

FRED HUTCHINSON CANCER RESEARCH CENTER
 UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE

1. TITLE

PROTOCOL: A Trial of Pembrolizumab in Combination with Doxorubicin as Treatment for Patients with Advanced Sarcomas

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Investigators:

Investigators	Title	Telephone
Seth M. Pollack, MD	Assistant Member, FHCRC	206-667-6629

Research Coordinator: Taylor Hain, CCRC 206-667-4802
 Jackie Vandermeer 206-667-6110
 Jeff Gregory 206-667-5892
 Sabrina McDonnell 206-667-1583

FHCRC IRB Approval

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Statistician: Mary Redman PhD, FHCRC

1.1 TRIAL SUMMARY

Abbreviated Title	Pembrolizumab and Doxorubicin
Trial Phase	Phase I/II
Clinical Indication	Sarcoma
Trial Type	Single arm, open-label
Type of control	Historical
Route of administration	IV
Trial Blinding	None
Treatment Groups	Low and high dose doxorubicin/ phase I and phase II expansion
Number of trial subjects	maximum 47 (44 expected)
Estimated enrollment period	24 months
Estimated duration of trial	48 months
Duration of Participation	48 months

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1.3 Commonly Used Abbreviations:

AE	Adverse Event
APC	Antigen Presenting Cell
APP	Advanced Practice Provider (Nurse practitioners or physician assistants)
BMP	Basic Metabolic Panel
CBC	Complete Blood Count
CMP	Complete Metabolic Panel
CR	Complete Response
CRF	Case Report Forms
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T Lymphocyte
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
ECI	Events of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
IB	Investigator Brochure
IV	Intravenous
mAb	Monoclonal Antibody
MHC	Major Histocompatibility Complex
OS	Overall Survival
OTC	Over the Counter
PD-1	Programed Death Receptor 1
PD-L1 & 2	Program Death Receptor Ligands 1 & 2
PFS	Progression-free Survival

RECIST	Response Evaluation Criteria in Solid Tumors
RR	Response Rate
SAE	Serious Adverse Event
SD	Stable Disease
SBRT	Stereotactic Body Radiation Therapy
STS	Soft Tissue Sarcoma
TSH	Thyroid Stimulating Hormone
Treg	Regulatory T cell

2.0 TRIAL DESIGN

2.1 Introduction

This is a Phase I/II, non-randomized, open-label, interventional study of Pembrolizumab combined with doxorubicin for patients with advanced sarcoma. Most patients will receive this as front line therapy. As a rule, the trial is generally inclusive for most sarcoma subtypes. However, it excludes patients with prior anthracycline treatment. Patients with Ewings Sarcoma, Osteosarcoma, and some Rhabdomyosarcomas are excluded as these histologic sarcoma subtypes have well-established, evidence-based treatment paradigms combining anthracyclines with other chemotherapy.

The Phase I stage will evaluate two dose levels of doxorubicin (45 and 75 mg/m²) combined with Pembrolizumab. The 75 mg/m² doxorubicin dose is widely considered standard of care for sarcoma, as is being used as the “control” arm for recent and on-going phase III trials (NCT02451943) (Judson, Verweij et al. 2014). All patients will receive Pembrolizumab at the flat dose of 200 mg given intravenously every 3 weeks. Unless serious adverse events are observed, the Phase II expansion will combine the 75 mg/m² dose of doxorubicin with Pembrolizumab.

The phase II portion will use a two stage design treating an initial 20 patients with the combination of Doxorubicin and Pembrolizumab. If two or more objective responses are seen (either complete or partial responses), an additional 15 patients will be treated for a total of 35 patients. In summary, we expect that 44 patients will be treated on the trial (9 in the phase I portion and 35 on the phase II portion). If an additional 3 patients needed to be treated in the initial phase I cohort this could potentially increase to a maximum enrollment of 47.

2.2 Dosing Schedule

In order to “prime” the immune system prior to combination therapy, patients will receive one cycle of Pembrolizumab as a single agent before starting the combination of doxorubicin and Pembrolizumab. Patients will receive a maximum of 6 cycles of doxorubicin. After this, patients with clinical benefit may continue on study with single agent Pembrolizumab.

Pembrolizumab has been given q2 weeks and q3 weeks and the optimal schedule is unclear. However, it is approved by the FDA for use every 3 weeks, and this dosing will also minimize the necessary infusion center visits. Patients will receive Pembrolizumab and doxorubicin sequentially at the same infusion center visit. Doxorubicin will be given first.

Patients with SD, PR or CR may continue to take Pembrolizumab for 2 years (and no more than 35 cycles). After this, they must discontinue Pembrolizumab. If the patient had been responding prior to discontinuation and they immediately progress 8-12 weeks after discontinuation, they may then resume pembrolizumab for one year or until progression.

2.3 Management of Normal Doxorubicin Toxicity and use of Growth Factors

Dosing will be every 3 weeks as is standard of care when doxorubicin is used as a single agent. There are no restrictions any other anti-emetics (NK1 or 5HT3 inhibitors) however, steroids are occasionally used as antiemetics for doxorubicin but are not recommended for patients on this trial as they may interfere with the efficacy of Pembrolizumab.

In general, supportive care will be given according to standard practice. No serious toxicities have been observed to date when Pembrolizumab has been combined with filgastrim and peg-filgastrim so these medications will be generally be allowed to support patients receiving doxorubicin. However, during the first cycle combining doxorubicin with Pembrolizumab (cycle 2) while in the phase I dose escalation portion of the trial, no growth factor will be given. This will allow a simplified look at the safety of the Pembrolizumab and doxorubicin combination.

Patients on single agent doxorubicin sometimes have dose delays secondary to toxicity. Dose delays up to 3 weeks for toxicity not otherwise outlined in section 5.2 will be permitted with PI approval. Lab abnormalities may also necessitate delay in doxorubicin. Detailed information about delays and dose reductions for patients on doxorubicin is given in **section 5.2**. Should either drug be delayed for any reason, the other drug may be given at the discretion of the treating physician in order to minimize infusion center appointments for patients and focus study on the combination.

If a toxicity is clearly attributable to only one drug, the other may be continued per protocol.

2.4 Assessment of Response

Response assessment will be based on RECIST 1.1. Patients with clinical benefit (SD, PR, CR) after 6 cycles of doxorubicin will continue on single agent Pembrolizumab until confirmed progression RECIST, severe toxicity (see **Section 5**), or 2 years of therapy whichever comes first. Patients who receive a CR will be treated until they have had at least 24 weeks of treatment and have been treated for at least 2 cycles after their CR was declared. Patients who are able to be brought to a CR surgically should be treated just as if they had a CR in response to the medication. Patients confirmed to have a CR who have been taken off treatment will continued to be monitored radiographically every 12 weeks. Upon relapse they can be re-treated with Pembrolizumab for up to one year.

While, all patients will start therapy with unresectable/metastatic disease, it is possible that a responding patient becomes surgically resectable so that they have no evidence of disease. These patients may undergo surgery and afterwards should be followed as if they had a CR, with the rules regarding progression and restarting treatment.

Patients will have their first post-treatment scan after 3 cycles of doxorubicin, prior to receiving their fourth cycle of doxorubicin. Patients with PR or SD will have their second post treatment scan 3-6 weeks after their last (sixth) cycle of doxorubicin. Responses will be determined by RECIST 1.1. After 6 cycles of doxorubicin have been completed and Pembrolizumab is being given as a single agent, scans will be performed every 12 weeks (+/- 1 week) until progression.

Subjects with an *unconfirmed* progression of disease may discontinue but will be encouraged to continue trial treatment until progression is confirmed following two additional cycles of therapy or until disease progression becomes symptomatic. However, subjects may only receive study treatment while waiting for confirmation of PD if the following criteria are met:

- 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

2.5 Phase I dose Escalation of Doxorubicin

A dose limiting toxicity (DLT) will be defined as a possibly-related, unexpected SAE of grade 3 or higher or any adverse event at least possibly related to either agent requiring discontinuation of either drug. The DLT monitoring period will be six weeks (2 cycles) after the patient receives both Doxorubicin and Pembrolizumab.

The Phase I dose escalation will use a “3+3” phase I trial design. All patients will receive a flat dose of 200 mg Pembrolizumab every 3 weeks. Patients will have “priming” with a dose of single agent Pembrolizumab before receiving the combination of Pembrolizumab with doxorubicin. Three patients will be treated at the 45mg/m² dose of doxorubicin. Although this is lower and has considerably less toxicity than the standard of care dosing of 75 mg/m², this dose has clinical activity and is still within the range of acceptable dosing, particularly for sarcoma patients with poor performance status or comorbidities (O'Bryan, Baker et al. 1977). In order to prevent accumulation of unexpected serious adverse events (SAEs), the second patient will not start treatment with Pembrolizumab until 10 days after the first patient has received the combination of Pembrolizumab with doxorubicin. Patients will be monitored for adverse events that might be study related until their last study related visit 30 days after discontinuation of therapy. If the first patient develops a DLT, a data safety monitor board (DSMB) will meet before the second patient is treated in order to discuss the toxicity and make recommendations regarding trial modifications.

If at least one of the first three patients develops DLT, a total of six patients will be treated at this dose level. If two patients develop DLT at the 45mg/m² dose level, the trial will immediately stop accrual and a data safety monitoring board (DSMB) will meet to discuss whether to modify, stop or continue the trial.

Dose escalation to the 75 mg/m² dose of doxorubicin will be contingent upon acceptable safety data following the combination of Pembrolizumab and doxorubicin at the 45 mg/m² dosing. If only one of the six patients develops a DLT, a DSMB will meet prior to dose escalation to review the specific nature of the toxicity and determine if any protocol modifications are necessary prior to proceeding with the dose escalation. If there is no DLT among the first three patients, the trial may proceed immediately to the 75 mg/m² once the third patient receives cycle three (the second cycle including both Pembrolizumab and doxorubicin) without DSMB review.

As was done in the previous cohort, the second patient at the 75 mg/m² dose will not start treatment until 10 days after the first patient has received the combination of Pembrolizumab and doxorubicin at the 75 mg/m² dose level. If the first patient treated has a DLT, a DSMB will meet prior to treatment of the second patient. If two of the first six patients treated using 75 mg/m² doxorubicin develop a DLT, the phase II extension will occur using the 45 mg/m² dosing. The DSMB will meet prior to the phase II expansion. After this, the DSMB will continue to meet at least every six months while the study is enrolling.

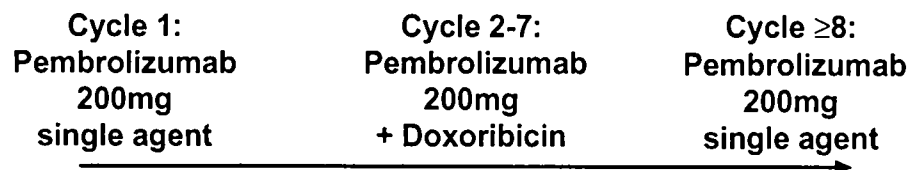
During the dose escalation period of the trial (up to the first six patients at each dose level), patients will be monitored for 4 hours in the clinical trials unit after receiving their first infusion with the drug combination; monitoring is not required for the Cycle 1 dose of single agent pembrolizumab. After this first combination dose, patients may leave the infusion center immediately after receiving their infusions.

2.6 Phase II extension

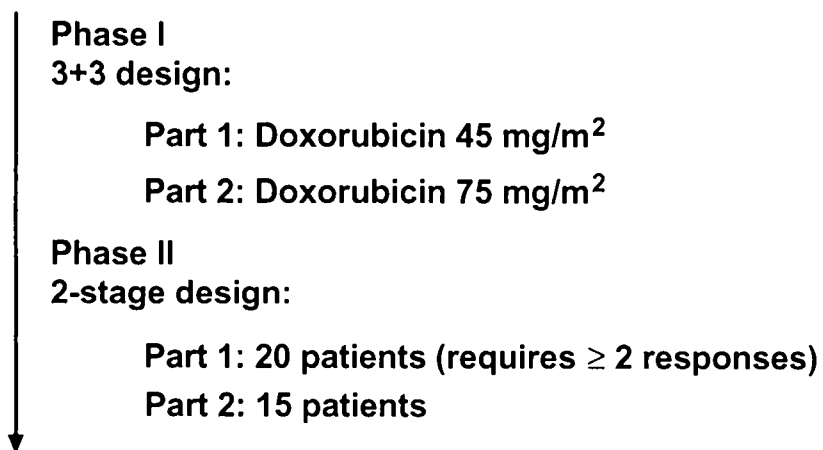
The phase II extension will use a SWOG 2-stage design (modified Simon's 2 stage design) in order to detect a response rate (CR + PR) of 35%. This is based on a predicted overall response rate for single agent doxorubicin of 15%. 20 patients will be treated in the first stage. If 2 or more patients have CR or PR, an additional 15 patients will be treated. If at least 10 CR or PR's are seen, this will be considered a positive study. Patients treated in the phase I portion of the study will not be included in the phase II analysis. Any toxicity defined as a DLT for the phase I portion will also trigger a meeting of the DSMB during the phase II portion of the trial. Should 2 of these events occur, enrollment must halt until the DSMB meets.

2.7 Trial Diagram

A: Treatment Schedule Diagram



B: Study Design Diagram



3.0 OBJECTIVES & HYPOTHESES

3.1 Primary Objectives & Hypotheses

3.1.1 Objective: To assess the safety and tolerability of the combination of Pembrolizumab and Doxorubicin in patients with advanced soft tissue sarcoma (STS).

Hypothesis: The combination of Doxorubicin and Pembrolizumab will be similar to the toxicity of standard Doxorubicin and Pembrolizumab therapy when these drugs are used as single agents.

3.1.2 Objective: To assess the clinical response rate of advanced soft tissue sarcoma (STS) patients receiving the combination of Pembrolizumab and Doxorubicin.

Hypothesis: The addition of Pembrolizumab to Doxorubicin will result in a 20% increase in the objective response rate (CR + PR) compared with historical controls.

3.2 Secondary Objectives & Hypotheses

Objective: To explore the clinical activity of Pembrolizumab in subjects with advanced STS with respect to the following endpoints:

- Time to response
- Duration of response
- Progression-free survival (PFS)
- Overall survival

Hypothesis: Induction of a meaningful objective response rate with Pembrolizumab will be reflected in other clinical outcome parameters including duration of response, progression-free survival, and overall survival.

3.3 Exploratory Objective

Objective: To compare response rates between patients with high levels of PD-L1 expression with those who have PD-L1 absent.

Hypothesis: Patients with very strong PD-L1 expression will have more profound responses than those with weak or absent PD-L1 expression.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on Pembrolizumab.

4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

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 that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). 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, PD-1 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 CD3 ζ , PKC θ 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 States for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

4.1.2 Preclinical and Clinical Trial Data

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

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Soft tissue sarcomas (STS) are a heterogeneous group of mesenchymal neoplasms together comprising 1% of all cancers and with a median overall survival of approximately 1 year in the metastatic setting. Biologically, STS are often divided into genetically "complex" tumors, having highly mutated genomes and complex karyotypes, and genetically "simple" tumors, which are often driven by a single translocation and in some cases express highly immunogenic self-antigens.

Currently, the standard front line therapy for STS is single agent Doxorubicin that has a objective response rate (CR+PR) of 15% and results in a median progression free survival (PFS) of approximately 4.6 months (Santoro, Tursz et al. 1995, Judson 2013, Gelderblom, Blay et al. 2014). The oral tyrosine kinase inhibitor, pazopanib (Votrient), was approved by the FDA for second line treatment of STS based on the PALLETE study where an improvement in PFS of 3.2 months was observed compared with placebo (van der Graaf, Blay et al. 2012, Rajendra, Jones et al. 2013). There is currently no other approved therapy for STS though other standard cytotoxic chemotherapies including ifosfamide, gemcitabine/docetaxel and DTIC are commonly used in clinical practice. PD-1 inhibition has been shown to improve outcomes in other difficult to treat cancers such as melanoma and lung cancer (Brahmer, Drake et al. 2010, Topalian, Hodi et al. 2012, Hamid, Robert et al. 2013).

We have seen T-cell tumor infiltration in a variety of sarcoma subtypes and the amount of infiltrating T cells has been associated with shorter disease specific survival, supporting the idea that check point inhibition might be an effective strategy (Sorbye, Kilvaer et al. 2011). One recent study found PD-1⁺ lymphocytes in 65% of STS tumors and PDL-1 expression by IHC in 58% of STS tested (Kim, Moon et al. 2013). To better define the pattern of PDL-1

expression in specific STS subtypes, our tissue collaboration with Merck analyzed 81 FFPE sarcoma samples from the University of Washington Tissue Bank for PD-L1 and PD-1 by IHC at Merck Research Laboratories. 90% of tumors tested positive for PD-1 staining and 59% for PD-L1. Significantly higher expression levels were seen in higher grade tumors and pleomorphic undifferentiated sarcoma.

There are currently no published reports regarding the use of checkpoint inhibitors in sarcoma. Two presentations were made at the 2016 ASCO meeting. In one study of twelve patients with uterine leiomyosarcoma no responses were seen. Another study looking at 40 patients with several histologies saw 5 responses (4 pleomorphic undifferentiated sarcomas and 1 synovial sarcoma). These results demonstrate that checkpoint inhibition may have activity for some patients with soft tissue sarcoma but that combination therapies will really be necessary to make it broadly applicable.

4.2.2 Rationale for Dose Selection/Regimen/Modification

The safety of Pembrolizumab has been evaluated extensively as a single agent. An open-label Phase I trial (Protocol 001) was being conducted to evaluate the safety and clinical activity of single agent Pembrolizumab. 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 Pembrolizumab 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 Pembrolizumab program has shown that a lower dose of Pembrolizumab and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of Pembrolizumab 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). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

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 Pembrolizumab 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. Pembrolizumab 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 Pembrolizumab 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.

Although chemotherapy causes a temporary disruption in the immune response by inducing neutropenia and lymphopenia, chemotherapy also has the potential to bolster immunotherapy and create therapeutic synergy by directly removing barriers to the immune response such as regulatory T cells and myeloid derived suppressor cells (Ko, Kim et al. 2007, Hirschhorn-Cymerman, Rizzuto et al. 2009). Furthermore, the anti-tumor cytotoxic effects of chemotherapy can lead to increased presentation of tumor antigens by dendritic cells resulting in a tumor specific T cell response (Hirschhorn-Cymerman, Rizzuto et al. 2009, Tesniere, Schlemmer et al. 2010). In this proposal, we will test whether the addition of immunotherapy can bolster the efficacy of front line Doxorubicin in patients with STS by using the PD-1 inhibitor Pembrolizumab.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

Historically, doxorubicin has been used in combination with Ifosfamide as front line therapy for patients with advanced sarcomas. However, the EORTC randomized patients to receive single agent doxorubicin or the combination with ifosfamide. Although the combination did lead to improved progression free survival, the trial found no significant

change in overall survival associated with the combination therapy and significantly increased toxicity associated with the combination. This study established single agent doxorubicin as standard front line therapy for patients with advanced sarcoma. In patients with advanced STS, doxorubicin has a response rate of 15% and results in a median progression free survival (PFS) of approximately 4.6 months (Santoro, Tursz et al. 1995, Judson 2013, Gelderblom, Blay et al. 2014). The primary objective of the phase II design is to compare the objective response rate (ORR) with historical rates.

4.2.3.2 Biomarker Research

We tested over 80 sarcoma tumors including both LMS and SS for expression of PD-L1 and PD-1; we found some degree of PD-1 expressing cells in over 90% of tumors examined. Detectable PD-L1 was seen in a subset of each sarcoma subtype tested, including n=11 (58%) of LMS and n=7 (47%) SS. PD-1 expressing lymphocytes were also seen in a majority of tumors including n=16 (84%) LMS and n=15 (100%) SS. High (4+) or very high (5+) PD-L1 expression was seen in 10 sarcoma including 3 LMS (**Figure 2 A and B**). Seven tumors had high or very high PD-1 expression including one SS, and two LMS. In contrast, even though 100% of the SS tumors had some PD-1 expression, none of the SS tumors had either 4+ or 5+ PD-1 expression. Only n=4 (27%) of SS tumors had >2+ expression for PD-L1. Higher-grade tumors were associated with higher levels of both PD-L1 ($p = 0.03$) and PD-1 expression ($p = 0.05$).

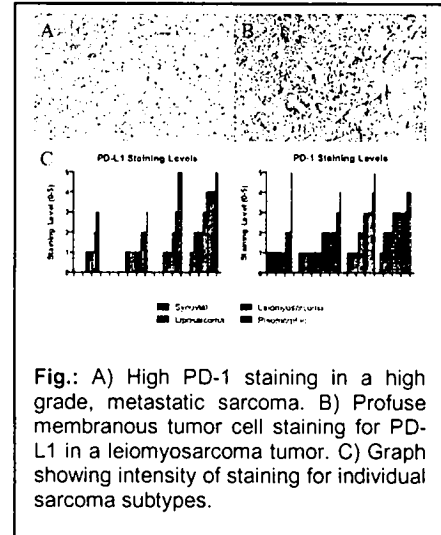


Fig.: A) High PD-1 staining in a high grade, metastatic sarcoma. B) Profuse membranous tumor cell staining for PD-L1 in a leiomyosarcoma tumor. C) Graph showing intensity of staining for individual sarcoma subtypes.

5.0 METHODOLOGY

5.1 Entry Criteria

This trial is designed for both male and female patients ≥ 18 years of age with unresectable sarcoma not amenable to surgery or radiation with curative intent and an ECOG performance status of 0 or 1. We expect 9 patients will be treated on the phase I dose escalation portion of the trial (it is possible as few as 6 and as many as 12 patients could be treated on the phase I portion) and 35 additional patients will be treated on the phase II expansion. All patients meeting the eligibility criterion will be considered for enrollment. No exceptions to eligibility will be granted.

5.1.1 Diagnosis/Condition for Entry into the Trial

As is the standard practice in the Seattle Cancer Care Alliance Sarcoma Clinic, all patients must have had their pathology reviewed at the University of Washington sarcoma clinic. Certain sarcoma subtypes such as Osteosarcoma and Ewings sarcoma almost always receive anthracyclines in combination with other agents as part of their standard of care and therefore it would not make sense for those patients to participate in this study. Both patients with soft tissue sarcoma as well as patients with bone sarcomas (for example chondrosarcoma, leiomyosarcoma of the bone etc.) may be allowed on this trial as this is an anatomic distinction rather than a biologic or immunologic distinction.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Be willing and able to provide written informed consent/assent for the trial.
2. Be ≥ 18 years of age on day of signing informed consent.
3. Have measurable disease based on RECIST 1.1.
4. Have metastatic or unresectable sarcoma.
5. Have a performance status of 0 to 1 on the ECOG Performance Scale.
6. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 10 days of treatment initiation.

Table 1: Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	$\geq 1,500$ /mcL

Platelets	$\geq 100,000$ / mL
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 ^a creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤ 1.5 X upper limit of normal (ULN) OR ≥ 60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN OR Direct bilirubin \leq 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 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤ 1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤ 1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
^a Creatinine clearance should be calculated per institutional standard.	

7. Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
8. Female subjects 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 study medication (Reference Section 5.7.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.
9. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.
10. Ejection Fraction >45% by either MUGA scan or echocardiogram.

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Has prior treatment using an anthracycline.
2. Has one of the following sarcoma subtypes where combining anthracyclines with other chemotherapies is established as the standard of care: Osteosarcoma, Ewings sarcoma, Embryonal Rhabdomyosarcoma, Alveolar Rhabdomyosarcoma.
3. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.
4. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
5. Has a known history of active TB (Bacillus Tuberculosis)
6. Hypersensitivity to pembrolizumab or any of its excipients.
7. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., \leq Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
8. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., \leq Grade 1 or at baseline) from adverse events due to a previously administered agent.
 - Note: Subjects with \leq Grade 2 neuropathy are an exception to this criterion and may qualify for the study.
 - Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
9. Has 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.
10. Has 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 trial 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 trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.
11. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or

physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

12. Has known history of, or any evidence of active, non-infectious pneumonitis.
13. Has an active infection requiring systemic therapy.
14. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, 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.
15. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
16. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.
17. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2 agent or anti-CTLA4.
18. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
19. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
20. Has received a live vaccine within 30 days of planned start of study therapy.

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.

5.2 Trial Treatments

The treatment to be used in this trial is outlined below in Table 2

Table 2 Trial Treatment

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental
Doxorubicin	45 or 75	Q3W	IV infusion	Day 1 of	Standard

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
	mg/m ²			each 3 week cycle	

All trial treatments will be administered on an outpatient basis.

Pembrolizumab will be administered as a 30 minute IV infusion. However, given the variability of infusion pumps, a window of -5 minutes and +10 minutes will be permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

A Procedures Manual will contain specific instructions for Pembrolizumab dose calculation, reconstitution, preparation of the infusion fluid, and administration.

Anti-emetics given to prevent and treat doxorubicin associated nausea and vomiting may be given according to the standard of care at the discretion of the treating clinician with the exception that corticosteroids are not recommended as their immunosuppressive effects may impact the efficacy of Pembrolizumab. While steroids are discouraged, they are not absolutely forbidden as there could be an individual situation where the benefits would be worthwhile (e.g. a specific case of very severe and refractory nausea).

As stated in **Section 2.5**, a dose limiting toxicity (DLT) will be defined as a possibly-related, unexpected SAE of grade 3 or higher or any adverse event at least possibly related to either agent requiring discontinuation of either drug.

5.2.1.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background and Rationale.

Details on preparation and administration of Pembrolizumab are provided in the Pharmacy Manual.

If a toxicity is clearly attributable to only one drug, the other may be continued per protocol. If a toxicity is clearly attributable to one agent and the dose adjustment or drug withdrawal is not required by the protocol, the treating physician may have the discretion to make dose adjustments as dictated by their clinical judgement.

5.2.1.2 Dose Modification of Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than 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, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in

Table

3.

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

General instructions:				
<ol style="list-style-type: none"> 1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks. 2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks. 3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids. 				
Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	<ul style="list-style-type: none"> • Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper 	<ul style="list-style-type: none"> • Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	<ul style="list-style-type: none"> • Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper 	<ul style="list-style-type: none"> • 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 \geqGrade 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.
	Grade 4	Permanently discontinue		

AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	<ul style="list-style-type: none"> Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper 	<ul style="list-style-type: none"> Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4	Permanently discontinue	<ul style="list-style-type: none"> Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper 	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β -cell failure	Withhold	<ul style="list-style-type: none"> Initiate insulin replacement therapy for participants with T1DM Administer anti-hyperglycemic in participants with hyperglycemia 	<ul style="list-style-type: none"> Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	<ul style="list-style-type: none"> Administer corticosteroids and initiate hormonal replacements as clinically indicated. 	<ul style="list-style-type: none"> Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue ¹		
Hyperthyroidism	Grade 2	Continue	<ul style="list-style-type: none"> Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate 	<ul style="list-style-type: none"> Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue ¹		
Hypothyroidism	Grade 2-4	Continue	<ul style="list-style-type: none"> Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care 	<ul style="list-style-type: none"> Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	<ul style="list-style-type: none"> Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper. 	<ul style="list-style-type: none"> Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	<ul style="list-style-type: none"> Based on severity of AE administer corticosteroids 	<ul style="list-style-type: none"> Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		

All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	<ul style="list-style-type: none"> Based on type and severity of AE administer corticosteroids 	<ul style="list-style-type: none"> Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		
<p>1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.</p> <p>NOTE: For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to \leqGrade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).</p>				

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

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

Table 4 Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 4 hrs	<p>Stop Infusion. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics</p> <p>Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose.</p> <p>Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment</p>	Participant may be premedicated 1.5h (\pm 30 minutes) prior to infusion of _____ with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

<p>Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated</p>	<p>Stop Infusion. Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment.</p>	<p>No subsequent dosing</p>
<p>Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov</p>		

Other allowed dose interruption for pembrolizumab

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

5.2.1.3 Dose Modification of Doxorubicin

Doxorubicin is a cytotoxic chemotherapy that has a well-defined safety profile and will be given as per the standard of care. Doxorubicin will not be given while a patient's ANC is < 1000 cells/m³ or if the platelet count is <75,000 cells/m³. When necessary, the next treatment cycle should be delayed until these counts have recovered to these levels. Transfusions of red blood cells and platelets are permitted as clinically indicated. If a patient has a grade 3 febrile neutropenia, doxorubicin should be reduced to approximately 75% of the previous dose (first to 60mg/m² then to 45 mg/m²). Dose reductions of doxorubicin are also required for patients having Grade 4 neutropenia lasting more than 1 week. For patients with grade 3 febrile neutropenia or grade 4 neutropenia without fever lasting less than a week, dose reduction may be made at the discretion of the treating physician. Patients with grade 3 fatigue and/or malaise, may have one dose reduction at the discretion of their treating physician.

Patients may not have more than 2 dose reductions of doxorubicin, and must come off doxorubicin should they continue to have prolonged cytopenias (>21 days) after their second dose reduction. If these patients are responding they may stay on Pembrolizumab as a single agent until progression.

LFT abnormalities may also necessitate a dose reduction. For a bilirubin 1.2-1.5, dose reduction may be made at the discretion of the treating clinician. For bilirubin 1.5 -3, 50% dose reduction. For bilirubin 3.0-5.0, give no more than 25% of the prior dose and consider delaying the next cycle.

EKG's will be collected periodically while a patient is receiving doxorubicin and any other times as the treating clinician deems necessary (see section 6.1). If clinically significant findings are observed on EKG, they should be evaluated as seen as appropriate by the treating clinician. An echocardiogram or MUGA scan will be performed prior to starting therapy for all patients. Should a second echocardiogram or MUGA be performed (this is required for patients on the phase I portion of the study), a drop in ejection fraction by more than 15% or to a total ejection fraction of less than 40% means that doxorubicin should be discontinued. While cardiac toxicity is an expected toxicity of doxorubicin, these events should be explicitly pointed out to the DSMB as frequent or severe occurrences could raise the possibility that pembrolizumab is worsening doxorubicin mediated cardiac toxicity.

Dose delays of doxorubicin may be permitted for up to 3 weeks with PI approval for medical reasons not otherwise outlined in this section. The reason and length of the delay should be discussed with PI during the approval process.

5.2.1.4 Mid-Cycle Labs for Patients on Doxorubicin

As is our standard practice, all patients receiving doxorubicin will have a CBC and CMP drawn 10-14 days after their infusion. If these labs are drawn at an outside lab they must be faxed to the Seattle Cancer Care Alliance and reviewed by a nurse and the study team. A nurse will call the patient to inquire about any unexpected subjective toxicity. The patient's physician will be made aware of any unexpected toxicity and any critical lab values.

5.2.2 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each 21-day cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab will be administered as a 30 minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible.

However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

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

Doxorubicin is typically given over a 1-hour infusion but this could be stretched to 3 hours for relief of acute symptoms such as nausea.

5.2.3 Trial Blinding/Masking

This is an open-label trial; therefore, the investigator and subject will know the treatment administered.

5.3 Concomitant Medications/Vaccinations (allowed & prohibited)

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

5.3.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

5.3.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab

- Radiation therapy
 - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion. Because doxorubicin increases radiation related toxicity, the patient must have completed doxorubicin and be on the Pembrolizumab alone portion of the treatment to undergo radiation. Radiation must begin at least 1 week after the last pembrolizumab dose and complete 1 week prior to the following dose. Dose delays of up to 3 weeks are acceptable in order to achieve this.
 - If the radiation is necessary as a result of progression, the patients should be treated as if they had progressed (e.g. they can continue pembrolizumab and have a confirmatory scan done after 2 cycles).
- Live vaccines within 30 days prior to the first dose of trial 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 for refractory doxorubicin-related nausea and vomiting. The use of physiologic doses of corticosteroids may be approved after consultation with the principal investigator and Merck.

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.

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

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

5.4 Rescue Medications & Supportive Care

5.4.1 Supportive Care Guideline

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 along with the dose modification guidelines in Section 5.2.1.2, [Table 3]. 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 to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Table 3 in Section 5.2.1.2 for dose modification guidelines and supportive care.

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

While not an absolute protocol requirement, investigators are highly encouraged to use a cardioprotective agent such as dexrazoxane beginning at cycle 5 to doxorubicin. This will help to lower the cardiac risk if the patient progresses and chooses to receive additional doxorubicin along with olaratumab in a subsequent line of therapy.

5.5 Diet/Activity/Other Considerations

5.5.1 Diet

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

5.5.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥ 5 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 7.2.2-Reporting of Pregnancy and Lactation to the Sponsor-Investigator and to Merck. If there is any question

that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.5.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. 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 7.2.2.

5.5.4 Use in Nursing Women

It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

5.6 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw 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 considered withdrawn and no longer followed if they enroll onto hospice care. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.4 – Other Procedures.

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression

Note: For unconfirmed radiographic disease progression, please see Section 5.2.2

- Unacceptable adverse experiences as described in Section 5.2.1.2

- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study medication, whichever is later.

Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab after 24 months 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 7.1.5.5

- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.5 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 30 days after the end of treatment as described in Section 7.2.3.1). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.7 Subject Replacement Strategy

The phase II expansion dose will treat up to 35 patients evaluable for response to therapy (20 in the first stage, then if at least 2 responses are seen, an additional 15 patients). If patients become ineligible prior to starting therapy or for some other reason fail to be evaluable for response assessment, additional patients will be treated in their place.

5.8 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects

4. Plans to modify or discontinue the development of the study drug

In the event of Merck decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Trial Period:	Screening	Pembro Only	Doxorubicin/Pembrolizumab Combination							Pembrolizumab Only (repeat)				End of Treatment	
Treatment Cycle/Title:	Screening	1	2	3	4	5	6	7	8	9	10	11	At time of Discon	30 days post discon	
Scheduling Window (Days):	see section 7.1.5	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	

Trial Period:	Screening	Pembro Only	Doxorubicin/Pembrolizumab Combination							Pembrolizumab Only (repeat)				End of Treatment	
Treatment Cycle/Title:	Screening	1	2	3	4	5	6	7	8	9	10	11	At time of Discon	30 days post discon	
Scheduling Window (Days):	see section 7.1.5	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	
Informed Consent	X														
Inclusion/Exclusion Criteria	X														
Demographics and Medical History	X														
Prior and Concomitant Medication Review	X														
Trial Treatment															

Trial Period:	Screening	Pembro Only	Doxorubicin/Pembrolizumab Combination							Pembrolizumab Only (repeat)				End of Treatment	
Treatment Cycle/Title:	Screening	1	2	3	4	5	6	7	8	9	10	11	At time of Discon	30 days post discon	
Scheduling Window (Days):	see section 7.1.5	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	
Administration															
Post-study anticancer therapy status													X	X	
Survival Status													X	X	
Review Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	
Full Physical Examination	X														
Directed Physical Examination		X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs and	X	X	X		X			X	X		X	X	X	X	

Trial Period:	Screening	Pembro Only	Doxorubicin/Pembrolizumab Combination							Pembrolizumab Only (repeat)				End of Treatment	
Treatment Cycle/Title:	Screening	1	2	3	4	5	6	7	8	9	10	11	At time of Discon	30 days post discon	
Scheduling Window (Days):	see section 7.1.5	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	
Weight				X		X	X			X					
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
EKG (Phase I portion)	X		X	X	X	X	X	X					X	X	
EKG (Phase II portion)	X		X			X							X	X	
Echo/MUGA (phase I)	X				X										
Echo/MUGA (phase II)	X														

Trial Period:	Screening	Pembro Only	Doxorubicin/Pembrolizumab Combination							Pembrolizumab Only (repeat)				End of Treatment	
Treatment Cycle/Title:	Screening	1	2	3	4	5	6	7	8	9	10	11	At time of Discon	30 days post discon	
Scheduling Window (Days):	see section 7.1.5	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	
Pregnancy Test – Urine or Serum (in appropriate study subjects)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PT/INR and aPTT	X														
CBC with Differential	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Comprehensive Serum Chem Panel	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X														

Trial Period:	Screening	Pembro Only	Doxorubicin/Pembrolizumab Combination							Pembrolizumab Only (repeat)				End of Treatment	
Treatment Cycle/Title:	Screening	1	2	3	4	5	6	7	8	9	10	11	At time of Discon	30 days post discon	
Scheduling Window (Days):	see section 7.1.5	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	
T3, FT4 and TSH	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Tumor Imaging ¹	X			X					X						
Archival Tissue Collection (slides)	X														
Correlative Studies Blood Collection	X	X	X			X			X				X		

1: Tumor imaging may be performed with a +/- 1-week window. Scans will take place per the schedule even if there are treatment delays.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor-Investigator and/or Merck for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB requirements, applicable laws and regulations and Sponsor-Investigator requirements.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

7.1.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

7.1.1.5.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30-day Safety Follow-up visit must occur before

the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

7.1.1.6 Assignment of Screening Number

The Sponsor-Investigator will assign each patient a de-identified screening number that will be used for data tracking purposes.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 11.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial 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); see the separate ECI guidance document in Appendix 4 regarding the identification, evaluation and management of potential irAEs.

Please refer to section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening.

7.1.2.3 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

7.1.2.4 Vital Signs

Vital signs will be taken at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 10.4) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

7.1.2.6 Tumor Imaging and Assessment of Disease

Radiology at the Seattle Cancer Care Alliance will perform RECIST. Patients will have a CT of the chest, abdomen and pelvis at each imaging visit. Patients whose RECIST evaluable disease is only outside the chest abdomen and pelvis (e.g. neck or extremities) must also have this disease imaging. For patients who have RECIST evaluable disease in their chest/ abdomen/ pelvis as well as outside this area, additional imaging may be performed as deemed appropriate or necessary by their treating clinician.

7.1.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

At the time of enrollment, all patients will have 12 slides (5 microns of tissue on a baked, charged slide) cut. These will be kept at 2-8 degrees Celsius until they are ready to be either to QualTek for PD-L1 IHC or Merck Research Laboratories. Other biomarkers such as PD-1 expression, as well as potentially IHC for immune infiltrates and assessment of immune response related genes using an N-counter Nanostring assay. Additional archived tissue may also be requested for multiplex immunohistochemistry and gene expression assays. At time points specified in **section 6.1**, 30 mL PBMC and 10 mL serum will be frozen and delivered to the Pollack Laboratory at the Fred Hutchinson Cancer Research Center for flow cytometry and functional analysis.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below.

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 5.

Table 5 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 (<i>If abnormal</i>)	Total triiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free tyroxine (T4)
Absolute Lymphocyte Count	(<i>CO₂ or biocarbonate</i>)	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		PK
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin (<i>If total bilirubin is elevated above the upper limit of normal</i>)		
	Total protein		

Hematology	Chemistry	Urinalysis	Other
	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. ‡ If considered standard of care in your region.			

Laboratory tests for screening should be performed within 14 days prior to the first dose of treatment. If within 3 days of Cycle 1 Day 1, the screening lab results may be utilized for Cycle 1 Day 1. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.3.1 Pharmacokinetic/Pharmacodynamic Evaluations

7.1.3.1.1 Blood Collection for Serum Pembrolizumab

Given the prior extremely consistent pharmacokinetics of Pembrolizumab, no pharmacokinetic analysis will be performed in this study.

7.1.3.1.2 Anti-Pembrolizumab Antibodies

Given the lack of anti-pembrolizumab antibodies seen in prior trials, no assessment will be made for these in this study.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events, which are present at the time of discontinuation/withdrawal, should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.5.5. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.4).

A subject will be considered withdrawn and no longer followed if they enroll onto hospice care.

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Screening

The Sponsor-Investigator or a qualified designee will ensure that all inclusion and exclusion criteria have been met. Patients who initially fail screening may retake any test and enroll once they meet eligibility.

7.1.5.1.1 Screening Period

Unless otherwise specified, all clinical assessments including lab work must be done within 14 days of treatment initiation. Screening lab work may be utilized for Cycle 1 Day 1 lab work if done within 3 days of treatment initiation. Radiological assessment can be done within 28 days prior to first dose of study medication. Echocardiogram or MUGA scan may have been done up to 3 months of starting on study.

7.1.5.2 Treatment Period

Patients must be evaluated by a sarcoma provider prior to each infusion. In general, these visits will be the day of the infusion but could be up to 72 hours prior so long as labs are adequate. Visits where scan results will be reviewed should include an oncologist.

7.1.5.3 Post-Treatment Visits

Patients will be seen at the time of discontinuation and then again 30 days later. These visits may be conducted by an oncologist or one of the APP's.

7.1.5.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit 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-neoplastic therapy, whichever occurs first. SAEs that occur within 30 days of the end of treatment or before initiation of a new anti-cancer treatment, whichever is earlier, should also be followed and recorded. Subjects who are eligible for retreatment with pembrolizumab (as described in Section 7.1.5.5) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

If a patient goes onto hospice, then they will no longer be followed and considered withdrawn from the study.

7.1.5.3.1 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.2 Assessing and Recording Adverse Events

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

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

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

Adverse events may occur during the course of the use of Merck product in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Progression of the cancer under study is not considered an adverse event unless it is considered to be drug related by the investigator.

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1.

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor-Investigator and to Merck

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (\geq 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.

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

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor-Investigator and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor-Investigator and to Merck

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 90 days of completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor-Investigator and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

7.2.3 Immediate Reporting of Adverse Events to the Sponsor-Investigator and to Merck

7.2.3.1 Serious Adverse Events

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

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

- Is associated with an overdose;
- Is another important medical event

Refer to Table 6 for additional details regarding each of the above criteria.

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 30 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, must be reported within 24 hours to the Sponsor-Investigator and within 2 working days to Merck Global Safety.

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

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

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-993-1220

The Sponsor-Investigator will report significant new safety information associated with use of drugs in this trial (including serious, unexpected, suspected adverse reactions) to FDA in accordance with regulations under 21 CFR 312.32. 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 FDA.

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

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 661-6229).

Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor-Investigator, that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 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. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

7.2.4 Evaluating Adverse Events

The Sponsor-Investigator or a qualified designee will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

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

Table 6 Evaluating Adverse Events

An Sponsor-Investigator or qualified designee, will evaluate all adverse events as to:

V4.0 CTCAE Grading	Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
	Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental 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 Merck product 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 [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); 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) or	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. 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.	
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. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Merck product to be discontinued?	
Relationship to test drug	<p>Did the Merck product cause the adverse event? The determination of the likelihood that the Merck product 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 the test drug and the adverse event based upon the available information. The following components are to be used to assess the relationship between the Merck product and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Merck product caused the adverse event (AE):</p>	
	Exposure	Is there evidence that the subject was actually exposed to the Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	<p>Did the AE follow in a reasonable temporal sequence from administration of the Merck product?</p> <p>Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?</p>
	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

Relationship	The following components are to be used to assess the relationship between the test drug and the AE:
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to Merck product (continued)	(continued)	
	Dechallenge	<p>Was the Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Merck product; or (3) the trial is a single-dose drug trial); or (4) Merck product(s) is/are only used one time.)</p>
	Rechallenge	<p>Was the subject re-exposed to the Merck product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Merck product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE MERCK PRODUCT, OR IF REEXPOSURE TO THE MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.</p>
	Consistency with Trial Treatment Profile	<p>Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Merck product or drug class pharmacology or toxicology?</p>
<p>The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.</p>		
Record one of the following	<p>Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Merck product relationship).</p>	
Yes, there is a reasonable possibility of Merck product relationship.	<p>There is evidence of exposure to the Merck product. The temporal sequence of the AE onset relative to the administration of the Merck product is reasonable. The AE is more likely explained by the Merck product than by another cause.</p>	

No, there is not a reasonable possibility Merck product relationship

Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of the Merck product is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)

7.2.5 Sponsor-Investigator Responsibility for Reporting Adverse Events

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

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

This is Phase I/II trial. The initial phase of the trial will use a “3+3” design. The phase II portion of the trial will use a two stage design and will not include patients treated in the phase I dose escalation for the efficacy analysis.

8.2 Statistical Analysis Plan

Phase I Design:

The primary objective of the phase I component of this study is to evaluate the safety of Pembrolizumab given in combination with Doxorubicin among patients with advanced soft tissue sarcoma. The phase I component of this study will use a 3+3 design to evaluate the 45 mg/m² and 75 mg/m² Doxorubicin dosing in combination with Pembrolizumab. Dose-limited toxicities will be evaluated through the end of the first cycle combining Pembrolizumab with Doxorubicin.

The study design is as follows:

- Initially enroll 3 patients into the 45 mg/m² cohort
 - If 2 of 3 experience a DLT, stop and conclude that Pembrolizumab may not be given safely with Doxorubicin at the protocol-specified dose levels.
 - If 1 of 3 patients experiences a DLT, enroll 3 more patients.
 - If less than 2 of 6 experiences a DLT then initiate enrollment to the 75 mg/m² cohort.
 - If 2 or more experience a DLT, stop and conclude that Pembrolizumab may not be given safely with Doxorubicin at the protocol-specified dose levels. Should this occur, discussions will initiate with the DSMB and Merck about whether the protocol could be altered to make the regimen safe or whether the study should be halted.
 - If 0 of 3 patients experience a DLT then initiate enrollment to the 75 mg/m² cohort
- If 45 mg/m² is determined safe, enroll 3 patients into the 75 mg/m² cohort
 - If 2 of 3 experience a DLT stop and conclude that the MTD is 45 mg/m²
 - If less than 2 of 3 patients experience a DLT, enroll 3 more patients.
 - If less than 2 of 6 experience a DLT then conclude 75 mg/m² is the MTD
 - If 2 or more experience a DLT, stop and conclude that that the MTD is 45 mg/m²

The maximum sample size for the phase I component is 12 patients.

Phase II Design:

The primary objective of the phase II design is to compare the objective response rate (ORR) with historical rates. Patients at the final phase I dose will not be included in the phase II analysis. Our null hypothesis estimates the overall response rate of single agent doxorubicin based on the EORTC randomized study of doxorubicin alone or in combination with Ifosfamide, the largest study using modern imaging and supportive care. A two-stage design with null hypothesis of 15% using a 1-sided 0.05 α level test has 85% power to detect an increase to 35%. This design requires a total of 35 patients, 20 in the 1st stage and 15 in the second stage. If 2 or more responses (CR or PR) are observed in the 1st stage, the study will continue accrual to the second stage, accruing 15 more patients. If at least 10 responses are seen out of the 35 patients (29%), then this will be considered evidence to rule out an ORR of 15% or less.

Secondary objectives include the estimation of the median PFS, time to and duration of response, and the frequency and severity of toxicities. With 51 patients, this design can estimate frequencies (and single time point estimates of PFS/OS) to within 14% with 95% confidence. The Kaplan-Meier method will be used to estimate median PFS and OS.

Correlative Endpoints: The study is not powered to detect specific hypotheses with regards to correlative endpoints, rather this data and analysis will help better identify patients having the potential to benefit from this therapy and aid in designing larger Phase III studies.

Summary statistics will be used to for describing changes across time. In addition, the time course of biomarker outcomes will be investigated graphically by summary plots or individual patient plots. Categorical data analysis and logistic regression will be used to evaluate the associations between correlative measures and clinical outcome (eg, response, clinical benefit, time to progression, progression-free survival, and survival). If there is suggestion of meaningful trend, methods such as linear mixed models may be used to characterize the pattern of change over time. Kaplan-Meier methodology and Cox Proportional Hazards models will be used to evaluate time to event endpoints.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Clinical Supplies will be provided by Merck as summarized in Table 7.

Table 7 Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 50 mg	Lyophilized Powder for Injection
Pembrolizumab 100 mg/ 4mL	Solution for Injection

9.2 Packaging and Labeling Information

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

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor-Investigator and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

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 investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

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

9.6 Doxorubicin

Clinical Doxorubicin will be used and standard practices regarding storing and handling the drug will apply. More detailed information can be found in the doxorubicin package insert.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Institutional Review Board

In accordance with federal regulations (21 CFR 312.66), an Institutional Review Board (IRB) that complies with regulations in 21 CFR 56 must review and approve this protocol and the informed consent form prior to initiation of the study.

10.2 Consent

The Principal Investigator or his associate must explain verbally and in writing the nature, duration, and purpose of the study and possible consequences of treatment. Patients must also be informed that they may withdraw from the study at any time and for any reason without jeopardizing their future treatment. In accordance with federal regulations (21 CFR 312), all patients must sign the IRB-approved consent form.

10.3 Termination of Study

The Sponsor-Investigator reserves the right to terminate this study at any time. The FDA may also terminate the study.

10.4 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. Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (<http://ctep.cancer.gov/reporting/ctc.html>)

10.4 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

RECIST version 1.1* will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

* As published in the European Journal of Cancer:

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009 Jan;45(2):228-47.

In addition, volumetric analysis will be explored by central review for response assessment.

11.0 DATA AND SAFETY MONITORING PLAN

Institutional support of trial monitoring will be in accordance with the FHCRC/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, FHCRC Clinical Research Support (CRS) coordinates data and compliance monitoring conducted by consultants, contract research organizations, or FHCRC employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), FHCRC Scientific Review Committee (SRC) and the FHCRC/University of Washington Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating subjects. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.

During the phase I portion of the trial, a data safety monitoring board will meet regularly to oversee the trial.

Appendix A:

Data Safety Monitoring Board Charter

Title: A Trial of Pembrolizumab in Combination with Doxorubicin as Treatment for Patients with Advanced Soft Tissue Sarcomas

Protocol number:

Date:

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1. Introduction

This Charter is for the Data and Safety Monitoring Board (DSMB) for Protocol:

A Trial of Pembrolizumab in Combination with Doxorubicin as Treatment for Patients with Advanced Sarcomas

This Charter will define the primary responsibilities of the DSMB, its members, and purpose and timing of its meetings. The Charter will also provide the procedures for ensuring confidentiality and proper communication, the statistical monitoring guidelines to be implemented by the DSMB, and an outline of the content of Open Reports that will be provided to the DSMB.

2. Primary Responsibilities of the DSMB

The DSMB will be responsible for safeguarding the interests of trial participants, and assessing the safety and efficacy of the interventions during the trial. This responsibility will be exercised by providing recommendations about stopping or continuing the trial. To contribute to enhancing the integrity of the trial, the DSMB may also formulate recommendations relating to the recruitment/retention of participants, their management, improving adherence to protocol-specified regimens, and the procedures for data management and quality control.

The DSMB will be advisory to the principal investigator, Dr. Seth Pollack. The PI will be responsible for promptly reviewing the DSMB recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in study conduct are required. If an investigator does not agree with the DSMB recommendations then a memo justifying the reason for not complying with the recommendations must accompany the minutes.

3. Membership

a. Members

The DSMB will consist of at least 3 independent clinicians and biostatisticians that, collectively, have experience in the management of patients with solid tumors and hematologic malignancies in the conduct and monitoring of clinical trials. A quorum will require at least 3 members, including the chair.

Clinical Investigators:

Ed Kim, M.D.
Associate Professor
Dept of Radiation Oncology
Univ of Washington / Seattle Cancer Care Alliance
(T) 206-598-1168, edykim@seattlecca.org

Scott Tykodi, M.D.
Assistant Professor /Assistant Member
Division of Oncology
Univ of Washington / FHCRC
(T) 206-288-7763, stykodi@fhcrc.org

Ted Gooley Ph.D. (chair)
Member
Clinical Research Division

Fred Hutchinson Cancer Research Center
(T) 206-667-6533, tgooley@fredhutch.org

b. Conflicts of Interest

No DSMB members have any conflicts of interest related to the study. Any DSMB member who has or develops a significant conflict of interest should resign from the DSMB. DSMB membership is for the duration of the clinical trial. If any members leave the DSMB during the course of the trial, the PI will promptly appoint their replacement.

4. Timing and Purpose of the DSMB Meetings

The DSMB will meet and review all AEs as is specified in section **2.1 Trial Design**. The DSMB will also meet at least every 6 months during the phase I portion of the trial. During the phase II portion of the trial, the DSMB will meet every 6 months while the study is enrolling. Additionally, any toxicity defined as a DLT for the phase I portion will also trigger a meeting of the DSMB during the phase II portion of the trial. Should 2 of these events occur, enrollment must halt until the DSMB meets.

DSMB reviews may be held in person, via teleconferencing, or via electronic mail. The purpose of the DSMB meetings is to review the conduct of the trial to date and assess safety and toxicity of the study intervention. The DSMB will review all grade 3 or greater NIH CTC v4.03 toxicities and SAEs and determine whether the study should be prematurely discontinued due to toxicity. Ad hoc meetings may be scheduled as needed. The FHCRC also has a Protocol Data Monitoring Committee (PDMC) that reviews the progress of the protocol with respect to the monitoring plan at the time of each annual renewal

5. Confidentiality

All patient information will be coded to maintain confidentiality. The DSMB will have responsibility for assessing and making recommendations to correct any possible abuses of disclosure.

6. Communication

Initial Review

DSMB members are provided general study information by the study team; overall study progress, enrollment, or amendments at least 15 days prior to the regularly scheduled meeting. DSMB meetings will be open and may include the study investigators and DSMB members. The Open Session provides the DSMB an opportunity to query the study team about issues that have arisen during the review of the data. The DSMB will develop a

consensus on its list of recommendations, including whether the trial should continue.

DSMB Meeting Minutes

FHCRC Clinical Research Support (CRS) will provide staff to assist with minutes for the DSMB meeting. The FHCRC IRB and Regulatory Affairs Manager will be included on the distribution list. At the time of IRB annual renewal, DSMB minutes will be required, if not already provided.

7. Statistical Monitoring Guidelines

The DSMB will review all grade 3 or greater toxicities as defined by version 4.0 of NCI Common Toxicity Criteria and determine whether the study should be prematurely discontinued due to toxicity. Toxicity grading will be evaluated by the clinical investigators. Criteria for discontinuing of therapy in an individual patient are described in protocol section titled "Management of Toxicities and Complications". Criteria for discontinuing the trial is described in section titled "Data and Safety Monitoring".

The type and grade of toxicities noted during therapy will be summarized for each dose level. All adverse events noted by the investigator will be tabulated according to the affected body system. Descriptive statistics will be used to summarize changes from baseline in clinical laboratory parameters. Tumor responses will be determined as specified above.

8. Content of Reports for the DSMB

- Study number and title. Brief summary of the study design.
- Protocol amendments
- Status of accrual. If accrual is slower than expected, a plan for increasing enrollment.
- Compliance

- Analyses of primary and secondary endpoints
- Analyses of adverse events and overall safety data. A listing of SAEs by subject and by body system.
- Analysis of lab values

APPENDIX B:

ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
<i>*As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.</i>	

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