Protocol #: LCI-SAR-STS-PEM-001

TITLE: A PILOT STUDY EVALUATING THE SAFETY, TOLERABILITY AND EFFICACY OF DOXORUBICIN AND PEMBROLIZUMAB IN PATIENTS WITH METASTATIC OR UNRESECTABLE SOFT TISSUE SARCOMA

LAY TITLE: DOXORUBICIN AND PEMBROLIZUMAB IN SOFT TISSUE SARCOMA PATIENTS

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Investigational drug:
Pembrolizumab

Investigational New Drug (IND)#: 133024

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The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

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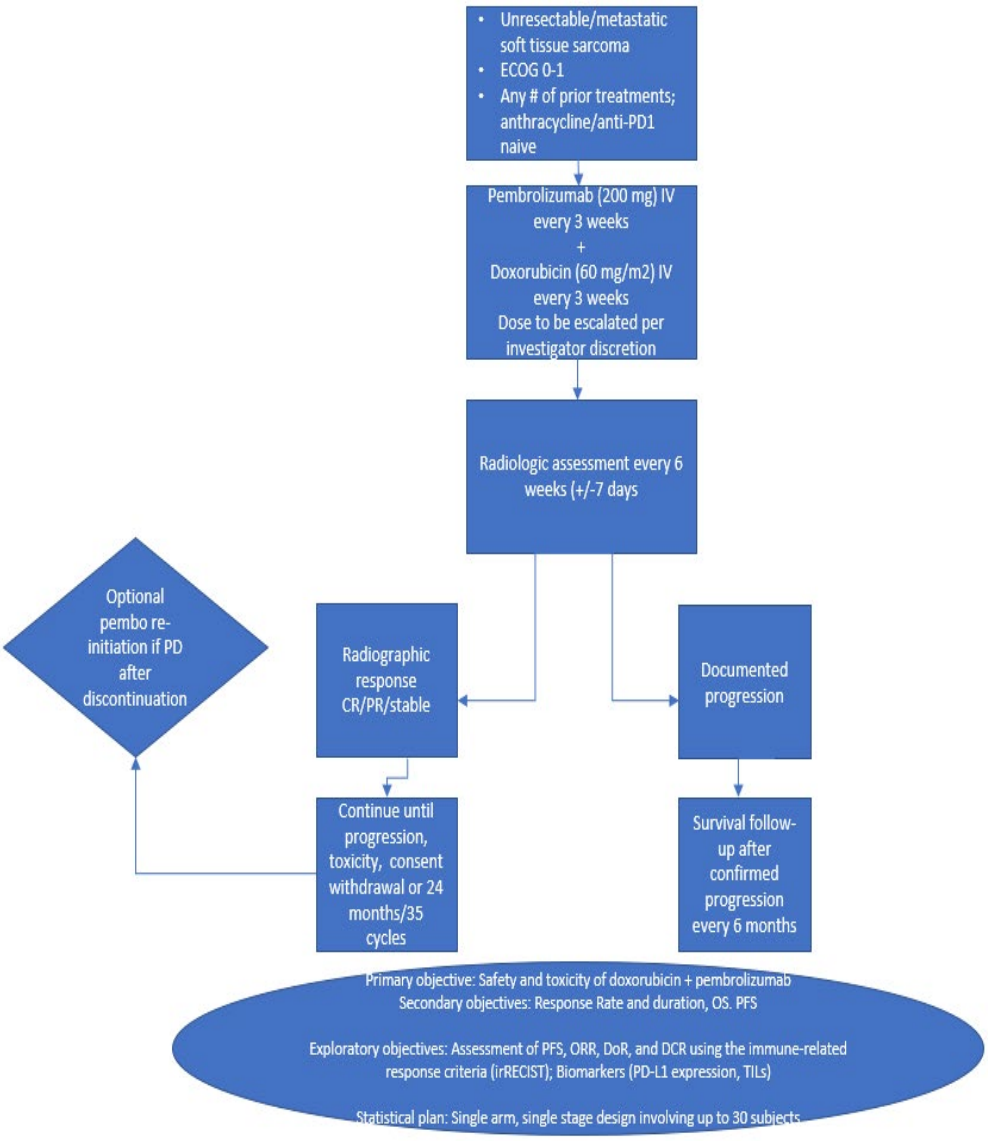
Original Phase 2 / Version 9 / April 13, 2021

PROTOCOL SUMMARY	
A. Study Title	A pilot study evaluating the safety, tolerability and efficacy of doxorubicin in combination with pembrolizumab in patients with metastatic or unresectable soft tissue sarcoma
B. Indication	Metastatic/unresectable soft tissue sarcoma
C. Clinical Phase	II
D. Summary of Rationale	Based on previous studies, pembrolizumab may be an effective treatment for patients with solid tumors. The purpose of this study is to determine whether the addition of pembrolizumab to doxorubicin will yield an acceptable response rate in subjects with advanced soft tissue sarcoma. We will also examine if PD-L1 expression in sarcoma can predict for therapeutic response to pembrolizumab in subjects with soft tissue sarcoma.
E. Study Objectives	The primary objective of this study is to assess the safety and toxicity profile of doxorubicin and pembrolizumab in previously treated or untreated subjects with unresectable or metastatic soft tissue sarcoma. The secondary objectives are to assess overall survival, response rate, duration of response, and progression-free survival with this regimen using RECIST 1.1 criteria. The exploratory objectives are to assess PFS, ORR, DoR, and DCR using the immune-related RECIST (irRECIST) criteria, evaluate the correlation between PD-L1 expression levels and antitumor activity of MK-3475, investigate other biomarkers that may correlate with tumor responses, evaluate differences in tumor tissue characteristics in biopsies taken during treatment with MK-3475 versus baseline, and evaluate ORR and PFS after second course treatment of pembrolizumab.
F. Sample	≤ 30 subjects
G. Inclusion/ Exclusion	• Recurrent/metastatic soft tissue sarcoma not appropriate for surgical therapy. • No prior anthracycline and/or immunotherapy. • ECOG 0 to 1 with normal organ function.
H. Dosage/ Dosage Form, Route, And Dose Regimen	Pembrolizumab 200 mg will be delivered by 30 minute IV infusion every 3 weeks until progression. Subjects 12-17 years of age will receive pembrolizumab at 2 mg/kg IV (up to 200 mg) every 3 weeks until progression. Doxorubicin 60-75 mg/m^2 will be delivered by IV infusion per institutional protocol (infusion, IV push) every 3 weeks until progression. Subjects will receive doxorubicin 60 mg/m^2 IV on Cycle 1 Day 1. Escalation to 75 mg/m^2 is allowed after Cycle 1 per investigator discretion. Re-initiation of pembrolizumab after discontinuation and presence of progressive disease is an additional option. Total dose of doxorubicin should not exceed cumulative lifetime dose of 450 mg/m^2.
I. Statistical Analysis	Previous reports have demonstrated that the rate of any severe or life-threatening toxicity with a median of 3 courses of doxorubicin and dacarbazine every 3 weeks is 55%. If it becomes evident that the rate of severe or life-

	threatening toxicity convincingly exceeds 55%, the study will be halted. Response rates will be calculated with corresponding 95% confidence intervals based on the Clopper-Pearson method. Duration of response and PFS distributions will be estimated using Kaplan-Meier techniques. Exploratory correlative analyses will be conducted on biomarkers using logistic regression (response rate) and Cox proportional hazards models (duration of response and PFS). Incident rates for adverse events, SAEs, and deaths on study therapy will be summarized.

SCHEMA



* Subjects 12-17 years of age will receive pembrolizumab 2 mg/kg IV (up to 200 mg) every 3 weeks

LIST OF ABBREVIATIONS

Abbreviation	Definition of Term
AE	Adverse event
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
CI	Confidence interval
CHF	Congestive heart failure
CFR	Code of Federal Regulations
CNS	Central nervous system
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical trial management system
CrCl	Creatinine clearance
DCSI	Development Core Safety Information
DNA	Deoxyribonucleic acid
DSMC	Data and Safety Monitoring Committee
eCRF	Electronic case report form
ECG	Electrocardiogram
ECI	Events of clinical interest
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice

G-CSF	Granulocyte-colony stimulating factor
GIST	Gastrointestinal stromal tumor
GMP	Good Manufacturing Practices
HIV	Human immunodeficiency virus
IB	Investigator brochure
IDS	Investigational drug services
IHC	Immunohistochemistry
INR	International normalized ratio
IRB	Institutional Review Board
irRC	Immune related response criteria
IV	Intravenous
LCI	Levine Cancer Institute
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody
MEL	Melanoma
MRI	Magnetic resonance imaging
MUGA	Multigated acquisition scan
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OTC	Over the counter
PI	Principal Investigator
PK	Pharmacokinetics
PR	Partial response
PT	Partial thromboplastin
Q2W	Every two weeks
Q3W	Every three weeks
RCC	Renal cell carcinoma

RNA	Ribonucleic acid
SAE	Serious adverse event
SAR	Serious adverse reaction
SOC	Standard of care
SOP	Standard operative procedure
STS	Soft tissue sarcoma
TIL	Tumor infiltrating lymphocyte
TSH	Thyroid stimulating hormone
UAP	Unanticipated problem

TABLE OF CONTENTS

1. OBJECTIVES

1.1. Primary Objective

The primary objective of this study is to evaluate the severe and life-threatening toxicity rate observed in metastatic or unresectable soft tissue sarcoma subjects treated with doxorubicin and pembrolizumab, and compare to historical control.

1.2. Secondary Objectives

The secondary objectives are to assess overall survival (OS), and objective response rate (ORR), duration of response (DoR), and progression-free survival (PFS) with this regimen using RECIST 1.1 criteria.

1.3. Safety Objectives

To assess treatment administration, safety, tolerability and adverse event profile of doxorubicin and pembrolizumab.

1.4. Exploratory Objectives

The exploratory objectives of this study include:

- Assessment of PFS, ORR, and DoR, using the immune-related RECIST (irRECIST) criteria
  - Analyze immune response endpoints
  - Concordance analysis relative to standard RECIST
  - Evaluate impact of treating after progression to see impact on concordance
- Evaluate the correlation between PD-L1 expression levels and antitumor activity of MK-3475
- Investigate other biomarkers (e.g. tumor infiltrating lymphocytes) that may correlate with tumor responses
- Evaluate differences in tumor tissue characteristics in biopsies taken during treatment with MK-3475 versus baseline
- Evaluate objective response rate to second course treatment of pembrolizumab
- Evaluate progression-free survival after second course treatment of pembrolizumab (PFS2)

Whole blood samples will also be collected at baseline for germ line DNA analysis in select subjects for extended genomic analysis.

2. BACKGROUND AND RATIONALE

2.1. Study Disease

Sarcomas are a heterogeneous group of rare, malignant tumors, with over 50 histologic subtypes[1] which are generally categorized as bone and soft tissue sarcomas. The exact incidence of soft tissue sarcoma is not precisely known. A recent study in the Rhone-Alps region in France identified 748 new cases in a cohort of roughly 6 million residents[2]. The estimated world age-standardized incidence rate was, 4.8/100,000, which was higher than previously reported (1-3/100,000). Historically, soft tissue sarcomas have been treated similarly. Doxorubicin-based chemotherapy has been the first line standard of care for more than 20 years. Adding additional cytotoxic agents (e.g. ifosfamide, dacarbazine) to doxorubicin improves response rates, but at the expense of increased toxicity and no clear increase in survival. Some histologic subtypes respond better than others. Anti-angiogenic and targeted therapies (e.g. sunitinib) to this point have been of marginal benefit in the treatment of soft tissue sarcomas. Further progress is needed.

2.2. Experience with Pembrolizumab

2.2.1. Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades[3]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [4-37]. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in solid malignancies such as ovarian, colorectal and pancreatic cancer, hepatocellular carcinoma, malignant melanoma (MEL) and renal cell carcinoma (RCC). TILs can be expanded ex vivo and re-infused, inducing durable objective tumor responses in cancers such as MEL[38,39].
The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PDL2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The

mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during -thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. Both ligands are type I transmembrane receptors containing both IgV- and IgC--like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda (pembrolizumab) has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

2.2.2. Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure (IB) for preclinical and clinical data.

2.2.3. Experience with Doxorubicin

Doxorubicin is a cytotoxic antibiotic of the anthracycline family of compounds. Its cytotoxic effects are believed to stem from intercalation with DNA nucleotides and binding to cellular membrane lipids. Investigations of cellular exposure to doxorubicin have shown morphological changes associated with apoptosis. Currently, doxorubicin is the standard of care for

most subtypes of unresectable locally advanced or metastatic STS for disease which is not resectable for cure.

In the 1970s, this anthracycline was studied in a clinical trial as monotherapy directed against disseminated sarcomas.[40] Of 36 patients, 9% experienced a CR and 32% a PR. Patients who had these responses also had prolonged survival. Since then, doxorubicin has been used as single-agent therapy in the treatment of advanced and/or metastatic STS and has shown to be the most effective single agent in this setting, alternative treatments being single agent ifosfamide and more recently gemcitabine plus/minus taxotere. Comparison of doxorubicin monotherapy versus epirubicin monotherapy has shown slightly favorable response rates for doxorubicin.[41] Although ifosfamide shows a similar level of effectiveness against tumor growth, doxorubicin tends to be better tolerated.[42]

Single-agent doxorubicin has also been compared against combination therapies with and without doxorubicin. Examples include a two-arm study of doxorubicin versus the combination of vincristine plus actinomycin-D plus cyclophosphamide,[43] and a three-arm study of doxorubicin versus the combination therapies of doxorubicin/ifosfamide and doxorubicin/mitomycin/cisplatin as first-line treatment.[44] In the former study, doxorubicin was shown to be more effective, and in the latter, the combination treatment arms demonstrated improved response rate compared to single-agent therapy, but the doxorubicin/ifosfamide combination was significantly more myelosuppressive without a clear improvement in clinical benefit. An additional eight randomized, controlled trials have been analyzed to determine if doxorubicin combination therapy provided substantial clinical benefits compared to single-agent doxorubicin[45]. With regard to response rate, survival, and toxicity across studies, it was determined that improved response rate was marginal for combination therapy, survival did not differ between the two groups, and the safety profile for combination therapy was worse than that of single-agent therapy.

Acute and chronic cardiomyopathy has occurred in patients receiving doxorubicin, and the probability of developing such cardiac complications is increased with increase in total cumulative dose of doxorubicin. Therefore, IV dexrazoxane is indicated for use as a cardioprotective agent in patients concurrently receiving a cumulative doxorubicin dose of 300 mg/m^2 or greater.[46]

2.3. Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent MK-3475. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well

tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days).

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage. The weight-based pediatric dosing regimen of 2 mg/kg Q3W was determined using a model-based PK bridging analysis. The model included PK data from pembrolizumab pediatric trial KN051 which also serves to establish safety of this does in pediatric subjects. Analysis of the model showed a dose of 2 mg/kg Q3W (up to 200mg) in pediatric subjects displayed similar PK exposures to those in adults using the same dose. The weight based dosing regimen of 2 mg/kg Q3W displayed comparable pembrolizumab exposures in pediatric subjects and adults, and PK simulation supports the dosing regimen for the pediatric population.

2.4. Rationale for Use of irRECIST Criteria

Immunotherapeutic agents may produce antitumor effects by potentiating endogenous cancer-specific immune responses, which may be functionally anergic prior to treatment. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions (transient tumor flare). Thus, standard RECIST criteria may not provide a complete response assessment of immunotherapeutic agents, such as pembrolizumab. To address this issue, RECIST 1.1 with the adaptation outlined in Section 11.1.2, termed irRECIST, will also be used.

3. SUBJECT SELECTION

3.1. Subject Accrual

A maximum of 30 subjects with soft tissue sarcoma will be enrolled as a single cohort over a 24-month period. Both men and women of all races and ethnic groups are eligible for this trial.

3.2. Eligibility Criteria

3.2.1. Inclusion Criteria

Subjects must meet all the following criteria:

a. Be willing and able to provide written informed consent for the trial.
b. Must have a diagnosis of unresectable or metastatic soft tissue sarcoma that is histologically confirmed and not amenable to curative treatment with surgery or radiotherapy. Patients with Ewing's sarcoma, osteosarcoma, chondrosarcoma, Kaposi's sarcoma, gastrointestinal stromal tumors (GIST), clear cell sarcoma, alveolar soft part sarcoma and any other soft

tissue or bone sarcoma felt to be chemotherapy resistant in the opinion of the Sponsor-Investigator will be excluded.

c. Must not have received prior treatment with an anthracycline chemotherapy (e.g., doxorubicin) and/or anti-PD-1/PD-L1 therapy.
d. May have had any number of prior systemic therapies for unresectable/metastatic disease.
e. Must have measurable or non-measurable disease as per RECIST 1.1
f. All subjects with accessible tumor will be asked to provide a fresh tumor biopsy if they can be safely biopsied in the opinion of the investigator. Recently obtained archived core or excisional biopsy of a tumor lesion (obtained up to 12 months prior to Cycle 1 Day 1) may be substituted only if the subject is unwilling or unable (e.g. inaccessible or subject safety concern) to undergo a fresh tumor biopsy. Subjects who are unwilling or unable to have a fresh tumor biopsy and do not have recently obtained archived tissue available may submit an archived specimen (obtained > 12 months prior to Cycle 1 Day 1) only upon approval from the Sponsor-Investigator.
g. Be ≥ 12 years of age on day of signing informed consent. Assent will be obtained in appropriately aged subjects per institutional guidelines.
h. ECOG performance status 0 or 1.
i. Life expectancy of at least 3 months per the Investigator.
j. Have adequate organ function as indicated by the laboratory values in Table 1. All screening labs should be performed within 10 days of study treatment initiation. PT/INR and PTT must be performed within 7 days of study treatment initiation for subjects on anti-coagulants such as coumadin/heparin.

Table 1. Adequate Organ Function Lab Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥ 1,500 /mcL
Platelets	≥ 100,000 / mcL
Hemoglobin	≥ 9 g/dL or ≥ 5.6 mmol/L– without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine OR measured or calculated creatinine clearance (CrCl)[a] (GFR can also be used in place of creatinine or CrCl)	≤ 1.5 X upper limit of normal (ULN) **OR** ≥ 60 mL/min for subjects with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR** Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN OR ≤ 5 X ULN for subjects with liver metastases
Albumin	≥ 2.5 g/dL
Coagulation	

International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤ 1.5 X ULN unless the subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range for intended use of coagulants ≤ 1.5 X ULN unless the subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range for intended use of coagulants
[a] Creatinine clearance should be calculated per institutional standard.	

k. The subject has left ventricular ejection fraction (LVEF) ≥ 50% assessed within 21 days prior to study treatment initiation.
l. Subjects must not be expecting to conceive or father children within the timeframe referenced below. Subjects of childbearing potential must be willing to adhere to the contraception requirement as described in Section 3.3.2 from the day of the screening visit (or 14 days prior to the initiation of study treatment for oral contraception) throughout the study period up to 120 days after the last dose of pembrolizumab and/or up to 180 days after the last dose of doxorubicin. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.
m. Female subjects of childbearing potential must have a negative urine or serum pregnancy test at screening (within 72 hours of first dose of study treatment). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. The serum pregnancy test must be negative for the subject to be eligible.
n. Subject has voluntarily agreed to participate by giving written informed consent for the trial. The subject may also provide consent for Optional and Future Studies-Biospecimen Collection. However, the subject may participate in the main trial without participating in Optional and Future Studies.

3.2.2. Exclusion Criteria

Subjects must not meet any of the following criteria**:**

a. Currently participating and receiving study therapy or have participated in a study of an investigational agent and received study therapy or used an investigational device within 30 days of the first dose of study treatment.
b. Have a diagnosis of immunodeficiency or are receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment.
c. Have a known history of active TB (Bacillus Tuberculosis).
d. Have had a prior anti-cancer monoclonal antibody (mAb) given to treat malignancy within 4 weeks prior to the first dose of study treatment or have not recovered (i.e. ≤ Grade 1 or at baseline) from adverse events due to previous mAbs.

e. Have had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to the first dose of study treatment or who have not recovered (i.e. ≤ Grade 1 or at baseline) from adverse events due to previous chemotherapy, targeted small molecule therapy, or radiation therapy.

Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

Note: If subjects have received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment as determined by the Investigator.

f. Have a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

g. Have known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of study treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to the first dose of the study treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

h. Have active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

i. Have known history of, or any evidence of active, non-infectious pneumonitis.

j. Have an active infection requiring systemic therapy (uncomplicated urinary tract infection treated with oral antibiotics is permitted).

k. Have a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subjects' participation for the full duration of the trial, or is not in the best interest of the subjects to participate, in the opinion of the treating Investigator.

l. Have known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial as determined by the Investigator.

m. Are pregnant or breastfeeding.

n. Have received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

o. Have a known history of Human Immunodeficiency Virus infection (e.g. HIV 1/2 antibodies).

p. Have known active Hepatitis B (e.g. HBsAg reactive) or Hepatitis C (e.g. HCV RNA [qualitative] is detected).
q. Have received a live vaccine within 30 days prior to first dose of study treatment.

Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.

For subjects entering the Second Course Phase, see Section 7 for entry criteria.

3.3. Diet/Activity/Other Considerations

3.3.1. Diet

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

3.3.2. Contraception/Reproduction

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

Female subjects will be considered of non-reproductive potential if they are either:

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

OR

(2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening; documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure otherwise the subject must be willing to use two adequate barrier methods throughout the study, starting with the screening visit through 120 days after the last dose of pembrolizumab and up to 180 days after last dose of doxorubicin as specified in the protocol.

OR

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

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, throughout the trial starting at the screening visit through 120 days after the last dose of pembrolizumab and/or for 180 days after receiving the last dose of doxorubicin by complying with one of the following:

(1) practice abstinence† from heterosexual activity;
OR

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

Acceptable methods of contraception are‡:

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

Combination method (requires use of two of the following):
- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

Male subjects with pregnant partners must agree to use a condom; no additional method of contraception is required for the pregnant partner.

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

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

Subjects should be informed that taking the study treatment may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of the screening visit (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of pembrolizumab and/or up to 180 days after the last dose of doxorubicin. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

3.4. Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study treatment. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor-Investigator and to Merck without delay and within 24 hours to the Sponsor-Investigator and within 2 working days to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor-Investigator. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor-Investigator and to Merck and followed as described above and in Section 10.

3.5. 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, subjects who are breast-feeding are not eligible for enrollment.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This is a single arm phase II study designed to investigate the safety, tolerability, and preliminary efficacy of the combination of pembrolizumab and doxorubicin in subjects with metastatic/unresectable soft tissue sarcoma. Following informed consent and eligibility check, all enrolled subjects will receive therapy with doxorubicin and pembrolizumab.

4.2. Informed Consent

The subject or subject's legal representative will sign and date the informed consent form prior to participating in any study-related procedures. Subjects under 18 years of age will sign and date the assent form prior to participating in any study-related procedures. Subjects who reach 18 years of age during study participation will sign the main consent form.

4.3. Registration/Enrollment/Discontinuation

4.3.1. Milestone Date Definitions

Eligibility date: the date of the last documented criterion that confirmed subject eligibility.

Enrollment date: the date subject initiates treatment with pembrolizumab and doxorubicin.

Treatment discontinuation date: the date investigator decides to discontinue subject from initial pembrolizumab treatment or the subject withdraws consent.

Second Course discontinuation date: the date the investigator decides to discontinue subject from Second Course pembrolizumab treatment.

4.3.2. Subject Registration/Enrollment

Following informed consent or assent, subjects will be registered by the Sponsor and assigned a Study ID number. The Study ID will be a four digit number sequentially assigned, where 1001 will be the Study ID number assigned to the first registered subject. Following eligibility check per standard operating procedures, eligible subjects will be enrolled on the first date of protocol treatment administration. Study ID numbers assigned to registered subjects not ultimately enrolled will not be re-assigned.

4.3.3. Subject Withdrawal/Discontinuation Criteria

Any consenting, eligible subject who receives at least one dose of study treatment and then is removed from the trial (by self or investigator) is considered a "subject withdrawal" and will remain under medical supervision until discharge or transfer is medically acceptable.

In all cases, the reason for withdrawal must be documented. Subjects may withdraw study consent at any time for any reason or be dropped from the trial at the discretion of the Investigator should any untoward effect occur. In addition, a subject may be withdrawn by the Investigator or the Sponsor-

Investigator if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

A subject will be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws study consent
- The subject is lost to follow-up
- Investigator's decision to withdraw the subject
- Noncompliance with study regimen or procedure requirements
- Subject death

4.3.4. Discontinuation of Study Therapy after Complete Response

Discontinuation of treatment may be considered for subjects who have attained a confirmed complete response (CR) in the Initial Treatment Period that have been treated for at least 24 weeks with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared.

Subjects who then experience first documented disease progression (as defined in Section 4.4/ Additional Post-Treatment Follow-up Visits) may be eligible for up to one year of additional treatment with pembrolizumab via the Second Course Phase (See Section 7) at the discretion of the Investigator if no anti-cancer treatment was administered since the last dose of pembrolizumab, the subject meets the criteria for Entry into Second Course Phase per Section 7, has completed required study procedures per Entry into Second Course Phase requirements in the Study Calendar per Section 5.2, and the trial is open. Subjects will resume therapy at the same dose and schedule.

4.3.5. Screen Failures

A subject who, for any reason (i.e. failure to satisfy the eligibility criteria or withdraws consent), terminates the study before receiving first dose of study treatment is regarded as a "screen failure."

4.4. Study Procedures

Study procedures are listed in Section 5 – Study Calendar.

Demographics and Medical/Treatment History. Demographics and medical/treatment history will be collected during the screening visit. Medical and treatment history (oncological and relevant non-oncological) will be collected. Medical history will include all active conditions, and any condition diagnosed within

the prior 10 years that are considered to be clinically significant by the Investigator. Cancer history will be obtained and the following information (including but not limited to):

- Date of first histological/cytological diagnosis
- Primary tumor site
- Tumor histology and characteristics
- Prior cancer therapy

All relevant medical history findings that occurred prior to the subject signing informed consent will be documented including baseline signs and symptoms present at the time of informed consent. Updated medical history and baseline signs and symptoms findings will be recorded during the Entry into Second Course Phase (if applicable).

Pregnancy Test. A pregnancy test will be performed at screening/Entry into Second Course Phase (if applicable) and as clinically indicated for women of childbearing potential. Women who are pregnant and/or breast-feeding are ineligible for study participation. Women of child-bearing potential will be counseled regarding risk of teratogenicity and need to use contraception through the course of the study. Men will also be counseled on the need to use contraception for all sexual encounters.

Office Visit. Physical exam and documented evaluation by body system, height (screening only), weight, and body surface area (BSA) will be documented during screening/Entry into Second Course Phase (if applicable), repeated at Cycle 1 Day 1 (only if screening/Entry into Second Course Phase visit not done within 7 days of initiation/re-initiation of study treatment) and at each treatment visit during the Initial Treatment Period and Second Course Phase (if applicable). Vital signs will be recorded and should include temperature, pulse rate, blood pressure and either respiratory rate or oxygen saturation. ECOG performance status will be assessed.

ECG. ECG will be performed during screening. After discontinuation of doxorubicin, ECGs will be performed at the frequency described in the Study Calendars (Sections 5.1 and 5.2).

Echocardiogram. Echocardiogram will be performed during screening and after every third dose of doxorubicin (approximately 14-21 days after dose but prior to subsequent dose). After discontinuation of doxorubicin, echocardiograms will be performed at the frequency described in the Study Calendars (Sections 5.1 and 5.2).

Adverse Event Evaluation and Monitoring. All adverse events and serious adverse events will be monitored and documented (regardless of grade or attribution) and reported to applicable agencies on an ongoing basis as described in Section 10 during the Initial Treatment Period and Second Course Phase (if applicable). Investigators should refer to the Safety Information section of the current IB for pembrolizumab.

As with any agent, there is always the potential for unexpected AEs, including hypersensitivity reactions.

The Investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Study Calendar (Section 5.1 and 5.2) and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to study treatment.

For subjects receiving treatment with pembrolizumab, all AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs).

Concomitant Medications. All medication that is considered necessary for the subject's welfare, and which is not expected to interfere with the evaluation of the study treatment, may be given at the discretion of the Investigator. All medications taken within 28 days prior to initiation/re-initiation of study treatment and during study treatment must be recorded in the subject's medical record according to standard practice. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication. Acceptable and prohibited concomitant therapy during screening and treatment is listed in Section 6.7.

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

Laboratory Tests. Required laboratory tests are outlined in Table 2. Labs will be performed according to the schedule in Section 5.1 and 5.2. All screening/Entry into Second Course Phase (if applicable) labs should be performed within 10 days of treatment initiation/re-initiation. PT/INR and PTT must be performed within 7 days of treatment initiation/re-initiation for subjects on anti-coagulants such as coumadin/heparin. Results must be reviewed by the Investigator or qualified designee and found to be acceptable prior to each dose of study treatment.

Table 2. Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Total triiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free thyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or bicarbonate)*	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		
† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.			

Tissue and Blood Correlative Studies.
Tissue: Subjects who have disease that can be safely biopsied will be asked to have a tumor biopsy prior to initiation of study treatment (Initial Treatment Period only). However, if the subject is unwilling to undergo a tissue biopsy or it is determined by the Investigator to be unsafe to biopsy, recently obtained archival tissue will be acceptable if obtained within 12 months prior to initiation of study treatment on Cycle 1 Day 1. Subjects for whom recently obtained samples cannot be provided may submit an archived specimen collected more than 12 months prior to initiation of study treatment only upon approval from the Sponsor-Investigator. An additional optional tumor biopsy will be collected at any timepoint during study treatment only if the subject consents.

Biopsies will be obtained only if they can be performed under local anesthesia. General anesthesia will not be used to obtain biopsies that are to be used only for research purposes.

Biopsies performed for research purposes will only be obtained after the procedure has been explained to the subject, and per institution policy, the institution specific informed consent has been secured.

Archived tissue specimens will be collected at baseline (after enrollment) and stored at the AH Biorepository for future analyses.

Blood: Mandatory samples [(2) 8 ml CPT tubes, (1) 10 ml red top, and (1) 10 ml purple top)] will be collected on all subjects at the following timepoints:

- Anytime during screening/Entry into Second Course Phase (if applicable) prior to initiation/re-initiation of pembrolizumab
- Pre-dose prior to every other (odd numbered) cycle (Initial Treatment Period and Second Course Phase if applicable) starting with Cycle 3
- **Subjects in the Initial Treatment Period**: First documented disease progression (as defined later in this section in Additional Post-Treatment Follow-up Visits) or at the Post-Treatment Safety Follow-up Visit.
- **Subjects in the Second Course Phase:** Second documented disease progression (as defined later in this section in Additional Post-Treatment Follow-up Visits) or at the Post-Treatment Safety Follow-up Visit.

Additional blood [(1) 2.5 ml PAXgene tube)] will be collected only from subjects who consent (optional) at the same timepoints as described above for the mandatory blood correlatives.

Exploratory biomarker arrays may be used in analysis. Future tissue and blood-based biomarkers not described in this protocol may also be examined.

Radiology and Tumor Measurements.

Initial Treatment Period: Following consent, a computed tomography (CT) scan (IV contrast preferred) of the primary tumor, chest, abdomen and pelvis will be performed within 28 days prior to the first dose of study treatment (screening/baseline scan). Scans will then be performed every 6 weeks from study treatment initiation (± 7 days) until first documented disease progression or start of new anti-cancer therapy. Subjects who discontinue study treatment and have not had first documented disease progression or started new anti-cancer therapy should have tumor imaging per investigator discretion at a suggested frequency of every 9 weeks. After 1 year of follow-up, tumor imaging frequency can decrease to 12 week intervals per investigator discretion.

Second Course Phase (if applicable): It is recommended that scans are performed within 28 days of re-initiation of pembrolizumab but the interval may be determined per investigator discretion. Scans will then be performed per investigator discretion at a recommended interval of every 6-9 weeks until second documented disease progression or start of new anti-cancer therapy. Subjects who discontinue study treatment and have not had second documented disease progression or started new anti-cancer therapy should have tumor imaging per investigator discretion at a suggested frequency of every 9 weeks. After 1 year of follow-up, tumor imaging frequency can decrease to 12 week intervals per investigator discretion.

A contrast-enhanced MRI (contrast preferred) of the abdomen and pelvis and a non-contrasted CT scan of the chest may be substituted if clinically necessary; however, subsequent studies must be performed using the same imaging modality throughout the study period.

Post-Doxorubicin Cardiac Monitoring

- Subjects who have symptoms of cardiac disease during or after discontinuation of doxorubicin will be referred to cardiology for evaluation and management. The frequency of cardiac procedures (e.g. ECGs, echocardiograms, etc) will be determined by cardiology.
- All other subjects who do not have symptoms of cardiac disease will have post-doxorubicin ECGs and echocardiograms performed per the frequency described in the Study Calendars (Sections 5.1 and 5.2).

Post-Treatment Safety Follow-up Visit. The mandatory Safety Follow-Up Visit should be conducted approximately 30 days (± 7 days) after the last dose of study treatment (required for both Initial Treatment Period and Second Course Phase) or before the initiation of a new anti-cancer treatment, whichever comes first. The Investigator or qualified designee will review new anti-neoplastic therapy initiated after the last dose of study treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of study treatment, the Post-Treatment Safety Follow-Up Visit must occur before the first dose of the new therapy. Once new anti-cancer therapy (non-palliative) has been initiated, the subject will move into survival follow-up.

All AEs that occur prior to 30 days after the last dose of study treatment should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-cancer treatment, whichever occurs first. SAEs that occur within 90 days of the last dose of study treatment or 30 days if new anti-cancer therapy is initiated should also be followed and recorded. Subjects who are eligible for retreatment with pembrolizumab (Second Course Phase as described in Section 7) may have up to two safety follow-up visits, one after the Initial Treatment Period and one after the Second Course Phase.

Additional Post-Treatment Follow-Up Visits. Only subjects who discontinue study treatment without documented disease progression or initiation of new anti-cancer therapy move into the Additional Post-Treatment Follow-Up Phase and should be assessed by radiologic imaging to monitor disease status as described earlier in this section (Radiology and Tumor Measurements) and the Study Calendars in Section 5. Documented disease progression is defined as**:**

- Confirmed radiographic disease progression in subjects currently receiving pembrolizumab, or
- Unconfirmed radiographic disease progression in clinically unstable subjects currently receiving pembrolizumab
- Unconfirmed radiographic disease progression in subjects in the Additional Post-Treatment Follow-up Phase previously discontinued from pembrolizumab for reasons other than documented disease progression or initiation of new anti-cancer therapy, or
- Subjective disease progression as determined by the investigator

First documented disease progression is the disease progression meeting the criteria above that occurs during or following study treatment administered during the Initial Treatment Period. Second documented disease progression is the disease progression meeting the criteria above that occurs during or following pembrolizumab administered during the Second Course Phase.

Every effort should be made to collect information regarding disease status until the start of initial anti-cancer treatment, documented disease progression, death, or end of the study.

Subjects who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 7 will move from the Follow-Up Phase to the Second Course Phase after they experience first documented disease progression.

Survival Follow-Up. Once subjects experience documented disease progression or start a new anti-cancer therapy, the subjects move into the Survival Follow-Up Phase and should be contacted by telephone approximately every 6 months from the Post-Treatment Safety Follow-up Visit to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

5. STUDY CALENDAR

5.1. Initial Treatment Period

Initial Treatment Period	**Treatment Cycles[u]**									**Post-Treatment**			
						To be repeated beyond 7 cycles							
Treatment Cycle/Title:	Screening Visit	1	2	3	4	5	6	7	Every 6 weeks	After last dose of doxorubicin[t]	Post-Tx Safety Follow- Up Visit[a]	Additional Follow-Up Visits	Survival Follow-Up
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	From C1D1 ± 7	30 days (±7 days) after last dose of doxorubicin	30 days (± 7 days) post last dose of study treatment	Suggested every 9 weeks x 1 year; then every 12 weeks	Approximately every 6 months from Post-Tx Safety Follow-up Visit
Informed Consent	X												
Demographics and Medical History[r]	X												
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X			X		
Doxorubicin Administration[k]		X	X	X	X	X	X	X					
Pembrolizumab Administration		X	X	X	X	X	X	X					
Post-treatment anticancer therapy status											X		X
Survival Status		X											
Review Adverse Events[a]		X	X	X	X	X	X	X			X		
Physical Examination, Weight and ECOG Performance Status[b]	X	X[b]	X	X	X	X	X	X			X		
Vital Signs[c]	X	X	X	X	X	X	X	X			X		
ECG	X									X[t]			

Initial Treatment Period	**Treatment Cycles[u]**									**Post-Treatment**			
						To be repeated beyond 7 cycles				After last dose of doxorubicin[t]	Post-Tx Safety Follow- Up Visit[a]	Additional Follow-Up Visits	Survival Follow-Up
Treatment Cycle/Title:	Screening Visit	1	2	3	4	5	6	7	Every 6 weeks				
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	From C1D1 ± 7	30 days (±7 days) after last dose of doxorubicin	30 days (± 7 days) post last dose of study treatment	Suggested every 9 weeks x 1 year; then every 12 weeks	Approximately every 6 months from Post-Tx Safety Follow-up Visit
ECHO (Echocardiogram)	X[j]				X[h,t]			X[h,t]		X[t]	X[t]		
Pregnancy Test – Urine or Serum -HCG[d]	X												
PT/INR and aPTT	X[e]												
CBC with Differential[m]	X[p]		X	X	X	X	X	X			X		
Comprehensive Serum Chemistry Panel[i,m]	X[p]		X	X	X	X	X	X			X		
Urinalysis	X[p]												
T3, FT4 and TSH	X[p]												
Tumor Imaging and Assessments[f]	X								X			X	
Recently Obtained Tissue Collection (Archived if unable to obtain biopsy)	X[n,]		X[l]										
Correlative Studies Blood Collection[g]	X			X		X		X			X		
Optional Studies Blood Collection[o]	X			X		X		X			X		
Archived Tissue[q]	X												

a: Subjects will be followed for adverse events through 30 days after last dose of study treatment and for serious adverse events through 90 days after last dose of study treatment (or for 30 days if new anti-cancer therapy is initiated). Subjects who develop symptoms of cardiac disease as determined by the investigator after initiation of doxorubicin will be referred to cardiology.

b: Height will be measured at screening visit only. C1D1 Physical Exam/Performance Status/Weight not required if done within 7 days of screening exam/PS/weight.

c: To include temperature, pulse rate, blood pressure, and either respiratory rate or oxygen saturation

d: Collect within 72 hours prior to administration of study treatment in women of childbearing potential
e. Must be done within 7 days of C1D1 if on anti-coagulants such as warfarin/heparin. Otherwise to be done within 10 days of C1D1.
f: Perform every 6 weeks from C1D1 (+/- 7 days). Subjects who discontinue study treatment and have not had first documented disease progression or started new-anti-cancer therapy should have tumor imaging per investigator discretion at a suggested frequency of every 9 weeks (± 7 days) to monitor disease status. After 1 year of follow-up, tumor imaging frequency can decrease to 12 week intervals per investigator discretion.
g. Includes [(2) 8 ml CPT tubes, (1) 10 ml red top and (1) 10 ml purple top)]. Collect at screening, prior to dose administration every other (odd numbered) cycle (starting with Cycle 3), and at first documented disease progression or at the Post-Treatment Safety Follow-up Visit. The screening sample should ideally be collected after eligibility has been confirmed, preferably on C1D1 prior to study treatment initiation.
h. After every third dose of doxorubicin (approximately 14-21 days after dose but prior to subsequent dose) during treatment with doxorubicin. .
i. See Table 2 for complete list of required chemistries
j. LVEF must be assessed within 21 days of initiation of study treatment
k. Total dose of doxorubicin should not exceed cumulative lifetime dose of 450 mg/m^2
l. Optional fresh tumor biopsy will be collected anytime during study treatment only in subjects who consent
m: After cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing
n: Subjects who have accessible tumor that can be safely biopsied will be asked to have a tumor biopsy prior to initiation of study treatment. However, if the subject is unwilling or unable to undergo a tissue biopsy, recent archival tissue will be acceptable if obtained within 12 months prior to initiation of treatment on C1D1. If fresh or recent archived tissue is not available, archived tissue collected more than 12 months prior to C1D1 may be submitted only upon approval from the Sponsor-Investigator.
o. Optional blood correlatives (1) 2.5 ml Paxgene only to be collected in subjects who consent. Collected at screening, prior to dose administration every other (odd numbered) cycle (starting with Cycle 3), and at first documented disease progression or at the Post-Treatment Safety Follow-up Visit. The screening sample should ideally be collected after eligibility has been confirmed, preferably on C1D1 prior to study treatment initiation.
p. All screening labs must be done within 10 days of C1D1
q. Archived tissue specimens will be collected at baseline (after enrollment) and stored at the AH Biorepository for future analyses
r. To include baseline signs and symptoms
t. Subjects who do not have symptoms of cardiac disease as determined by the investigator will have an ECG and echocardiogram performed 30 days (± 7 days) after the last dose of doxorubicin. Echocardiogram will be repeated every 5 years (± 90 days) after the last dose of doxorubicin. These assessments are required regardless of the number of doxorubicin doses administered during the study. Subjects who develop symptoms of cardiac disease at any time after initiation of doxorubicin will be referred to cardiology. In this case, the frequency of cardiac evaluations will be determined by cardiology.
u. Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study treatment. However, subjects should be placed back on study treatment within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor-Investigator.

5.2. Second Course Phase

Second Course Phase	Treatment Cycles[n]									Post-Treatment		
						To be repeated beyond 7 cycles						
Treatment Cycle/Title:	Entry into Second Course Phase	1	2	3	4	5	6	7	Every 6-9 weeks	Post-Tx Safety Follow- Up Visit	Additional Follow-Up Visits	Survival Follow-Up
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	From C1D1 ± 7	30 days (± 7 days) post last dose of study treatment	Suggested every 9 weeks x 1 year; then every 12 weeks	Approximately every 6 months from Post-Tx Safety Follow-up Visit
Medical History Review[m]	X											
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X		X		
Pembrolizumab Administration		X	X	X	X	X	X	X				
Post-treatment anticancer therapy status										X		X
Survival Status		X										
Review Adverse Events[a]		X	X	X	X	X	X	X		X		
Physical Examination, Weight and ECOG Performance Status	X	X[b]	X	X	X	X	X	X		X		
Vital Signs[c]	X	X	X	X	X	X	X	X		X		
ECHO (Echocardiogram)	X[h]											
Pregnancy Test – Urine or Serum -HCG[d]	X											
PT/INR and aPTT	X[e]											
CBC with Differential [j]	X[l]		X	X	X	X	X	X		X		
Comprehensive Serum Chemistry Panel [i,j]	X[l]		X	X	X	X	X	X		X		
Urinalysis	X[l]											
T3, FT4 and TSH	X[l]											

Second Course Phase	**Treatment Cycles[n]**									**Post-Treatment**		
						To be repeated beyond 7 cycles						
Treatment Cycle/Title:	Entry into Second Course Phase	1	2	3	4	5	6	7	Every 6-9 weeks	Post-Tx Safety Follow- Up Visit	Additional Follow-Up Visits	Survival Follow-Up
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	From C1D1 ± 7	30 days (± 7 days) post last dose of study treatment	Suggested every 9 weeks x 1 year; then every 12 weeks	Approximately every 6 months from Post-Tx Safety Follow-up Visit
Tumor Imaging and Assessments[f]	X								X		X	
Correlative Studies Blood Collection[g]	X			X		X		X		X		
Optional Studies Blood Collection[k]	X			X		X		X		X		

a. Subjects will be followed for adverse events through 30 days after last dose of study treatment and for serious adverse events through 90 days after last dose of study treatment (or through 30 days if new anti-cancer therapy is initiated)
b. C1D1 Physical Exam/Performance Status/Weight not required if done within 7 days of Entry into Second Course Phase exam.
c. To include temperature, pulse rate, blood pressure, and either respiratory rate or oxygen saturation
d. Collect within 72 hours prior to administration of study treatment in women of childbearing potential. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required
e. Must be done within 7 days of C1D1 if on anti-coagulants such as warfarin/heparin. Otherwise to be done within 10 days of C1D1.
f. It is recommended that scans are performed within 28 days of re-initiation of pembrolizumab but the interval may be determined per the investigator. Scans will then be performed per investigator discretion at a recommended interval of every 6-9 weeks. Subjects who discontinue study treatment and have not had second documented disease progression or started new anti-cancer therapy should have tumor imaging per investigator discretion at a suggested frequency of every 9 weeks (±7 days) to monitor disease status. After 1 year of follow-up, tumor imaging can go from 9 to 12 week intervals per investigator discretion.
g. Includes [(2) 8 ml CPT tubes, (1) 10 ml red top and (1) 10 ml purple top)]. Collect at Entry into Second Phase, prior to dose administration every other (odd numbered) cycle (starting with Cycle 3), and at second documented disease progression or at the Post-Treatment Safety Follow-up Visit
h. Subjects who do not have symptoms of cardiac disease as determined by the investigator will have an echocardiogram to monitor LVEF every 5 years (± 90 days) from the last dose of doxorubicin. This is required regardless of the number of doxorubicin doses administered during the Initial Treatment Period. Subjects who develop symptoms of cardiac disease any time after initiation of doxorubicin will be referred to cardiology. In this case, the frequency of cardiac evaluations will be determined by cardiology.
i. See Table 2 for complete list of required chemistries
j. After cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing
k. Optional blood correlatives (1) 2.5 ml Paxgene only to be collected in subjects who consent. Collected at Entry into Second Phase, prior to dose administration every other (odd numbered) cycle (starting with Cycle 3), and at second documented disease progression or at the Post-Treatment Safety Follow-up Visit
l. All Entry into Second Course Phase labs must be done within 10 days of C1D1

m. To include baseline signs and symptoms present at the time of Entry into Second Course Phase
n. Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study treatment. However, subjects should be placed back on study treatment within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor-Investigator.

6. TREATMENT PLAN

6.1. Drug Dosage and Administration

The study drug (pembrolizumab) must be exclusively used for the investigation specified in this protocol and it will only be accessible to authorized staff. Treatment with doxorubicin IV and pembrolizumab IV will be administered every 3 weeks (21 days) +/- 3 days during the Initial Treatment Period. Day 1 of the cycle will be defined as the day that pembrolizumab is administered. In the event of a delay in pembrolizumab administration, doxorubicin may be continued to be administered every 21 days. This may result in more than one doxorubicin administration within a cycle. In the event of doxorubicin discontinuation due to toxicity, pembrolizumab will be allowed to continue until any of the criteria in Section 6.11 are met. In the event that the maximum allowable doxorubicin dosage of 450 mg/m^2 is reached and no toxicity has occurred, subjects will discontinue treatment with doxorubicin, but will continue treatment with pembrolizumab until any of the criteria in Section 6.11 are met. In the event of toxicity requiring discontinuation of pembrolizumab, treatment with doxorubicin on study will be discontinued. Subjects in the Second Course Phase will receive monotherapy pembrolizumab every 3 weeks (21 days) +/- 3 days.

Table 3. Drug dose and administration

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period
Pembrolizumab[a]	200 mg or 2mg/kg (up to 200 mg)[d]	Q3W	IV infusion	Day 1 of each 3 week cycle
Doxorubicin[b]	60- 75 mg/m^2 [c] Cycle 1 Day dose = 60 mg/m^2	Q3W	IV injection	Day 1 of each 3 week cycle 1

a 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 and +10 minutes is permitted. A sterile, non-pyrogenic, low-protein binding 0.2 to 5 µm in-line filter made of polyethersulfone (PES) must be used during administration to remove any adventitious particles. If the infusion set does not contain 0.2 to 5 µm in-line filter, it is recommended to use 0.2 to 5 µm add-on filter which may contain an extension line

b A single, 12mg dose of dexamethasone may be given prior to administration of doxorubicin. Administer doxorubicin intravenously over 10 (± 5) minutes. Decrease the rate of doxorubicin administration if erythematous streaking along the vein proximal to the site of infusion or facial flushing occurs. Dexrazoxane may be administered at a 10:1 ratio (dexrazoxane: doxorubicin) at the investigator's discretion, within 30 minutes prior to each doxorubicin infusion for prevention of cardiotoxicity. **It is recommended that all subjects receiving 5 or more cycles of doxorubicin receive dexrazoxane.**

c All subjects should initiate doxorubicin at a dose of 60 mg/m^2 at Cycle 1 Day 1. Dose may be escalated to 75 mg/m^2 per investigator discretion after Cycle 1. Total dose of doxorubicin should not exceed cumulative lifetime dose of 450 mg/m^2.

d Subjects 18 years of age or older will receive 200 mg IV every 3 weeks. Subjects 12-17 years of age will receive 2 mg/kg IV (calculated from weight at screening) (up to 200 mg) every 3 weeks. If the subject's (aged 12-17 years old) weight changes by more than 10% from the screening weight, the pembrolizumab dose should be recalculated. Subjects who turn 18 during treatment will receive the 200 mg dose after the 18th birthday.

Study treatment will begin on the day of enrollment. Study treatment will continue until any of the criteria in Section 6.11 are met. Subjects who stop treatment with pembrolizumab in the Initial Treatment Period may be retreated if they meet the criteria specified in Section 7.

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

6.2. Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 2.3. Details on preparation and administration of pembrolizumab (MK-3475) are provided in the Pharmacy Manual.

6.3. Dose Modification for Doxorubicin

Dose modifications to the administration of doxorubicin will be allowed per package insert. Pembrolizumab may be given if doxorubicin is held for toxicity, at the discretion of the Investigator.

6.4. Toxicity-Related Dose Delays/Dose Modifications/Discontinuations for Pembrolizumab

If a dose of pembrolizumab is withheld for toxicity, then subjects may resume dosing with pembrolizumab if that is appropriate at their next scheduled appointment or when toxicity has improved as described below.

Pembrolizumab will be withheld for ≥ Grade 3 drug-related toxicity including laboratory abnormalities and severe or life-threatening AEs per Table 4.

Growth factors are allowed for hematologic toxicities.

In case toxicity does not resolve to Grade 0-1 within 12 weeks after last infusion, pembrolizumab should be discontinued after consultation with the Sponsor-Investigator. Subjects who require corticosteroids to manage drug-related adverse events must be at an equivalent dose of ≤10mg per day of prednisone to resume dosing with pembrolizumab. Furthermore, an inability to reduce the corticosteroid dose for managing a drug-related adverse event to the equivalent of ≤10 mg prednisone per day

within 12 weeks of last pembrolizumab dose should prompt discussion with the Sponsor-Investigator regarding the subject's ability to continue on treatment in the trial. Subjects with a laboratory adverse event still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled. This includes subjects who experience drug induced hypothyroidism requiring replacement therapy. Resumption of pembrolizumab may occur once the subject is stable on adequate doses of replacement therapy and is clinically asymptomatic.

For subjects who experience a recurrence of the same AE(s) at the same grade or greater with rechallenge of pembrolizumab, a discussion should occur to determine whether the subject should continue in the trial. However, for a subject who experiences a recurrence of the same serious adverse event at the same grade or greater with rechallenge of pembrolizumab, the subject MUST discontinue study treatment. Dose increase or decrease of pembrolizumab will not be permitted in individual subjects.

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

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may, including coadministration with additional compounds, represent an immunologic etiology. These adverse events may occur shortly after the first dose of pembrolizumab/combination treatment or several months after the last dose of treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab/combination treatment, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per below. Doxorubicin should be given as described in Section 6.1 if pembrolizumab is withheld for toxicity.

Table 4. Dose Modification and Toxicity Management for Immune-related Adverse Events Associated with Pembrolizumab monotherapy and IO Combinations.

General instructions:

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

irAEs	Toxicity Grade (CTCAE v4.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AST or ALT Elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Endocrine disorders- other (hypophysitis)	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3 or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold		

	Grade 3 or 4	Permanently discontinue	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

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

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

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

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

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

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

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

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study treatment (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study treatment within 3 weeks of the scheduled interruption, unless otherwise discussed with the

Sponsor-Investigator. The reason for interruption should be documented in the subject's study record.

6.6. Timing of Doxorubicin/Pembrolizumab Dose Administration

Doxorubicin 60- 75 mg/m^2 will be administered via IV injection on Day 1 of each cycle over 10 (+/- 5) minutes for a total dose not to exceed cumulative lifetime dose of 450 mg/m^2. All subjects will receive doxorubicin 60 mg/m^2 IV on Cycle 1 Day 1. The dose may be escalated to 75 mg/m^2 after Cycle 1 per investigator discretion. Dexrazoxane may be administered at a 10:1 ratio (dexrazoxane: doxorubicin) at the investigator's discretion, within 30 minutes prior to each doxorubicin infusion for prevention of cardiotoxicity. It is recommended that all subjects receiving 5 or more cycles of doxorubicin receive dexrazoxane.

Pembrolizumab will be administered as a 30 minute IV infusion on Day 1 of each cycle after all procedures/assessments have been completed as detailed in Section 5 and after administration of doxorubicin (if doxorubicin is administered). Subjects 18 years of age and older will receive pembrolizumab at a dose of 200 mg. Subjects 12-17 years of age will receive pembrolizumab at a dose of 2 mg/kg (calculated from weigh at screening) (up to 200 mg). If the subject's (aged 12-17 years old) weight changes by more than 10% from the screening weight, the pembrolizumab dose should be re-calculated. Subjects who turn 18 during treatment will receive the 200 mg dose after the 18th birthday.

A sterile, non-pyrogenic, low-protein binding 0.2 to 5 µm in-line filter made of polyethersulfone (PES) must be used during administration to remove any adventitious particles. If the infusion set does not contain 0.2 to 5 µm in-line filter, it is recommended to use 0.2 to 5 µm add-on filter which may contain an extension line. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

Day 1 of the cycle will be defined as the day that pembrolizumab is administered. In the event of a delay in pembrolizumab administration, doxorubicin may be continued to be administered every 21 days. This may result in more than one doxorubicin administration within a cycle.

Study treatment may be administered up to 3 days before or after the scheduled day of treatment with pembrolizumab and/or doxorubicin due to administrative reasons.

Study treatment will be administered on an outpatient basis.

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

6.7. Concomitant Medications/Vaccinations (allowed and prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The Sponsor-Investigator should discuss any questions regarding this with the Merck Clinical team. The final decision on any supportive therapy or vaccination rests with the Sponsor-Investigator and/or the subject's primary physician.

6.7.1. Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare with the exception of those listed in Section 6.7.2 may be administered at the discretion of the investigator in keeping with the community standards of medical care.

All concomitant medications received within 28 days before the first dose of study treatment and 30 days after the last dose of study treatment should be recorded. Concomitant medications administered after 30 days after the last dose of study treatment should be recorded for SAEs and ECIs as defined in Section 10.

Permitted concomitant therapies include:

- Standard therapies for concurrent medical conditions.
- Supportive care for any underlying illness.
- Palliative radiation therapy is allowed if the target lesion(s) are not included within the radiation field and no more than 10% of the bone marrow is irradiated.
- Granulocyte colony-stimulating factor (G-CSF) and other hematopoietic growth factors may be used in the management of acute toxicity, such as febrile neutropenia, when clinically indicated or at the Investigator's discretion. However, they may not be substituted for a required dose reduction. Subjects are permitted to take chronic erythropoietin.
- Treatment with nonconventional therapies (such as acupuncture), and vitamin/mineral supplements are permitted provided that they do not interfere with the study endpoints, in the opinion of the Investigator.
- Bisphosphonates.
- Subjects who are therapeutically treated with an agent such as warfarin or heparin will be allowed to participate provided that their medication dose and INR/PTT are stable. Close monitoring (within 7 days of the treatment initiation/re-initiation and as clinically indicated) is mandatory. If either of these values are above the therapeutic range, the doses should be modified and the assessments should be repeated weekly until they are stable.

- Subjects taking narrow therapeutic index medications should be monitored proactively (e.g. warfarin, phenytoin, quinidine, carbamazepine, Phenobarbital, cyclosporine, and digoxin).

6.7.2. Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening/Entry into Second Course Phase (if applicable) and the Initial Treatment Period/Second Course Phase (if applicable) of this trial:

- Other investigational treatment during or within 30 days before initiation/re-initiation of study treatment.
- Systemic antitumor therapy, including cytotoxic therapy, biologic therapy, signal transduction inhibitors, immunotherapy, and hormonal therapy.
- Bone marrow transplant or stem cell rescue.
- Use of St. John's wort (Hypericum perforatum). Use of other herbal remedies is discouraged, and is permitted only with the specific assent of the Investigator. All herbal and vitamin supplement use must be carefully documented.
- Radiation therapy
- **Note:** Palliative radiation therapy is allowed if the target lesion(s) are not included within the radiation field and no more than 10% of the bone marrow is irradiated.
    - Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion. This will be recorded as progressive disease, but the subject will be allowed to continue treatment with pembrolizumab with Sponsor-Investigator approval.
- Live vaccines within 30 days prior to initiation/re-initiation of study treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology or as pre-medication for doxorubicin as specified in Table 3. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor-Investigator.
- Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

There are no prohibited therapies during follow-up.

6.8. Rescue Medications & Supportive Care

6.8.1. Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab. Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 6.5 for dose modification.
It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

- **Pneumonitis**:
  - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
  - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
  - 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.
  - For **Grade 3 or 4 diarrhea/colitis,** treat with intravenous steroids followed by high dose oral steroids.
  - 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 subjects with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
- **Hypophysitis**:
  - For **Grade 2** events, treat with 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.
  - 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 subjects 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 liothyroinine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism
  - Treat with an initial dose of IV corticosteroid 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.
- **Hepatic**:
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
  - Treat with IV or oral corticosteroids
  - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
  - 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.

- For **Grade 3-4** events, treat with systemic corticosteroids.
- 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.

Table 5 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 5. 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 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 study treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 25-50 mg po or iv (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)	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Vasopressors Corticosteroids Epinephrine	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 4: Life-threatening; pressor or ventilatory support indicated	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 study treatment administration.**	

6.9. Definition of Pembrolizumab Overdose

For the purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg (or greater ≥ 5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

6.10. Treatment Compliance

Subject compliance with the treatment and protocol includes willingness to comply with all aspects of the protocol. At the discretion of the Sponsor-Investigator, a subject may be discontinued from the protocol for non-compliance with visits or study treatment. Administration of study treatment will be witnessed by the Investigator and/or trial staff.

6.11. Duration of Therapy

Treatment will be discontinued (End of Treatment) for any of the following reasons:

- Documented disease progression as defined in Section 4.4. Note: *After confirmed progression, clinically stable subjects are allowed to continue on therapy beyond confirmed progression if determined to derive clinical benefit in the investigator's opinion*, or
- Unacceptable adverse experiences that prevents further administration of study treatment
- Intercurrent illness that prevents further administration of study treatment
- The subject has a confirmed positive serum pregnancy test
- The subject decides to withdraw consent for study treatment
- Initial Treatment Period: Completed 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of pembrolizumab, whichever is first. *Note: 24 months of pembrolizumab is calculated from the date of first dose. Subjects who stop pembrolizumab after 24 months/35 cycles may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 7.*
- Second Course Phase: Completed (1) year of treatment with pembrolizumab
- Administrative reasons

Follow-up procedures are listed in Section 4.4. After the last dose of study treatment, each subject will be followed for 30 days for adverse event monitoring

(serious adverse events will be collected for 90 days after the last dose of study treatment or 30 days if new anti-cancer therapy is initiated as described in Section 4.4). Subjects who discontinue study treatment for reasons other than documented progressive disease will have post-treatment follow-up for disease status until documented disease progression, initiating subsequent anti-cancer treatment, withdrawing consent, or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone or medical visit verification for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

In this trial, a subject may discontinue from study treatment but continue treatment with doxorubicin and participation in the regularly post discontinuation follow-up scheduled activities, as long as the subject does not withdraw consent for participation.

Any subject in the Initial Treatment Phase who stops pembrolizumab with SD or better may be eligible for up to one year of additional pembrolizumab therapy if they have first documented disease progression after stopping study treatment and meet the criteria in Section 7.

7. SECOND COURSE PHASE

Subjects who stop pembrolizumab in the Initial Treatment Period with SD or better may be eligible for up to one year of additional pembrolizumab therapy if they have first documented disease progression after stopping study treatment. This retreatment period is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets the following conditions:

EITHER

- Stopped initial treatment with pembrolizumab after attaining an investigator-determined confirmed CR according to RECIST 1.1, and
- Was treated for at least 24 weeks with pembrolizumab before discontinuing therapy
- Received at least two treatments with pembrolizumab beyond the date when the initial CR was declared

OR

- Had SD, PR or CR and stopped pembrolizumab treatment after 24 months/35 cycles (see Section 6.11) of study therapy for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined radiographic disease progression after stopping their initial treatment with pembrolizumab
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab
- Completed all required study procedures for Entry into Second Course Phase as detailed in the Study Calendar in Section 5.2
- Has a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrates adequate organ function as detailed in Section 3.2.1
- Female subject of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with pembrolizumab.
- Female subject of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of pembrolizumab (Reference Section 3.3.2). Subjects of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.
- Male subject should agree to use an adequate method of contraception starting with the first dose of pembrolizumab through 120 days after the last dose of pembrolizumab.
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

Subjects who restart treatment will be retreated at the same dose and dose interval as when they last received pembrolizumab. Treatment may be administered for up to one additional year.

8. DATA AND SAFETY MONITORING PLAN

8.1. Safety Monitoring

This protocol will be monitored according to the processes in effect for all Levine Cancer Institute investigator-initiated studies and the protocol-specific monitoring plan, and will abide by standard operating procedures set forth by both the Carolinas HealthCare System Office of Clinical and Translational Research and the Levine Cancer Institute Clinical Trials Office. It is the responsibility of the Sponsor-Investigator to monitor the safety data for this study. The Sponsor-Investigator, Statistician, and other team members as needed will meet regularly to monitor subject consents, enrollment and retention, safety data for all subjects [including adverse events (AEs) for all grades and attributions, serious adverse events (SAEs)], study drug administration, and validity/integrity of the data. Documentation of these meetings will be kept with study records. SAEs will be reported to the Food and Drug Administration (FDA) and the IRB per their requirements. Major protocol deviations that result in a threat to subject safety or the integrity of the study will be reported to the IRB per their requirements. The Sponsor-Investigator will submit data to the LCI

Data and Safety Monitoring Committee according to the protocol-specific Data and Safety Monitoring Plan.

The Sponsor-Investigator will monitor the study accrual data regularly.

8.2. Data Quality Assurance

This study will be organized, performed, and reported in compliance with the study protocol, standard operating procedures (SOPs) of the Levine Cancer Institute and Atrium Health (AH) Office of Clinical and Translational Research, the FDA, and other applicable regulations and guidelines (e.g. GCP).

Subjects will be monitored by LCI Research /Data Monitors per the study-specific monitoring plan and LCI/AH SOPs for data quality. This monitoring will be done by comparing source documentation to the eCRFs. Any variation between the two data sets will be discussed with the Treating Investigator, Sponsor- Investigator and/or other study team members as appropriate.

The study database will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification will be generated and addressed by the appropriate study team member. Only authorized personnel will make corrections to the study database and all corrections will be documented in an electronic audit trail.

8.3. Communication Between Investigational Sites

Investigational sites will be required to report AEs for all grades and attributions, SAEs, problems with study treatment administration, deviations, or any other problem that could affect the validity/integrity of the study data to the Sponsor-Investigator. All investigational sites will report AEs, ECIs and SAEs using the eCRFs and SAE reporting form. AEs will be reported within 5 business days of the investigator learning of the event. SAEs and ECIs will be reported within 1 business day of the investigator learning of the event. Problems with study treatment administration or any other problem affecting safety or data integrity should be communicated to the Sponsor-Investigator or designee per standard procedures by email or phone as soon as possible but within 2 business days of the Investigator learning of the event.

9. LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1. Investigational Product

The Sponsor-Investigator shall be accountable for maintaining appropriate records and ensuring appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical supplies will be provided by Merck as summarized in Table 6.

Table 6. Product Descriptions

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

9.2. Doxorubicin

Doxorubicin is commercially provided.

9.3. Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

9.4. Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5. Returns and Reconciliation

The Sponsor-Investigator is accountable for keeping accurate records of the clinical supplies received from Merck or designee and the amount dispensed to the subjects.

Upon completion or termination of the study, all unused investigational product will be destroyed at the site per institutional policy. It is the Sponsor-Investigator's or designee's responsibility to ensure arrangements are made for disposal of all empty or partially used containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

9.6. Drug Accountability

All study drug will be stored at the investigational site in accordance with Good Clinical Practice (GCP) and Good Manufacturing Practices (GMP) requirements and will be inaccessible to unauthorized personnel.

An adequate record of receipt, distribution, and destruction of pembrolizumab will be kept in the form of a Drug Accountability Form and maintained by the LCI IDS (Investigational Drug Services) Pharmacy. The Investigator, or responsible party

designated by the Investigator, will maintain a careful record of the inventory using the Drug Accountability Form. Doxorubicin will be administered commercially.

9.7. Destruction

At the end of the study, unused supplies of pembrolizumab will be destroyed according to LCI IDS pharmacy policies.

10. SAFETY DATA COLLECTION, RECORDING AND REPORTING

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, regular monitoring of hematology, blood chemistry and liver function test values, regular measurement of vital signs, and performance of history and physical examinations. These assessments should be performed per the study calendar. Adverse events will be evaluated continuously throughout the study. Safety and tolerability, relationship to treatment and intensity will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All adverse events (Grades 1 – 5) will be documented in subject study charts, and recorded in the eCRF.

10.1. Unanticipated Problem Definition

An UAP is any incidence, experience or outcome that is unexpected, given the information provided in research-related documentation (e.g., Investigator's brochure, informed consent) and the study population characteristics that is related or possibly related to participation in the research study and places the participant at an increased risk.

10.2. Adverse Event

10.2.1. Adverse Event Definition

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

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events.

Examples of this may include, but are not limited to, typical crying in children and onset of menses or menopause occurring at a physiologically appropriate time in minor subjects.

Progression of the cancer under study is not considered an adverse event.

10.3. Evaluation of Adverse Events

A qualified investigator will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0.

Reporting period: AEs will be captured from the time of treatment initiation/re-initiation through 30 days following cessation of study treatment.
Exception:

- Adverse events that meet the definition of an Event of Clinical Interest (ECI) as defined in Section 10.11 will be reportable from informed consent if the ECI causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Please refer to Section 10.11 for the definition and expedited reporting requirements for ECI's.

Adverse events will be evaluated for relatedness to both doxorubicin and pembrolizumab.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness. Adverse events will be evaluated according to Table 7.

Table 7. Adverse Event Evaluation

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of study treatment that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor-Investigator within 24 hours and to Merck within 2 working days to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose of pembrolizumab is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours to the Sponsor-Investigator and to Merck within 2 working days.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	

Duration	Record the start and stop dates of the adverse event.	
Action taken	Did the adverse event cause pembrolizumab and/or doxorubicin to be discontinued?	
Relationship to study treatment	Did pembrolizumab and/or doxorubicin cause the adverse event? The determination of the likelihood that pembrolizumab and/or doxorubicin caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between pembrolizumab and/or doxorubicin and the adverse event based upon the available information. **The following components are to be used to assess the relationship between** pembrolizumab and/or doxorubicin **and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely pembrolizumab and/or doxorubicin caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to pembrolizumab and/or doxorubicin such as: reliable history, acceptable compliance assessment (expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of pembrolizumab and/or doxorubicin? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

10.3.1. Relationship to Study Drug

The relationship to study drug therapy should be assessed using the following definitions:

Not Related: Evidence exists that the AE has an etiology other than the study drug (i.e., pre-existing condition, underlying disease, intercurrent illness, or concomitant medication). This includes events that are considered remotely or unlikely related to study drug.

Related: A temporal relationship exists between the event onset and administration of the study drug. It cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies. In the case of cessation or reduction of the dose, the event abates or resolves and reappears upon rechallenge. It should be emphasized that ineffective study drug treatment should not be considered as causally related in the context of AE reporting. This includes events that are considered possibly, probably, or definitely related to study drug.

All adverse events (including event name, grade, start/stop date and attribution) will be documented in the medical record and/or research chart and recorded on the case report form for this protocol.

The Investigator is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial.

10.4. Suspected Adverse Reaction Definition

A SAR is an adverse event in which there is reasonable possibility that the study drug caused the adverse event as defined by 21 CFR 312.32. The Investigator is responsible for judging whether it is a reasonable possibility that the study drug caused the adverse event.

10.5. "Unexpected" Definition

An AE or SAR is to be considered unexpected if the event is not listed in the current Investigator Brochure, package insert or label or is not listed in the severity or specificity observed.

10.6. Serious Adverse Event Definition

An AE or SAR is to be considered serious if the Investigator deems it as such and the event results in any of the following outcomes:

- Death;
- Life-threatening situation (patient is at immediate risk of death);
- Inpatient hospitalization or prolongation of an existing hospitalization (excluding those for study drug administration, protocol-related procedures,

palliative or hospice care, or placement of an indwelling catheter, unless associated with other serious events);
- Persistent or significant disability/incapacity;
- Congenital anomaly/birth defect in the offspring of a subject who received study treatment;
- Development of a new cancer (that is not a condition of the study)
- Overdose of pembrolizumab as defined in Section 6.9, that is associated with an adverse event even if no other seriousness criteria are met;
- Other: Important medical events that may not result in death, be immediately life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
    - **Examples of such events are:**
        - Intensive treatment in an emergency room or at home for allergic bronchospasm;
        - Blood dyscrasias or convulsions that do not result in hospitalization;
        - Development of drug dependency or drug abuse.
        - An AE or SAR is to be considered life-threatening if the Investigator deems it as such and the event poses an immediate threat of death.

Pregnancy and Lactation

Although pregnancy and lactation are not considered adverse events, pregnancies and lactations must be reported from informed consent through 120 days after last dose of pembrolizumab, or 30 days if the subject initiates new anti-cancer therapy, whichever is earliest. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as SAEs. If the pregnancy continues to term, the outcome (health of infant) must also be reported.

10.7. Events of Clinical Interest Associated with Pembrolizumab

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI). ECIs for this trial include:

- An overdose of pembrolizumab, as defined in Section 6.9, that is not associated with clinical symptoms or abnormal laboratory results.
- An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

10.8. Expedited Safety Reporting to the Sponsor-Investigator

SAEs, ECIs, pregnancies and lactation exposure must be reported to the Sponsor-Investigator within 1 business day of awareness.
Reporting Period: SAEs and ECIs will be captured from the time of study treatment initiation/re-initiation through 90 days after the date of the last study treatment administration or 30 days if new anti-cancer therapy is initiated.
Exceptions:

- Reportable from informed consent:
  - Events that meet the definition of a SAE that are determined to be related and unexpected to a research procedure
  - Pregnancy and lactation; reportable through 120 days after last dose of pembrolizumab or 30 days if the subject initiates new anti-cancer therapy, whichever is earliest.
  - Events that meet the definition of an ECI (as defined per Section 10.7) if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure (reportable until study treatment initiation).
- Reportable from study treatment initiation through duration of the subject's participation on the trial (treatment and follow-up):
  - Events occurring after the 30-day reporting period that are determined to be related to study treatment or a research procedure

SAEs will be followed until clinical recovery is complete and laboratory tests have returned to baseline, until progression has been stabilized, or until there has been acceptable resolution of the event. This may at times cause the follow-up period for SAEs to be greater than 90 days. Similarly, the Sponsor-Investigator is responsible for

following the subject during the required follow-up period even if the subject lives elsewhere or has been released from his or her care and is being treated under another service at LCI.
Please refer to Section 10.11 for the definition and expedited reporting requirements for ECI's.

10.9. Safety Reporting to the FDA

For investigator-initiated studies where the Sponsor-Investigator holds an IND, safety reporting requirements for the FDA apply in accordance with the regulations set forth in 21 CFR 312.32. The Sponsor-Investigator, or designee, will be responsible for notifying FDA (using a MedWatch form) and all participating Investigators of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the Sponsor's initial receipt of the information. For all other serious and unexpected safety events, the Sponsor-Investigator, or designee, will notify the FDA within 15 calendar days.

It is the responsibility of the Sponsor-Investigator, Investigators and the Protocol Team to ensure SAEs are reported according to the Federal Regulations, ICH E6 Good Clinical Practices, the protocol guidelines, and Institutional Review Board reporting requirements.

Planned protocol deviations will be submitted to the FDA for prior approval only if the deviation affects the scientific validity of the study and/or the rights, safety, or welfare of subjects.

10.10. Safety Reporting to the IRB

All events occurring during the conduct of a protocol and meeting the definition of a UAP or SAE will be reported to the IRB per their reporting requirements.

Protocol deviations that, in the Investigator's judgment, potentially caused harm to participants or others or indicates that the participants or others are at an increased risk of harm, or has adversely impacted data integrity will be reported promptly to the IRB per their reporting requirements.

10.11. Safety Reporting to Merck

Any serious adverse event or ECI, or follow up to a serious adverse event or ECI, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time of study treatment initiation/re-initiation through 90 days following cessation of study treatment, or 30 days if new anti-cancer therapy is initiated, whichever is earlier, whether or not related to pembrolizumab, will be reported within 2 working days of Sponsor-Investigator awareness to Merck Global Safety by the Sponsor-Investigator. SAEs that cause the subject to be excluded from the trial, or is a result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure are

reportable to Merck from the time period beginning with informed consent until study treatment initiation/re-initiation. Pregnancies and lactations must be reported from informed consent through 120 days after last dose of pembrolizumab, or 30 days if the subject initiates new anti-cancer therapy, whichever is earliest.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to pembrolizumab that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor-Investigator and to Merck.

SAE/ECI and pregnancy/lactation reports and any other relevant safety information are to be forwarded to Merck by the Sponsor-Investigator to Global Safety facsimile number: +1-215-993-1220

If the Sponsor-Investigator holds an IND, a copy of all 15 Day Reports and Annual Progress Reports are to be submitted as required by the FDA or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally, investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to the appropriate regulatory agency.

10.12. Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to Merck unless there is evidence suggesting a causal relationship between pembrolizumab and the event. Any such event will be submitted to the Sponsor-Investigator within 24 hours and to Merck Global Safety within 2 working days either by electronic or paper media.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The Sponsor-Investigator will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the subjects in the trial.

Hospitalization related to convenience (e.g. transportation issues etc.) will not be considered a SAE.

11. MEASUREMENT OF EFFECT

11.1. Anti-tumor Effect – Solid Tumor

Response and progression will be evaluated in this study using the Revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline version 1.1. Clinically stable

patients may continue to be treated beyond radiologic progression per the Investigator's discretion, however, at the time of RECIST-defined progression, progressive disease will be documented in the study records.

11.1.1. 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. Baseline evaluations prior to Second Course Phase will be performed per the investigator's discretion.

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 when both methods have been used to assess the anti-tumor effect of a treatment. The Sponsor-Investigator or designee will be responsible for performing tumor measurements. The tumor measurements will be recorded on the eCRF.

11.1.2. Response Criteria

Response will be evaluated using RECIST 1.1 criteria.[47]

Complete Response:

- Target lesion: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Non-target lesion: Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).

Partial Response:

- Target lesion: At least a 30% decrease in the sum of diameters of target, taking as reference the baseline sum diameters.
- Non-target lesion: Not applicable

Stable Disease:

- Target lesion: Neither sufficient shrinkage to qualify for a partial response, nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study.
- Non-target lesion: Not applicable.

Progressive Disease:

- Target lesion: At least a 20% increase in the sum of 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 progression).

- Non-target lesion: *Unequivocal progression* (as described in RECIST version 1.1) of existing non-target lesions. (*Note:* the appearance of one or more new lesions is also considered progression).

Non-Complete Response / Non-Progressive Disease:

- Target lesion: Not applicable
- Non-target lesion: Persistence of one or more non-target lesion(s)

Table 8. Summary of RECIST 1.1 (Subjects with measurable disease)

Target Lesions	Non-target Lesions	New Lesions	Overall Response	Best Response for this Category also requires
CR	CR	No	CR	Documented at least once ≥ 4 weeks from baseline
CR	Non-CR/Non-PD	No	PR	Documented at least once ≥ 4 weeks from baseline
CR	Not evaluated	No	PR	
PR	Non-PD or not all evaluated	No	PR	
SD	Non-PD or not all evaluated	No	SD	Documented at least once ≥ 4 weeks from baseline
Not all evaluated	Non-PD	No	NE	N/A
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression

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

Table 9. Summary of RECIST 1.1 (Subjects with non-measurable disease only)

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/ Non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

RECIST 1.1 will be adapted as follows to account for the unique tumor response seen in this class of therapeutics, **irRECIST**.

If imaging shows PD, tumor assessment should be repeated ≥ 4 weeks later in order to confirm PD with the option of continuing treatment for clinically stable subjects as discussed below in Table 10.

Clinically stable is defined by the following criteria:

- Absence of signs and symptoms indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

Table 10. irRECIST: Imaging and Treatment after 1st Radiologic Evidence of PD

	Clinically Stable		Clinically Unstable	
	Imaging	Treatment	Imaging	Treatment
1st radiologic evidence of PD	Repeat imaging at ≥ 4 weeks at site to confirm PD	May continue study treatment at the Investigator's discretion while awaiting confirmatory scan by site	N/A	Discontinue treatment
Repeat scan confirms PD	No additional imaging required	Discontinue treatment. In the event of confirmed progression, if the subject is clinically stable and in the investigator's opinion would derive clinical benefit from remaining on pembrolizumab, the subject may continue treatment beyond confirmed progression.	N/A No additional imaging required	N/A

Repeat scan shows SD, PR or CR	Continue regularly scheduled imaging assessments	Continue study treatment at the Investigator's discretion	N/A	N/A

In determining whether or not the tumor burden has increased, decreased or stayed stable, site investigators should consider all target lesions as well as non-target lesions.

Any subject deemed clinically unstable should be discontinued from study regimen at first evidence of progressive disease by tumor imaging and is not required to have repeat tumor imaging for confirmation.

For a clinically stable subject with first radiologic evidence of progressive disease (i.e., unconfirmed progression of disease), it is at the discretion of the site investigator to continue treating the subject with the assigned treatment per protocol until progression of disease is confirmed at least 28 days from the date of the tumor imaging first suggesting PD. If progression is not confirmed on the subsequent tumor imaging, the subject should continue to receive study therapy and have tumor imaging performed every 6 weeks (± 7 days) to monitor disease status. If radiologic progression is confirmed by subsequent tumor imaging, then the subject will be discontinued from study treatment.

NOTE: If a subject with confirmed progression by tumor imaging (i.e. 2 scans at least 28 days apart demonstrating progressive disease) is clinically stable or clinically improved, and there is no further increase in the tumor burden at the confirmatory scan, an exception may be considered to continue treatment upon consultation with the Sponsor-Investigator. Subjects exhibiting unacceptable toxicity from trial therapy may NOT continue to receive trial therapy.

NOTE: In subjects who discontinue study therapy without first documented disease progression, every effort should be made to continue monitoring disease status by tumor imaging with a suggested interval of every 9 weeks in the first year and every 12 weeks (after year 1 per investigator discretion until (1) the start of new anti-cancer treatment, (2) documented disease progression (3) death, or (4) the end of the study, whichever occurs first. The same imaging modality (i.e. CT or MRI), acquisition and technical parameters should be used throughout the study for a given subject.

12. STATISTICAL CONSIDERATIONS

12.1. Sample Size

This study is primarily designed to assess the safety of doxorubicin (60-75 mg/m^2) and pembrolizumab (200 mg) in previously treated or untreated subjects with

unresectable or metastatic soft tissue sarcoma. Based on the Bayesian stopping rules described in Section 12.5, 30 subjects will enable an assessment regarding whether or not the severe or life-threatening treatment emergent adverse event rate convincingly exceeds 0.55.[48]

12.2. Endpoint Definitions

12.2.1. Severe or Life-Threatening Adverse Event

Severe or life threatening adverse event will be determined for each subject indicating whether or not the event meets all criteria listed below:

- Meets the definition of seriousness as defined in Section 10.6, and
- Pembrolizumab-related or doxorubicin-related toxicity per the Sponsor-Investigator and
- Considered to be clinically significant by the Sponsor-Investigator as to contribute to the stopping rule.

12.2.2. Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from the start of protocol treatment to first occurrence of either progressive disease or death. Disease progression can be objectively determined as per Section 11 or progression can be subjective as determined by the investigator. Evidence for subjective progression must be documented in the medical records. For objective disease progression, the date of PD is the date of the radiologic assessment that identified RECIST-defined progressive disease. For subjective disease progression, the date of PD is the date that the clinician makes the determination of disease progression. If the subject died without documented disease progression, the date of progression will be the date of death. For surviving subjects who do not have documented disease progression, PFS will be censored at the date of last radiologic assessment. For subjects who receive subsequent anti-cancer therapy prior to documented disease progression, PFS will be censored at the date of last radiologic assessment prior to the commencement of subsequent therapy. Subjects who have an initial PFS event immediately following 2 or more consecutive missed assessments will be censored at the date of the last assessment prior to those missed assessments. For participants with only one missed assessment, the documented progressive disease status and assessment date will be used.

PFS will be determined for each subject using both the RECIST 1.1 and irRECIST criteria.

12.2.3. Overall Survival

Overall survival (OS) is defined as the duration of time from the start of protocol treatment to death from any cause. Subjects who are alive or lost to

follow-up at the time of the analysis will be censored at the last known date they were alive.

12.2.4. Objective Response

Objective response will be determined for each subject as a binary variable indicating whether or not the subject achieved a best overall response of CR or PR. Objective response will be determined for each subject with measurable disease at baseline using both the RECIST 1.1 and irRECIST criteria.

12.2.5. Duration of Response

Duration of response will be determined for each subject achieving an objective response. Duration of response will be defined from time that response was initially documented until progression or death. The censoring mechanism for duration of response will be the same as that described for PFS. Duration of response will be determined for each subject using both the RECIST 1.1 and irRECIST criteria.

12.2.6. Safety Endpoints

Safety endpoints will include treatment administration (total number of doses taken, and total doses taken as a percent of total number of intended doses), AEs, SAEs, and deaths while on study therapy.

12.2.7. Second Course Objective Response

Second Course Objective response will be determined for those subjects who initiate second course treatment of pembrolizumab as a binary variable indicating whether or not the subject achieved a best overall response of CR or PR after starting second course treatment with pembrolizumab. Second Course Objective response will be determined for each subject with measurable disease at entry into Second Course Phase using both the RECIST 1.1 and irRECIST criteria.

12.2.8. Second Course Progression-Free Survival (PFS2)

PFS2 will be calculated for those subjects who initiate second course treatment of pembrolizumab in the same fashion as described in Section 12.2.2. The start date for PFS2 will be the first dose of second course treatment of pembrolizumab. PFS2 will be determined for each subject using both the RECIST 1.1 and irRECIST criteria.

12.3. Analysis Populations

All subjects starting study therapy will be included in the analysis of safety data, OS, and PFS. Objective response will be analyzed on the population of subjects who begin study treatment and have measurable disease at baseline. Duration of response will be analyzed on the population of subjects who achieve an objective response. Second course response rate and progression free survival will be conducted on subjects who initiate second course treatment of pembrolizumab.

12.4. Analysis Methods

12.4.1. Timing of Analysis

Analyses on this study will be conducted on a continuous basis in order to assess the Bayesian stopping rules for toxicity described in Section 12.5. An analysis of all endpoints will occur after the best overall response for each subject has been determined for all subjects. An updated analysis of the study will be conducted after the PFS censoring rate reduces to 20% or when all subjects have been on study at least two years (whichever occurs first). A final analysis of the study will be conducted after the overall survival censoring rate reduces to 20% or when all subjects have been on study at least five years (whichever occurs first).

12.4.2. Subject Disposition

An accounting of all consenting subjects will be provided at the end of the study. This will include a breakdown of subjects who consented, were treated, discontinued treatment, died, and were lost to follow-up or withdrew consent.

12.4.3. Baseline Subject and Disease Characteristics

A summary of subject demographics and disease-related characteristics will be completed.

12.5. Primary Analysis

A maximum of 30 evaluable subjects with soft tissue sarcoma will be enrolled as a single cohort. It is not anticipated that the addition of pembrolizumab to standard chemotherapy will increase the rate of severe or life-threatening toxicity. It has been reported that the rate of any severe or life-threatening toxicity of doxorubicin and dacarbazine every 3 weeks is 55%[48].

If it becomes evident that the rate of severe or life-threatening toxicity convincingly exceeds 55%, enrollment to the study will be halted.

The stopping rule will hold enrollment if the posterior probability of severe or life-threatening toxicity risk exceeding 0.55 is 75% or higher. In this event, data will be evaluated to inform the subsequent conduct of the study. The prior for this monitoring rule is beta (11,9). This means that our prior assumption regarding the proportion of severe or life-threatening toxicity is 0.55, and there is 90% probability that this proportion is between 0.368 and 0.726. The operating characteristics of the stopping rule are given in Table 11 and are based on 5000 simulations:

Table 11. Operating characteristics of the stopping rule

Number of Subjects with Severe or Life-Threatening Toxicities	Max. Denominator Cutoff for Early Stopping	Posterior Probability: Pr(Risk>0.55|Data)
4	4	0.7834
5	6	0.7536
6	7	0.8056
7	9	0.7728
8	11	0.7694
9	13	0.7558
10	14	0.7944
11	16	0.7812
12	18	0.7592
13	19	0.8002
14	21	0.7818
15	23	0.7710
16	25	0.7594
17	26	0.7988
18	28	0.7828
19	30	0.7706

12.6. Secondary Analyses

Response rates (based on RECIST 1.1 criteria) will be calculated with corresponding 95% confidence intervals based on the Clopper-Pearson method. The duration of response, overall survival, and progression free survival (PFS) distributions will be estimated using Kaplan-Meier techniques. Secondary correlative analyses will be conducted on baseline subject and disease characteristics, and selected biomarkers using logistic regression (response rate) and Cox proportional hazards models (duration of response, overall survival, and PFS).

12.7. Safety Analyses

Incident rates for adverse events, treatment-emergent adverse events, SAEs and deaths while on study therapy will be summarized. Treatment-emergent adverse events are defined as follows:

- An adverse event that occurs after treatment start that was not present at the time of treatment start; or
- An adverse event that increases in severity after treatment start if the event was present at the time of treatment start.

12.8. Exploratory Analyses

Analysis of objective response, duration of response, and PFS whereby the endpoints are based on irRECIST will be conducted using methods as described in Section 12.6. Correlative analysis will be conducted on PD-L1 and other biomarkers using logistic regression for objective response and Cox proportional hazards models for time to event endpoints. Other exploratory analysis will be conducted as deemed necessary. Summaries of second course objective response rate and progression free survival will be conducted.

12.9. Interim Analyses

This study will be continuously evaluated as described previously in Section 12.4.

13. STUDY COMPLETION

13.1. Completion

The study will be considered complete when one or more of the following conditions is met:

- All subjects have completed all study visits.
- All subjects have discontinued from the study.
- The IRB, FDA, LCI DSMC, Sponsor-Investigator or Merck discontinues the study because of safety considerations.
- The Sponsor-Investigator defines an administrative or clinical cut-off date.

13.2. Termination

The study will be terminated when one or more of the following conditions occur:

If risk-benefit ratio becomes unacceptable owing to, for example:

- Safety findings from this study (e.g. SAEs)
- Results of any interim analysis
- Results of parallel clinical studies
- Results of parallel animal studies (e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity).
- If the study conduct (e.g. recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.

The Sponsor-Investigator has the right to close the trial at any site and at any time. For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties.
- All affected institutions must be informed as applicable according to local law.
- In case of a partial study closure, ongoing subjects, including those in follow-up, must be taken care of in an ethical manner.

Details for individual subject's withdrawal can be found in Section 4.3.3.

14. RETENTION OF RECORDS

Essential documentation (e.g. adverse events, records of study drug receipt and dispensation), including all IRB correspondence, will be retained for at least 2 years after the investigation is completed. Documentation will be readily available upon request.

15. PUBLICATION POLICY

The Investigator must send a draft manuscript of the publication or abstract to Merck, prior to submission of the final version for publication or congress presentation. All relevant aspects regarding data reporting and publications will be part of the contract between Merck and the Investigator.

16. ETHICAL AND LEGAL ISSUES

16.1. Ethical and Legal Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Investigator abide by Good Clinical Practice (GCP) guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate agencies (e.g. DSMC, IRB, FDA) will be obtained for all participating centers before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of IRB approval must be obtained and forwarded to Merck.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the Investigators may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by the Sponsor-Investigator without discussion and agreement by Merck. However, the Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior approval from applicable agencies. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the appropriate agencies. Any deviations from the protocol must be explained and documented by the Investigator.

The Sponsor-Investigator is responsible for the conduct of the clinical trial at the sites in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Sponsor-Investigator is responsible for personally overseeing the treatment of all study subjects. The Sponsor-Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all applicable regulations and guidelines regarding clinical trials both during and after study completion.

The Sponsor-Investigator will be responsible for assuring that all the required data will be collected and properly documented.

16.2. Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

16.3. Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor-Investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

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