2 elevation of AST/ALT, pembrolizumab will be permanently discontinued if AST/ALT increase ≥ 50% relative to baseline and lasting ≥ 1 week)
- Total serum bilirubin >3 times upper limit of normal
- Severe (i.e., CTCAE grade 3 or 4) motor or sensory neuropathy, Guillain-Barré syndrome, or myasthenia gravis or other neurologic symptoms that impact activity of daily living
- Severe immune-mediated reactions involving any other organs (e.g., nephritis, pneumonitis, pancreatitis, non-infectious myocarditis)
- Immune-mediated ocular disease that is unresponsive to topical immunosuppressive therapy
- Grade 4 infusion reaction

- Confirmed diagnosis of Stevens-Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN)

b. Inability to reduce corticosteroid dose for immune-related adverse reactions to ≤ 10 mg prednisone or equivalent per day

c. New or worsening ophthalmologic disorders, including loss of visual acuity or visual field and evidence of retinopathy.

6.2 Withholding/Resuming Therapy

Study therapy will be withheld for the following adverse reactions:

a. A drug-related clinically significant toxicity ≥ Grade 2, with the exception of the adverse reactions listed under requirement of permanent discontinuation of study therapy.

b. Grade 2 fatigue does not require the withholding of pembrolizumab.

c. When toxicity resolves or improves to ≤ grade 1, therapy with pembrolizumab will resume.

d. In case toxicity does not resolve or improve to ≤ grade 1 within 12 weeks after last administration of pembrolizumab, study drug discontinuation should be considered after discussion with SARC and overall study PI. If SARC, study PI and Merck are in agreement, patients who still have grade 2 toxicity at 12 weeks may continue on study only if asymptomatic and controlled.

e. Two dosing delays due to toxicity will be permitted. In the event of a third occurrence of a toxicity, which would require dosing delay, study therapy will be discontinued permanently.

f. For signs or symptoms of SJS or TEN, withhold KEYTRUDA® and refer the patient for specialized care for assessment and treatment.

Dose modification and toxicity management for immune-related AEs associated with pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than on body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical trial data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, 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. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 4.

Table 4: Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea,

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
	Grade 4	Permanently discontinue		abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold		• Monitor for signs and symptoms of

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
	Grade 3 or 4	Withhold or permanently discontinue[1]	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	hypophysitis (including hypopituitarism and adrenal insufficiency)
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:

For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

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

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 5.

Table 5: Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject 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 subject 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 subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of_____with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Subject is permanently discontinued from further study drug treatment.**	No subsequent dosing
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 v4.0 (CTCAE) at http://ctep.cancer.gov		

Other allowed dose interruption for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Adverse Events and Laboratory Abnormalities

7.1.1 Adverse Events (AEs)

7.1.1.1 Definition of Adverse Events

Per the International Conference of Harmonization (ICH), an AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. Pre-existing conditions which worsen during a study are to be reported as AEs.

7.1.1.2 CTCAE term (AE description)

The descriptions found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov). All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

7.1.1.3 Intensity

Intensity of all adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events v 4.0 (CTCAE) on a five-point scale (grades 1 to 5) and reported in detail on the CRF. Adverse events not listed on the CTCAE should be graded as follows:

CTC Grade	Equivalent To:	Definition
Grade 1	Mild	Discomfort noticed but no disruption of normal daily activity
Grade 2	Moderate	Discomfort sufficient to reduce or affect daily activity; no treatment or medical intervention is indicated although this could improve the overall well-being or symptoms of the patient
Grade 3	Severe	Inability to work or perform normal daily activity; treatment or medical intervention is indicated in order to improve the overall well-being or symptoms; delaying the onset of treatment is not putting the survival of the patient at direct risk.
Grade 4	Life threatening/ disabling	An immediate threat to life or leading to a permanent mental or physical conditions that prevents work or performing normal daily activities; treatment or medical intervention is required in order to maintain survival.
Grade 5	Death	AE resulting in death

7.1.1.4 Drug-Adverse Event relationship

The causality relationship of study drug to the adverse event will be assessed by the investigator as either: **Yes or No.**

If there is a reasonable suspected causal relationship to the study medication, i.e. there are facts (evidence) or arguments to suggest a causal relationship, drug-event relationship should be assessed as **Yes**.

The following criteria should be considered in order to assess the relationship as **Yes:**

- Reasonable temporal association with drug administration
- Known response pattern to suspected drug
- Disappears or decreases on cessation or reduction in dose
- Reappears on re-challenge

The following criteria should be considered in order to assess the relationship as **No**:

- It does not follow a reasonable temporal sequence from administration of the drug
- It may readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient
- It does not follow a known pattern of response to the suspected drug

- It does not reappear or worsen when the drug is re-administered.

7.1.1.5 Progression of Underlying Malignancy

Progression of underlying malignancy is not reported as an adverse event if it is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST criteria, or other criteria as determined by protocol.

Hospitalization due solely to the progression of underlying malignancy should NOT be reported as a serious adverse event. Clinical symptoms of progression may be reported as adverse events if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.

Symptomatic deterioration may occur in some patients. In this situation, progression is evident in the patient's clinical symptoms, but is not supported by the tumor measurements or, the disease progression is so evident that the investigator may elect not to perform further disease assessments. In such cases, the determination of clinical progression is based on symptomatic deterioration. These determinations should be a rare exception as every effort should be made to document the objective progression of underlying malignancy.

If there is any uncertainty about an adverse event being due only to the disease under study, it should be reported as an AE or SAE.

7.1.1.6 Treatment and Follow-up AEs

After the discontinuation of therapy with pembrolizumab continue to follow up AEs as follows:

Related AEs: Follow until one of the following occurs:

- Resolved or improved to baseline
- Relationship is reassessed as unrelated
- Death
- Start of new anti-cancer regimen
- Investigator confirms that no further improvement can be expected
- Clinical or safety data will no longer be collected or final database closure

Unrelated severe or life threatening AEs: Follow until one of the following occurs:

- Resolved or improved to baseline
- Severity improved to grade 2
- Death
- Start of new anti-cancer regimen
- Investigator confirms that no further improvement can be expected

- Clinical or safety data will no longer be collected or final database closure

Unrelated Grade 1 or Grade 2 AEs: Follow as clinically indicated.

The final outcome of each adverse event must be recorded on the eCRF.

7.1.2 Laboratory Test Abnormalities

7.1.2.1 Abnormal Laboratory Tests

Laboratory test results will be recorded as adverse events only if they meet criteria for CTCAE v 4.0 grade 1 or greater. These data will be captured on the adverse events eCRF.

Any laboratory result abnormality fulfilling the criteria for a SAE should be reported as such, in addition to being recorded as an adverse event on the eCRF.

7.1.2.2 Follow-up of Abnormal Laboratory Test

In the event of medically significant unexplained abnormal laboratory test values, the test should be repeated and followed until it has returned to the normal range, baseline value and/or an adequate explanation of the abnormality is found. If a clear explanation is established it should be recorded on the eCRF.

7.1.3 Serious Adverse Events

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

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose;
- Is another important medical event

Progression of the disease under study is not considered an adverse event unless it results in hospitalization or death.

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer that occurs to any patient from the time treatment is started (Day 1) through 30 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to pembrolizumab, must be reported **within 24**

hours to the SARC. SARC will notify Merck within 1 working day as outlined in the section 7.2.2.

Non-serious Events of Clinical Interest will be handled in the same manner as SAEs.

Additionally, any serious adverse event assessed by a site Investigator as related to pembrolizumab, regardless of the time elapsed, even if the study has been closed, should be reported to SARC and Merck (as outlined in the section 7.2.2).

A copy of all reports submitted to FDA will be sent to Merck at:
Merck Global Safety,
Attn: Worldwide Product Safety;
Fax: 215-993-1220

7.1.4 Pembrolizumab Overdose

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for pembrolizumab by 20% (> 240 mg). No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, pembrolizumab should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

7.1.5 Events of Clinical Interest

Events of clinical interest (ECI) are selected adverse events for this trial including:

1. An overdose of pembrolizumab, as defined in Section 7.1.4, that is not associated with clinical symptoms or abnormal laboratory results.

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

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

7.2 Handling of Safety Parameters

7.2.1 Reporting of Adverse Events

All adverse events (related and unrelated) grade 1-5 occurring during the study and up to 30 days after the last dose of study medication must be reported and recorded in the study database. Reporting the specific time of onset of a given AE is only necessary when it occurs in relation to study drug administration.

7.2.2 Reporting of Serious Adverse Events (immediately reportable)

Any clinical adverse event or abnormal laboratory test value that is *serious* and which occurs during the course of the study (as defined in section 7.1.3below), must be reported to SARC **within *24 hours*** of the site investigator becoming aware of the event. If only limited information is initially available, follow-up reports are required. The original SAE form must be kept on file at the study site.

SAEs must be reported on the MedWatch Form 3500A along with the completed Fax/Email Coversheet and faxed or emailed to SARC office (See Appendix B). SARC will notify Merck within 1 working day by faxing the complete report to:

Merck Global Safety
Attn: Worldwide Product Safety
Fax: 215-993-1220

Related Serious Adverse Events ***MUST*** be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed.

Unrelated Serious Adverse Events must be collected and reported during the study and for up to 30 days after the last dose of study medication

7.2.3 Reporting of Overdose to the Sponsor and to Merck

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

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

All reports of overdose with and without an adverse event must be reported **within 24 hours** to SARC. SARC will notify Merck within 1 working day as outlined in the section 7.2.2.

7.2.4 Reporting of Pregnancy and Lactation to the Sponsor and to Merck

Although pregnancy and lactation are not considered adverse events, it is the responsibility of the site investigators or their designees to report any pregnancy or lactation in a patient (spontaneously reported to them), including the pregnancy of a male patient's female partner that occurs during the trial or within 120 days of completing the trial completing the trial, or 30 days following cessation of treatment if the patient initiates new anticancer therapy, whichever is earlier. All patients and female partners of male patients who become pregnant 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 SARC. SARC will notify Merck within 1 working day as outlined in the section 7.2.2.

7.2.5 Reporting of Serious Adverse Events

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer that occurs to any patient from the start of study treatment (Day 1) through 30 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to pembrolizumab, must be reported **within 24 hours** to SARC. SARC will notify Merck within 1 working day as outlined in the section 7.2.2.

Non-serious Events of Clinical Interest will be forwarded to Merck Global Safety and will be handled in the same manner as SAEs.

Additionally, any serious adverse event assessed by a site Investigator, who is a qualified physician as related to pembrolizumab, regardless of the time elapsed, even if the study has been closed, should be reported to SARC and Merck (as outlined in the section 7.2.2).

A copy of all 15 Day Reports and Annual Progress Reports will be submitted as required by FDA and will be cross referenced according to local regulations to Merck's Pembrolizumab IND Number at the time of submission

A copy of all reports submitted to FDA will be sent to Merck at:
Merck Global Safety,
Attn: Worldwide Product Safety;
Fax: 215-993-1220

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

8. PHARMACEUTICAL INFORMATION

8.1 Study Agent

Pembrolizumab is a potent and highly selective humanized mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2.

8.2 Preparation and Administration

Pembrolizumab will be given at 200 mg intravenously every 3 weeks.

8.3 Formulation, Packaging and Labelling

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements. Pharmacist will receive open label packages of the drug. Clinical Supplies will be provided by Merck as summarized in Table 7.

Table 7. Product Descriptions

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

8.4 Storage and Handling Requirement

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site. Clinical supplies may not be used for any purpose other than that stated in the protocol.

8.5 Agent Ordering

Pembrolizumab will be provided by Merck. Details will be provided in the Operations Manual.

8.6 Agent Accountability

Accountability and patient compliance will be assessed by maintaining adequate drug dispensing and return records. Compliance with individual patient dosing is assured as the drug is administered intravenously and recorded at the clinical site.
Accurate records must be kept for each study drug provided by Merck. The drug dispensing log must be kept current and contain the following information:

- documentation of drug shipments received from Merck (date received and quantity)
- disposition of unused study drug not dispensed to patient
- the identification of the patient to whom the study medication was dispensed
- the date(s) and quantity of the study medication dispensed to the patient

This inventory must be available for monitoring. All supplies, including unused, partially used or empty containers will be destroyed according to sites drug destruction policy. Copies of the dispensing & inventory logs will be sent to SARC for remote monitoring.

8.7 Destruction of Pembrolizumab

Local or institutional regulations may require immediate destruction of used pembrolizumab for safety reasons e.g., cytotoxicity. In these cases, it may be acceptable for investigational site staff to destroy dispensed pembrolizumab before monitoring is done provided that source document verification is performed on the remaining inventory and reconciled against the documentation of quantity shipped, dispensed, returned and destroyed.

Written documentation of destruction must contain the following:

- Identity (batch numbers or patient numbers) of pembrolizumab destroyed
- Quantity of pembrolizumab destroyed
- Date of destruction (date discarded in designated hazardous container for destruction)
- Method of destruction (the site must provide the sponsor with documentation of their institutional policy and procedures for handling and disposing of hazardous drugs)
- Name and signature of responsible person (or company) who destroyed pembrolizumab.

A list of the adverse events and potential risks associated with pembrolizumab can be found in Section 7.1.

9. CORRELATIVE/SPECIAL STUDIES

9.1 Laboratory Correlative Studies

All biospecimens collected from patients enrolled in SARC028 study will be kept at a SARC designated specimen bank

9.1.1 Collection, Handling and Shipping of Specimens

Details for collection, handling and shipment of specimens will be provided in the Operations Manual.

9.1.2 Correlative Studies

The following correlative studies will be performed using blood for research studies and tumor tissues collected from the patients included in the study. In the expansion cohort, correlative tumor samples will be collected from 20 patients in each of the expansion cohorts of UPS and LPS. Ten (10) patients in each expansion cohort

whose disease is not amenable to biopsy can be enrolled and for these patients, tissue correlative samples will not be collected.

All subjects enrolled will have correlative blood samples collected.

- Evidence of immune up-regulation at tumor sites:
  - Increased tumor-infiltrating CD8+ T cells using immunohistochemistry (IHC).
  - Evaluation of PD-1and PD-L1 expression by T cells and malignant cells, respectively, using IHC.

  Sections of formalin-fixed, paraffin-embedded tumor samples will be obtained from tumor biopsies of the patients as previously indicated. Standard immunohistochemistry (IHC) will be performed using antibodies against human B7-H1/PD-L1, human PD-1, CD3, CD8, CD4 and may include additional markers: CCR7, CD45RO, CD68 and CSPG4. Slides will be evaluated and scored independently by two experienced pathologists. PD-L1 expression will be expressed as % of positive cells among malignant cells. PD-1 expression will be expressed as % of PD-1 positive cells relative to the total number of CD3 cells. We expect to observe a significant increase of $CD8^+$ TILs after treatment with pembrolizumab as compared to pre-treatment. We also expect that PD-L1 expression by malignant cells will increase after treatment with pembrolizumab as compared to pre-treatment.
- Inhibition of malignant cell proliferation, increased pro-apoptotic activity, up-regulation of HLA antigen and MA expression, and inhibition of STAT signaling pathways associated with sarcoma cell proliferation and survival:
  - The expression of β2m-associated HLA-A and HLA-B/C loci gene products and of HLA class II antigens will be assessed by immunostaining of frozen tissue sections. The HLA-A-specific mAb LGIII-147.4.1[46], the HLA-B/C-specific mAb B1.23.2 [47] and the HLA class II antigen-specific mAb LGII-612.14 [48] will be used as molecular probes.
  - The expression of APM components LMP2, LMP7, LMP10, TAP1, TAP2, calnexin, calreticulin, ERP57 and tapasin will be assessed by staining formalin fixed, paraffin embedded tissue sections with the mAb SY-1, HB2, TO-7, NOB1, NOB2, TO-5, TO-11, TO-2 and TO-3 [49, 50].
  - To investigate the effect of therapy on sarcoma cell proliferation and apoptosis, sections of formalin fixed, paraffin embedded sarcoma metastases will be analyzed for p-Histone H3 and Cleaved Caspase-3 expression by IHC staining. The results will be expressed as the positive cell numbers from 10 randomly selected high-power (magnification ×200) fields per section by quantitative analysis.
  - Other immunological endpoints will include studies of STAT 1/3/5a/5b and IFNAR, MHC class I and pERK expression.
- Reversal of $PD1^+$ TA-specific $CD8^+$ and $CD4^+$ T cell dysfunction and rescue of memory TA-specific $CD8^+$ and $CD4^+$ T cells from terminal exhaustion:
  Tumor biopsy samples will be processed to obtain single cell suspensions to isolate TILs and tumor cells. Multiparameter flow cytometry will be used to

investigate the phenotype and functions of TILs and the expression of PD-L1 by sarcoma cells and tumor-infiltrating cells ex vivo. $CD3^+$ T cells will be isolated with magnetic beads (Miltenyi, Biotec) and $CD3^+$ and non-$CD3^+$ cells will be used for flow cytometry studies. We expect that therapy with pembrolizumab will result in increased number and function of $CD8^+$ and $CD4^+$ TILs at tumor sites.

Evaluation of NY-ESO-1-specific $CD8^+$ and $CD4^+$ T cells in patients with NY-ESO-1 expressing sarcoma at periphery (leukapheresis) and at tumor sites using flow cytometry including tetramer and intracellular cytokine staining. CD8+ and CD4+ T cell responses against NY-ESO-1 and other sarcoma antigens will be evaluated from PBLs of the sarcoma patients using peptide libraries and flow cytometry assay.

9.1.3 Biopsy

Pre- and post-treatment biopsies will be required for 20 patients in each of the expansion cohorts of UPS and LPS. Mandatory biopsies will be obtained during screening prior to first study drug administration (week 0), and at week 8 (± 1 week). Additional optional biopsies of easily accessible tumors may also be performed at cycle 12 (week 34) and at time of progression. Surgical excisional or core biopsies are acceptable. Ten patients whose disease is not amenable to biopsy can be enrolled in each of the expansion cohorts of UPS and LPS and no biopsy will be required.

Archival tissue will be mandatory for PD-L1 testing on all patients.

Schedule for Tumor Biopsy Samples Collection			
Time points for Tumor biopsy samples collection		20 Patient Cohorts (UPS and LPS)	10 Patient Cohorts (UPS and LPS) without disease amenable to
Archival Tumor Samples	After eligibility is confirmed	Mandatory	Mandatory
Mandatory , pre-treatment	After eligibility is confirmed, prior to first study drug administration	Mandatory	
Mandatory, on-treatment	At week 8 (+/- 1week)	Mandatory	
Optional, cycle 12	At week 34 (+/- 1week)	Optional	
Optional, end of study treatment	At disease progression	Optional	

Biopsies will be processed for IHC:

1. Evaluation of PD-L1 expression

2. Evaluation of $CD8^+$ and $CD4^+$ T cell infiltrates.

Biopsies will be processed for single cell suspensions for intracellular cytokine assays:

1. Expression of inhibitory receptors including Tim-3 and BTLA by $CD8^+$ and $CD4^+$ TILs.

2. Expression of a number of inhibitory ligands including PD-L1, HVEM, and galectin-9 by tumor cells and tumor-infiltrating antigen presenting cells.

10. STUDY EVALUATIONS AND STUDY CALENDAR

10.1 SCREENING STUDIES

The following procedures will be performed during the screening period:

- Informed consent
- History/demographics updated within 2 weeks prior to patient enrollment
- Documentation of sarcoma histology and grade, and prior sarcoma therapies
- Physical exam, including height, weight, vital signs, ECOG performance status
- CBC with differential
- Comprehensive Serum Chemistry Panel
- T3, FT4, and TSH
- PT (or INR) and aPTT
- Urinalysis
- Serum β–HCG or urine pregnancy test for women of childbearing potential
- Archival Formalin Fixed Paraffin Embedded (FFPE) Tumor Samples (on patients enrolled in the expansion cohorts)
- Blood for research studies will be collected (pre-treatment) after eligibility for study is confirmed
- Tumor Biopsy (pre-treatment) after eligibility for study is confirmed.
- Baseline radiologic imaging that is appropriate for the specific histologic subtype per National Comprehensive Cancer Network guidelines for sarcoma (see http://www.nccn.org/professionals/physican_glas/PDF/sarcoma.pdf and http://www.nccn.org/professionals/physician_gls/PDF/bone.pdf)
- EKG within 30 days prior to first study drug administration.

The screening period will be up to 30 days prior to first study drug administration (Day1 Cycle1). Laboratory baseline evaluations are to be conducted within 14 days prior to first administration of study drug. Radiologic imaging must be done 30 days prior to first study drug administration

10.2 ON STUDY EVALUATIONS

Patients who have previously met laboratory inclusion criteria at screening may potentially receive Cycle 1 dose of medication even if laboratory studies drawn on Cycle 1 day one do not meet the eligibility criteria. Study drug may be given as long as labs do not meet threshold for dose delay/schedule modification. Cycle visits will occur at each treatment visit (i.e. every 3 weeks) from study initiation. The following procedures will be performed during the treatment period:

- Physical exam, including weight, vital signs, ECOG performance status
- Administration of study drug
- Recording of adverse events
- Relevant laboratory evaluations, WBC, Hgb, Plt, ANC, Cr, K, Ca, ALT, AST, Total Bilirubin, alkaline phosphatase, PT (or INR), PTT, TSH, Free T4, T3
- Blood for research studies will be collected at week 8 (± 1 week) and then every 12 weeks (± 1 week) subsequently until patient completes 12 cycles
- Disease assessments will be performed at week 8 (± 1 week) and then every 12 weeks (± 1 week) subsequently
- Biopsy at week 8 (± 1 week) and optional biopsy may be collected at cycle 12.

NOTE: All studies can be obtained ± 3 days of stated time point unless otherwise noted.

10.3 OFF TREATMENT EVALUATIONS

Final visit is to be performed at the time (or within 30 days +/- 14 days of removal from the treatment). Off treatment evaluations will include:

- Physical exam: height, weight vital signs, ECOG performance status
- Serum β–HCG or urine pregnancy test for women of childbearing potential
- Relevant laboratory evaluations, including CBC with differential and comprehensive serum chemistry panel
- Urinalysis
- PT (or INR) and PTT
- EKG
- Recording of adverse events (for unresolved adverse events, patients should be monitored for 30 days following the last dose of study drug)
- Extent of disease evaluation with appropriate radiographic procedures if not performed within 30 days of the final visit
- Off treatment Biopsy collected due to progression (optional).

Follow-Up:
Patients who complete study treatment should be followed for survival every 6 months. Patient will be contacted by phone at a minimum and survival status will be collected and documented. Survival status can also be assessed via patient's medical records or via certified letter.

STUDY CALENDAR

	Pre-Study	Wk 1	Wk 4	Wk 7	Wk 10	Wk 13	Wk 16	Wk 19	Wk 22	Wk 25	Wk 28	Wk 31	Wk[K] 34+	Off Treatment[l]
Study Drug Admin [a]		X	X	X	X	X	X	X	X	X	X	X	X	
Informed consent	X													
History/Demographics	X													
Physical exam [b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC with Differential [c]	X [f]	X	X	X	X	X	X	X	X	X	X	X	X	X
Comprehensive Serum Chemistry Panel[d]	X [f]	X	X	X	X	X	X	X	X	X	X	X	X	X
TSH, FT4, T3	X [f]	X	X	X	X	X	X	X	X	X	X	X	X	
PT (or INR) and PTT	X [f]	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X [f]													X
Serum or urine pregnancy test [e]	X [f]													X
EKG	X [g]													X
Archival Tumor Samples (FFPE) (only patients from expansion)	X													
Adverse event evaluation		X ---------- X												X
Biopsies	X	X[J] ---------- X [J]												X[J]
Radiologic evaluation	X [h]	First radiologic measurements will be performed at 8 weeks (± 1 week) initially, then every 12 weeks subsequently.												X [i]
Blood Sample Collection	X [m]	Blood samples will be collected at 8 weeks (± 1 week), week 20 (± 1 week), week 32 (± 1 week). Collection will end after patient completes cycle 12												
Follow up														X [n]

a: Pembrolizumab
b: Including height, weight ,vital signs, ECOG performance status
c: WBC, Hgb, Plt, ANC, PT (or INR), PTT
d:Cr, K, Ca, ALT, AST, Alkaline phosphatase, Total bilirubin
e: Women of childbearing potential
f: Laboratory baseline evaluations are to be conducted within 14 days prior to first study drug dose
g:EKG within 30 days prior to first study drug administration
h: Scans and x-rays must be performed within 30 days prior to first study drug dose
i: Extent of disease evaluation with appropriate radiographic procedures if not performed within 30 days of the final visit.
j: Mandatory biopsies will be collected pre and post treatment at week 0 and 8 and optional biopsies may be collected at cycle 12 (week 34) and at time of progression for 20 patients enrolled in the expansion cohorts of UPS and LPS.
k: Patients may continue on study drug beyond 12 cycles at discretion of study doctor. Use monthly visits as a template for every monthly evaluations as long as patient remains on study drug.
l: Off-study evaluation should be performed at the time (or within 30 days) of removal from study.
m: Blood samples will be collected pre-treatment (after eligibility is confirmed)
n: Patient will be followed for survival every 6 months via phone call at a minimum. Survival status will be documented after each call.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be evaluated for response initially after first 8 weeks on study and then every 12 weeks.

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) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with pembrolizumab.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray or as ≥ 10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area are not considered measurable unless there is evidence of progression after radiation therapy.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15

mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'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.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

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. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. 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. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. 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.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of target lesions, taking as

reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression (see comments below of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Note: *When the patient also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of*

SD or PR of target disease will therefore be extremely rare.

11.1.4.3 Evaluation of Tumor Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/ Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD
CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease, and NE = inevaluable * In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.			

11.1.4.4 Best Overall Response when confirmation of CR and PR required

The best overall response is the best response recorded from the start of the study treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best overall response assignment will depend on the achievement of both measurement and confirmation criteria.

Overall response First time point	Overall Response Subsequent time point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease, and NE = Inevaluable

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

11.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.1.6 Progression-Free Survival

Progression-Free Survival is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

11.1.7 Response Review

All responses will be investigator assessed. Responses may also be reviewed by an expert(s) independent of the study at the study's completion.

11.1.8 Definition of Tumor Response Using irRC

The sum of the products of diameters (SPD) at tumor assessment using the immune-related response criteria (irRC) for progressive disease incorporates the contribution of new measurable lesions. Each net percentage change in tumor burden per assessment using irRC criteria accounts for the size and growth kinetics of both old and new lesions as they appear.

11.1.8.1. Definition of Index Lesions Response Using irRC

- irComplete Response (irCR): Complete disappearance of all index lesions. This category encompasses exactly the same patients as "CR" by the modified WHO (mWHO) criteria.

- irPartial Response (irPR): Decrease, relative to baseline, of 50% or greater in the sum of the products of the two largest perpendicular diameters of all index and all new measurable lesions (i.e., Percentage Change in Tumor Burden). Note: the appearance of new measurable lesions is factored into the overall tumor burden, but does not automatically qualify as progressive disease until the SPD increases by ≥25% when compared to SPD at nadir.

- irStable Disease (irSD): Does not meet criteria for irCR or irPR, in the absence of progressive disease.

- irProgressive Disease (irPD): At least 25% increase Percentage Change in Tumor Burden (i.e., taking sum of the products of all index lesions and any new lesions) when compared to SPD at nadir.

11.1.8.2 Definition of Non-Index Lesions Response Using irRC

- irComplete Response (irCR): Complete disappearance of all non-index lesions. This category encompasses exactly the same patients as "CR" by the mWHO criteria.

- irPartial Response (irPR) or irStable Disease (irSD): non-index lesion(s) are not considered in the definition of PR, these terms do not apply.

- irProgressive Disease (irPD): Increases in number or size of non-index lesion(s) does not constitute progressive disease unless/until the Percentage Change in Tumor Burden increases by 25% (i.e., the SPD at nadir of the index lesions increases by the required amount).

11.1.8.3 Impact of New Lesions on irRC

New lesions in and by themselves do not qualify as progressive disease. However, the contribution of new measurable lesions to total tumor burden is included in the SPD which in turn feeds into the irRC criteria for tumor response. Therefore, new non-measurable lesions will not discontinue any patient from the study.

11.1.8.4 Definition of Overall Response Using irRC

Overall response using irRC will be based on these criteria:

- **Immune-Related Complete Response (irCR):** Complete disappearance of all tumor lesions (index and nonindex together with no new measurable/unmeasurable lesions) for at least 4 weeks from the date of documentation of complete response.

- **Immune-Related Partial Response (irPR):** The sum of the products of the two largest perpendicular diameters of all index lesions is measured and captured as the SPD baseline. At each

subsequent tumor assessment, the sum of the products of the two largest perpendicular diameters of all index lesions and of new measurable lesions are added together to provide the Immune Response Sum of Product Diameters (irSPD). A decrease, relative to baseline of the irSPD compared to the previous SPD baseline, of 50% or greater is considered an immune Partial Response (irPR).

- **Immune-Related Stable Disease (irSD)**: irSD is defined as the failure to meet criteria for immune complete response or immune partial response, in the absence of progressive disease.

- **Immune-Related Progressive Disease (irPD):** It is recommended in difficult cases to confirm PD by serial imaging. Any of the following will constitute progressive disease:

    - At least 25% increase in the sum of the products of all index lesions over baseline SPD calculated for the index lesions.

    - At least a 25% increase in the sum of the products of all index lesions and new measurable lesions (irSPD) over the baseline SPD calculated for the index lesions.

Table 8: Immune-Related Response Criteria Definitions

Index Lesion Definition	Non-Index Lesion Definition	New Measurable Lesions	New Unmeasurable Lesions	Percent change in tumor burden (including measurable new lesions when present)	Overall irRC Response
Complete Response	Complete Response	No	No	-100%	irCR
Partial Response	Any	Any	Any	≥ -50%	irPR
Stable Disease	Any	Any	Any	<-50% to <+25%	irSD
Progressive Disease	Any	Any	Any	≥ +25%	irPD

12. DATA REPORTING / REGULATORY CONSIDERATIONS

12.1 Data Reporting

12.1.1 Method

A final study report describing the outcome of the trial will be created at the end of the study.

12.1.2 Data Safety and Monitoring

SARC is responsible for the Data Safety Monitoring for this trial. SARC Clinical Trials Review Committee convenes monthly and will provide safety oversight for this trial. The purpose of the Clinical Trials Review Committee is to review the status of the on-going SARC studies, which includes, but is not limited to:

- Review of all safety data (Serious Adverse Events reported).
- Review of protocol deviations/violations.
- Review of study progress/accrual.
- Discussion of statistical aspects of all protocols.

The committee is chaired by the SARC Medical Officer, who is responsible for leading the meeting and providing medical oversight. Attendance includes all overall study Principal Investigators on active SARC studies, SARC Research Project Managers, SARC President, and a biostatistician.

Safety oversight for this trial is also supported by the SARC Clinical Research Committee which is made up of senior sarcoma investigators and the SARC President. This committee also convenes monthly. The Medical Officer updates the committee on the ongoing clinical trial status as well as any areas of concern particularly related to safety. This committee provides an additional level of medical oversight for this trial.

12.1.3 Patient Accrual and Participating Centers

There will be approximately 10 sites collaborating to accrue patients to this study. It is anticipated that accrual will take approximately 2 years.

This trial will be posted at ClinicalTrials.gov website.

12.2 Multi-institutional Guidelines

The trial coordinating center (Operations Center) will be SARC. Patients will be registered electronically via the study website, and adverse events (as defined in Section
7) will be reported to the SARC.

IRB Approvals:
The protocol must be approved at each participating site prior to enrolling patients. Documentation of individual institutional IRB approval, for the current protocol must be provided to SARC prior to enrolling patients in the trial. In addition, documentation

of approval of all protocol amendments and of yearly continuing review must be provided to the SARC Research Project Manager to allow patient entry. The mailing address is:

SARC
24 Frank Lloyd Wright Drive, PO Box
406 Ann Arbor, MI 48105
Phone: 734-930-7600
Fax: 734-930-7557
Email: sarc@sarctrials.org

Patient Registration:
Patient Registration will be centrally managed by SARC electronically via the study website (see Section 4.2).

Data Collection and Toxicity Reporting:
Registration reports will be generated by SARC RPM to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies by the Research Project Manager. Any potential problems will be brought to the attention of the site Principal Investigator for discussion and action.

Access to the password protected study website will be limited to individuals involved in the clinical trial: SARC, overall Study PI, participating site PIs, research nurses, and data managers responsible for this trial.

A phone conference will be held between the Study Principal Investigator, the Operations Center, site investigators, and participating sites staff biweekly to address issues, accrual, observed toxicities, and compliance with submission of required studies.

Adverse Events reporting will be performed as outlined in Section 7.

12.3 Data and Participating Site Monitoring

Data from participating sites should be available when the protocol is monitored. The site Principal Investigator is responsible for having all records and data for all patients enrolled at his/her site available at that site for monitoring. Queries as appropriate will be submitted to sites to clarify data. Submission of biologic specimens will be tracked on the study website.

12.4 Handling of Patient Data

All patient data will be captured and maintained in a study specific database with password protected access. Data is entered using an assigned patient identification

number.

The data provided to those reviewing the results, for example the study statistician will include the patient identification numbers, but will not include patient identifiable data.

The research samples obtained in this study will only be sent using the patient identification number which can only be linked to the patient at a given institution by the treating physician.

All documentation that contains personal health information that may include patient identifiable information will be maintained at the site to preserve patient confidentiality.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

A patient will be classified as a treatment success if he/she achieves a response of PR or better. On each arm of the study, we will test the hypothesis that pembrolizumab has clinical activity in patients with advanced sarcoma. An objective response rate of 25% will be considered clinically meaningful and a response rate less than 10% will be considered lack of efficacy. In a single stage design, we will accrue 40 patients in each arm. The treatment will be considered a success if 8 or more of 40 enrolled patients have a PR or better by RECIST 1.1. This design has a one-sided type I error of 4.2% and a power of 82% to detect a difference between 10 and 25%.

In the study expansion, the response rates for undifferentiated pleomorphic sarcoma cohort and the poorly differentiated/dedifferentiated liposarcoma cohort will be analyzed separately. In each subtype cohort, we will analyze a total of 40 evaluable patients (10 from part 1 of the study and 30 from the expansion cohort). An objective response rate of 25% will be considered clinically meaningful and a response rate less than 10% will be considered lack of efficacy. The treatment will be considered a success if 8 or more of 40 enrolled patients have a PR or better by RECIST 1.1. This design has a one-sided type I error of 4.2% and a power of 82% to detect a difference between 10 and 25%.

13.2 Sample Size/Accrual Rate

Initial enrollment was 86 patients: with soft tissue sarcomas and with bone sarcomas

In the expansion study, there will be an additional 60 patients with soft tissue sarcoma enrolled: 30 patients with undifferentiated pleomorphic sarcoma and 30 patients with poorly differentiated/dedifferentiated liposarcoma.

At least 20 patients in each of the undifferentiated pleomorphic sarcoma and poorly differentiated/dedifferentiated cohorts will have mandated biopsies for correlative analysis. The remaining 10 patients in each of the cohorts will not be required to obtain

baseline and 8-week tumor biopsies, although archival tissue will be required for PD-L1 testing.

13.3 Analysis of Secondary Endpoints

This design will also allow 87% power to detect an improvement in the 3-months PFS rate from 20% to 40% with a one-sided type I error of 4%.

Progression-free survival will be estimated by the product-limit method. PDL1 expression levels and baseline circulating T cell counts will be related to response via logistic regression, and to PFS via Cox regression. Changes in T cell counts will be related to outcome using appropriate landmarks. Several secondary objectives are clinical and include PFS, OS, ir-RC, and safety all of which will be analyzed taking into account the primary endpoint. All other correlative secondary objectives are exploratory as those data have not been previously reported in sarcoma and therefore will serve as hypothesis generating.

Mandatory pre/post biopsies will be performed for at least 20 patients enrolled in each of the expansion subtype cohorts. Because clear biomarkers for response to pembrolizumab remain to be determined and may not be histology specific, all samples will be evaluated as a single cohort for correlative assessments. PD1 expression on fresh biopsy tissue at both time points will be assessed. Cases will dichotomized into low/high expressers at baseline, and low/high expression changers from pre to post-treatment. Assuming an objective response rate of 10% in tumors with low expression at baseline, this will allow 90% power to detect a difference in objective response of 10% vs 40% using a two-sided 5% level test of proportions. Assuming up to 20% dropout between pre and post biopsies, if 64 patients have both pre and post biopsies, there will be 80% power to detect a difference in objective response of 10% vs 40% between low and high changers, using a two-sided 5% level test of proportions.

Any analyses by individual histologic subtypes will be exploratory only.

13.4 Reporting and Exclusions

13.4.1 Evaluation of toxicity: Safety evaluations will be done according to CTCAE v 4.0 with special emphasis on immune-related adverse events (ir-AEs).

13.4.2 Evaluation of response: Tumor measurements by CT/MRI imaging will be performed initially at 8 weeks and then every 12 weeks. (RECIST 1.1) will be the primary outcome measure and immune-related Response Criteria (ir-RC) will be a secondary outcome.