UCSF Helen Diller Family Comprehensive Cancer Center

Phase II study of Pembrolizumab in Multiple Myeloma Patients Relapsing After or Refractory to Anti-BCMA CAR-T Therapies

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Protocol Signature Page

1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Institutional Review Board (IRB), and Data and Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with Good Clinical Practices (ICH-GCP) and the applicable IRB, ethical, federal, state, and local regulatory requirements.
3. I certify that I, and the study staff, have received the required training to conduct this research protocol.
4. I agree to maintain adequate and accurate records in accordance with IRB policies, federal, state, and local laws, and regulations.

UCSF Principal Investigator

_____
Printed Name

_____ _____
Signature Date

Abstract

Title	Phase II study of Pembrolizumab in Multiple Myeloma Patients Relapsing After or Refractory to Anti-BCMA CAR-T Therapies (abbreviated title: Pembrolizumab for relapsed myeloma after anti-BCMA CAR-T)
Study Description	This is a single-arm, single-institution phase II study of the safety and efficacy of pembrolizumab in the treatment of relapsed/refractory multiple myeloma (RRMM) in patients who have relapsed or were refractory to anti-BCMA CAR-T therapies. A Simon's minimax two-stage design will be employed with Bayesian toxicity monitoring for assessment of adverse event data. We hypothesize that pembrolizumab will be able to elicit an overall response rate of 30% or better.
Phase of Study	Phase II
Investigational Products	Pembrolizumab
Study population	Patients ≥ 18 years of age with relapsed or refractory multiple myeloma after anti-BCMA CAR-T therapy
Primary Objective	To evaluate the efficacy of pembrolizumab therapy in patients who have relapsed MM after anti-BCMA CAR-T therapies. Specifically, we will examine the overall response rate (ORR), defined as the proportion of patients achieving a partial response (PR) or better based on IMWG criteria, after 4 cycles of pembrolizumab therapy.
Secondary Objectives	• To evaluate the safety and tolerability of pembrolizumab in participants who relapsed or were refractory to anti-BCMA CAR-T therapies • To evaluate the depth of response for patients treated with pembrolizumab who had previously relapsed after or were refractory to anti-BCMA CAR-T therapies • To evaluate time-to-event outcomes, including time-to-next treatment (TNT), progression-free survival (PFS), and overall survival (OS) after initiation of pembrolizumab therapy
Sample Size	Stage 1: 15 participants Stage 2: 10 participants 25-27 total participants expected
Duration of Study Treatment	Participants may continue study treatment for up to 2-years from the time of initiating treatment.

Duration of Follow up	Participants will be followed for at least 30 days after last treatment or removal from study, or until death. Participants who have completed 35 cycles of therapy or discontinued treatment for reasons other than disease progression will be followed for up to 1-year, until removal from study, start of new anti-cancer therapy, or death.

List of Abbreviations

AE	adverse event
ALC	absolute lymphocyte count
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCG	Bacillus Calmette–Guerin
BCMA	B-cell receptor maturation antigen
BMP	basic metabolic panel
BUN	blood urea nitrogen
CAR-T	chimeric antigen receptor T-cell
CBC	complete blood cell (count)
CD28	cluster of differentiation 28
CD3ζ	cluster of differentiation 3 zeta
CNS	central nervous system
CR	complete response
CRF	case report form
CRS	cytokine release syndrome
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CTMS	Clinical Trial Management System
DILI	drug-induced liver injury (DILI)
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECIs	events of clinical interest
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
FLC	free light chain
fT4	free thyroxine
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDFCCC	Helen Diller Family Comprehensive Cancer Center

List of Abbreviations

HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
ICANS	immune-effector cell-associated neurotoxicity syndrome
ICF	informed consent form
ICH	International Conference on Harmonization
IDS	Investigational Drug Services (UCSF)
Ig	immunoglobulin
IgG4	immunoglobulin G4
IgV-type	immunoglobulin-variable–type
IMWG	International Myeloma Working Group
IND	investigational new drug application
IP	investigational product
irAE	immune-related adverse event
IRB	Institutional Review Board
IV	intravenous
LDH	lactate dehydrogenase
LFT	liver function tests
mAb	monoclonal antibody
MM	multiple myeloma
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
OTC	over the counter
PD	disease progression
PD-L1	programmed cell death ligand 1
PET/CT	Positron emission tomography/computed tomography
PFS	progression-free survival
PI	Principal Investigator
PK	pharmacokinetics
PKCθ	protein kinase C theta
PO	*Per os* (by mouth, orally)
PR	partial response
PRC	Protocol Review Committee (UCSF)
Q3W	every 3 weeks

List of Abbreviations

RRMM	Relapsed/refractory multiple myeloma
SAE	severe adverse events
sCR	stringent complete response
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SPEP	serum protein electrophoresis
SPIE	serum protein immunofixation electrophoresis
T3	triiodothyronine
TMDD	target-mediated drug disposition
TNT	time-to-next treatment
TSH	Thyroid-stimulating hormone
UMVUE	uniformly minimum variance unbiased estimator
UP	unanticipated problem
UPEP	urine protein electrophoresis
UPIE	urine protein immunofixation electrophoresis
WOCB	woman of childbearing potential
Zap70	zeta-chain associated protein kinase

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1 Introduction

1.1 Background on Indication

Multiple myeloma (MM) is a hematologic malignancy caused by a monoclonal plasma cell neoplasm that leads to development of end-organ damage, including renal dysfunction, bone disease, and anemia. The treatment for multiple myeloma has evolved considerably over the last several years, with standard-of-care therapies now consisting of immune-modulatory agents, proteasome inhibitors, and monoclonal antibodies. Despite the advances in the treatment of multiple myeloma, the disease remains largely incurable, and most patients ultimately relapse and become refractory to available multiple myeloma therapies.

Chimeric antigen receptor t-cell (CAR-T) technologies have added a new tool in the armamentarium for treatment of hematologic malignancies. Given the success of CAR-T therapies in the treatment of relapsed acute lymphoblastic leukemia and diffuse large B-cell lymphoma, CAR-T therapies have been explored in the treatment of multiple myeloma, with most studies thus far being directed at the BCMA antigen, which is highly expressed in malignant plasma cells. Several BCMA-targeted CAR-T therapies have shown efficacy in early phase studies, with studies demonstrating overall response rates above 80%[1,2]. In the phase 1 study of the anti-BCMA CAR-T bb2121 in relapsed/refractory multiple myeloma (RRMM), the overall response rate was 85% (28/33 patients), including 45% of patients achieving a CR or stringent CR. Median progression-free survival was 11.8 months[1]. Although these results are promising in this heavily pretreated population, long-term durable responses have not yet been achieved with the majority of patients eventually progressing. The efficacy of salvage therapies after CAR-T is limited, highlighting the need for developing new treatment strategies for patients who relapse or are refractory CAR-T treatments.

Most recently, there has been increasing evidence that the immunosuppressive effects of the tumor microenvironment may play an important role in the development of resistance to CAR-T therapy. Programmed death-1 (PD-1) is one of the co-inhibitory receptors that can be upregulated following antigen exposure and underlying tumor cells may increase expression of PD-1 ligand (PD-L1) to promote immune evasion, leading to reduction in the activity of cytotoxic T-cells[3,4]. Antibody therapy targeting the PD-1/PD-L1 axis is thus a potentially attractive target in abrogating the immunosuppressive effects of the tumor microenvironment to restore potency and/or augment the activity of CAR-T therapies.

In-vitro and in-vivo studies have demonstrated blockade of PD-1/PD-L1 axis is able to rescue CAR-T cell function in various tumor models[4–7]. Furthermore, studies have shown increased expression of PD-L1 in various hematologic malignancies, including MM[8–10]. In several studies, increased levels of PD-L1 on multiple myeloma cells along with increased PD-1 expression in T-cells were found to be consistent with an “exhausted” phenotype, that was able to be ameliorated with PD-L1 blockade[11–13]. In addition, in the setting of active and relapsed MM, other cells in the tumor microenvironment including myeloid-derived suppressor cells and plasmacytoid dendritic cells were found to have higher levels of PD-L1, providing support that immunosuppressive effects of the tumor microenvironment may play an important role in relapsed disease[11,14,15]. An in-vivo murine myeloma model demonstrated that the combination of low-dose irradiation with anti-PD-1 treatment led to prolonged survival, with an increase in tumor-specific CD8+ T-cells[16]. One in-human study for patients with non-Hodgkin lymphoma who were refractory to or relapsing after CART19 therapy treated with pembrolizumab 200 mg IV every 3 weeks was able to show re-expansion of CART19 cells in 9 of 12 patients, eliciting an overall tumor response rate of 27% in evaluable patents[17]. Altogether, these studies suggest that combining blockade of PD-1/PD-L1 axis and induction of tumor-specific cytotoxic T-cells, such as those introduced by CAR-T therapies, may have a synergistic effect on tumor-killing[18].

With regards to in-human multiple myeloma studies of PD-1 inhibitors, several studies have been performed with varying results. An initial phase 1b study of 27 patients with relapsed/refractory MM treated with single agent nivolumab demonstrated a response rate of 4%, with one patient responding and achieving a CR[19]. Subsequently, combination therapy with immunomodulatory agents was conducted and demonstrated higher overall response rates. In the phase I KEYNOTE-023 study, pembrolizumab in combination with lenalidomide and low-dose dexamethasone in patients with relapsed/refractory MM previously treated with at least two lines of therapy, demonstrated an overall response rate of 44%, with 16% of patients achieving VGPR or better. Grade 3-5 treatment-related adverse events were observed in approximately 60% of patients treated on combination therapy[20]. In a phase II study of pembrolizumab with pomalidomide and low-dose dexamethasone for patients with relapsed/refractory myeloma, an overall response rate of 60% was seen with 24% achieving VGPR or better; adverse events grade 3-4 occurred in 40% of patients, with the majority consisting of hematologic toxicities[21].

Subsequently, two large Phase III trials were conducted with pembrolizumab and low-dose dexamethasone in combination with lenalidomide (KEYNOTE-185) in one study[22] and in combination with pomalidomide (KEYNOTE-183) in another study[23], both studies assessing for progression-free survival benefit over immunomodulatory and low-dose dexamethasone alone. On July 3, 2017, the FDA halted both trials due to inferior outcomes and increased risk of death in patients receiving pembrolizumab combination therapies. At database cut-off, the median progression-free survival was not reached in the KEYNOTE-185 trial in either arm (with 6-months PFS 82% for pembrolizumab-arm versus 85% for non-pembrolizumab arm) with serious adverse events and deaths occurring more frequently in the pembrolizumab arm (serious adverse events: 54% vs. 39%; deaths 4% vs 1%). Overall response rates were similar between the two arms (64% for pembrolizumab arm vs 62% for non-pembrolizumab arm)[22]. In the KEYNOTE-183 trial, the median progression-free survival was 5.6 months in the pembrolizumab plus pomalidomide and dexamethasone group versus 8.4 months in the pomalidomide and dexamethasone group alone. More serious adverse events occurred in the pembrolizumab plus pomalidomide and dexamethasone arm (63% with 3% treatment-related deaths) compared in the pomalidomide and dexamethasone alone arm (46% with no treatment-related deaths)[23].

Impairment of the immune system in these heavily pre-treated patient populations may have prevented tumor-specific T-cell responses after PD-1 blockade, hindering responses to pembrolizumab. Furthermore, combining pembrolizumab with immunomodulatory agents and dexamethasone may not be optimal, especially as concurrent steroid administration may attenuate the benefits of PD-1 blockade. Utilizing PD-1 blockade after tumor-targeted CAR-T cells are introduced could theoretically provide a more active and tumor-specific T-cell population that could better respond to PD-1 inhibition. In one small study, pembrolizumab therapy after BCMA CAR-T therapy was able to re-expand the CAR-T population in one out of 5 patients, eliciting a minor response, highlighting the potential of PD-1 blockage after CAR-T therapy relapse in multiple myeloma[24].

1.2 Background on the Investigational Product and Associated Known Toxicities

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of

indications because of its mechanism of action to bind the PD-1 receptor on the T cell. For more details on specific indications refer to the Investigator brochure.

1.2.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades[25]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma[26,27].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1 expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2)[28,29].

The structure of murine PD-1 has been resolved[30]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade[26,29,31,32]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins[33,34]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in multiple myeloma after CAR-T therapy, as blocking this pathway may potentiate CAR T-cell response.

1.2.2 Preclinical and Clinical Trial Data

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

1.3 Rationale for the Proposed Study

Currently, patients with multiple myeloma who relapse after BCMA CAR-T trials have limited treatment options and poor outcomes. Given the synergetic potential of PD-1 blockade and CAR-T therapy, we propose a phase II study for use of pembrolizumab in patients who have been treated with anti-BCMA CAR-T therapies and have evidence of relapsed or refractory disease.

1.4 Rationale for Endpoints

Primary Objective: To evaluate the efficacy of pembrolizumab therapy in patients who have relapsed or refractory MM (RRMM) after anti-BCMA CAR-T therapies. Specifically, we will

examine the rate of achieving a partial response (PR) or better after 4 cycles of pembrolizumab therapy.

Primary Efficacy Endpoint: Overall response rate, defined as proportion of patients achieving partial response (PR) or better by IMWG criteria after 4 cycles of pembrolizumab therapy.

Treatment options for RRMM after anti-BCMA CAR-T cell therapies are limited and identifying therapies that are able to elicit tumor responses are important. Studies have demonstrated that depth of response is associated with increased progression-free survival and that patients who do not achieve disease response to therapy have poor outcomes[35]. In the triple-class refractory setting for which the majority of anti-BCMA CAR-T patients belong, response rates of 30% or greater would be clinically meaningful and justify further evaluation. As an example, Selinexor with dexamethasone was recently FDA-approved for treatment of triple-class refractory multiple myeloma after the STORM trial found an overall response rate of 26%, with the lower limit of its confidence interval meeting statistical significance[36]. We hypothesize that pembrolizumab given after anti-BCMA CAR-T therapies would be associated with a 30% or greater disease response rate (PR or greater), and we anticipate that these responses should be observed within 4 cycles of starting therapy.

Secondary Objective (1): To evaluate the safety of pembrolizumab in patients who relapsed or were refractory to anti-BCMA CAR-T therapies.

Secondary Endpoint (1): Frequency of adverse events, defined by CTCAE V5.0 and ASTCT (for cytokine release syndrome [CRS] and immune-effector cell-associated neurotoxicity syndrome [ICANS]); frequency of Grade 3 or higher non-hematologic adverse events; frequency of treatment discontinuations due to toxicity.

Given that PD-1 therapies after CAR-T represent a relatively novel treatment paradigm, we will report rates of adverse events as defined by NCI CTCAE V5.0 and ASTCT (for CRS and ICANS). Previous data with pembrolizumab across various cancers have suggested a severe AE rate (Grade 3 or higher) of 15 – 20%[17,37–40], and thus we anticipate a similar frequency in our study irrespective of cause. Given that we hypothesize that pembrolizumab may be able to re-activate quiescent CAR-T cells, there is potential for additional toxicity including CRS and ICANS, and thus a reasonable definition of safety would be having less than 30% of all treated participants incurring a Grade 3 or higher non-hematologic adverse event.

Secondary Objective (2): To evaluate the depth of response for patients treated with pembrolizumab who had previously relapsed after or were refractory to anti-BCMA CAR-T therapies.

Secondary Endpoint (2): Rates of stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), stable disease (SD), and progressive disease (PD) at any time during pembrolizumab therapy

Depth of myeloma response has been correlated with progression-free survival[35]. Thus, we will plan to evaluate depth of response based on the percentage of patients that achieve a complete response (CR), very good partial response (VGPR), partial response (PR), stable disease (SD), or progressive disease (PD) at any time during pembrolizumab therapy.

Secondary Objective (3): To determine time-to-event outcomes, including time-to-next treatment (TNT), progression-free survival (PFS), and overall survival (OS) after initiation of pembrolizumab therapy

Secondary Endpoint (3): TNT, PFS, OS

We will explore time-to-event outcomes with Kaplan-Meier method after initiation of pembrolizumab. These results can potentially be compared to historical controls.

Exploratory Objective: To explore the immune profile after pembrolizumab treatment, including changes in absolute lymphocyte count (ALC) and lymphocyte subsets by flow-cytometry

Exploratory Endpoint: ALC, absolute CD3 T-cell count, absolute CD4 T-cell count, absolute CD8 T-cell count

We will assess whether participants have changes in their immune profile, specifically in their T-cell numbers and composition, after administration of pembrolizumab and will assess whether these changes correlate to clinical response. These analyses will be predominately descriptive and exploratory.

1.5 Rationale for the Dose Selection/Regimen

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

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

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

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

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides

similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed-dose and 2 mg/kg Q3W dose. Supported by these PK characteristics and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

PD-1 blockade given post-CAR T therapy has been shown to be safe and without increased risk of significant CRS, ICANS, or other immune-related adverse events. In a phase 1/2a study conducted by Chong et al. utilizing pembrolizumab for relapsed or refractory B-cell lymphomas after anti-CD19 CAR T cells, the only grade ≥3 adverse event observed was neutropenia in 3 of 12 patients; 1 of 12 patients had reported Grade 2 CRS and was managed with supportive care alone and there were no cases of ICANS. The median time from CAR-T infusion to first pembrolizumab dose was 3.3 months (range: 0.4 – 42.8 months) and no CRS/ICANS was observed for patients who received pembrolizumab within the first 3 months after CAR-T infusion[41]. In the ZUMA-6 study, patients with refractory DLBCL received atezolizumab 1200 mg every 21 days starting at either Day 21, 14, and 1 post-axicabtagene ciloleucel in 3 different cohorts respectively. Only one grade ≥3 adverse events was attributed to atezolizumab. There was no clinically significant evidence of increased incidence of adverse events with the addition of atezolizumab; Grade ≥3 CRS and neurologic events were observed in 3 of 12 patients and 6 of 12 patients respectively, comparable to those previously seen with axicabtagene-ciloleucel alone[42].

Furthermore, several studies have demonstrated that CAR-T persistence wanes over time and thus in may be advantageous to administer pembrolizumab earlier post-CAR-T. In the KarMMa study of idecabtagene-vicleucel, 99% of patients had detectable CAR-T cells at 1 month post-infusion, 75% at 3 months, 59% at 6 months, and 36% at 12 months[1]. For ciltacabtagene-autoleucel, in CARTITUDE-1, after cell expansion, the persistence phase of CAR-T was observed or all patients, and the reported median time for detectable CAR transgene levels was approximately 100 days (range: 28 – 365 days) post infusion [43]. In the preliminary assessment of CARTITUDE-2 which treated RRMM with ciltacabtagene-autoleucel, the median persistence was 153 days (range, 57.1 – 336.8 days)[44,45]

Given that there have been no safety concerns identified with administering PD-1 inhibitors less than 1 month after CAR-T infusion, we propose that pembrolizumab can be given as early as 30 days post-CAR-T in our study to increase likelihood of treatment response.

2 Study Objectives

2.1 Hypothesis

We hypothesize that, for multiple myeloma (MM) patients with relapsed or refractory disease after anti-BCMA CAR-T therapies, pembrolizumab will be associated with a 30% or greater disease response rate (PR or greater).

2.2 Primary Objective and Endpoint(s)

Primary Objective	Endpoint(s)	Time Frame
To evaluate the overall response rate (ORR) of pembrolizumab in patients with relapsed or refractory MM (RRMM) after anti-BCMA CAR-T therapies	• ORR (defined as the proportion of patients achieving a partial response (PR) or better based on IMWG criteria after 4 cycles of pembrolizumab therapy)	From initiation of study treatment until after 4 cycles of therapy

2.3 Secondary Objective(s) and Endpoint(s)

Secondary Objective	Endpoint(s)	Time Frame
1. To evaluate the safety and tolerability of pembrolizumab in participants who relapsed or were refractory to anti-BCMA CAR-T therapies.	• Frequency of adverse events, as graded by NCI CTCAE version 5.0, including frequency of non-hematologic grade 3 or higher adverse events • Frequency of CRS graded by ASTCT • Frequency of ICANS graded by ASTCT • Frequency of treatment discontinuations due to toxicity	From initiation of study treatment until safety follow-up following treatment discontinuation
2. To evaluate the depth of response for patients treated with pembrolizumab who had previously relapsed after or were refractory to anti-BCMA CAR-T therapies	• Rates of sCR, CR, VGPR, PR, SD, and PD at any time during pembrolizumab therapy	From initiation of study treatment until discontinuation of treatment
3. To evaluate time-to-event outcomes, including time-to-next treatment (TNT), progression-free survival (PFS), and overall survival (OS) after initiation of pembrolizumab therapy	• TNT, PFS, OS assessed using Kaplan-Meier survival analysis	From initiation of study treatment until end of follow-up

2.4 Exploratory Objective and Endpoint

Exploratory Objective	Endpoint(s)	Time Frame
To explore the immune profile after pembrolizumab treatment, including changes in absolute lymphocyte count (ALC) and lymphocyte subsets by flow-cytometry	• ALC, absolute CD3 T-cell count, absolute CD4 T-cell count, and absolute CD8 T-cell count	From initiation of study treatment until after 4 cycles of therapy

3 Study Design

3.1 Characteristics

This is a Phase II, single-center study of pembrolizumab for the treatment of relapsed or refractory multiple myeloma (RRMM) after anti-BCMA chimeric antigen receptor T-cell (CAR-T) therapy. Eligible patients will receive pembrolizumab 200 mg over 30 minutes, intravenously, every 3 weeks for up to 2 years (35 cycles) or until disease progression/dose-limiting toxicities/discontinuation. The study will utilize a Simon's two-stage design with 15 participants enrolled in stage I and 10 additional participants enrolled in stage II assuming that at least 2 or more participants achieve a treatment response after 4 cycles of therapy during stage I of the study. The primary endpoint will be overall response rate (partial response [PR] or better by International Myeloma Working Group [IMWG] criteria) after 4 cycles of therapy. A Bayesian toxicity monitoring design will be incorporated for ongoing safety analysis during the trial to pause enrollment if at any time the rate of grade 3 or higher non-hematologic adverse events exceeds 30%.

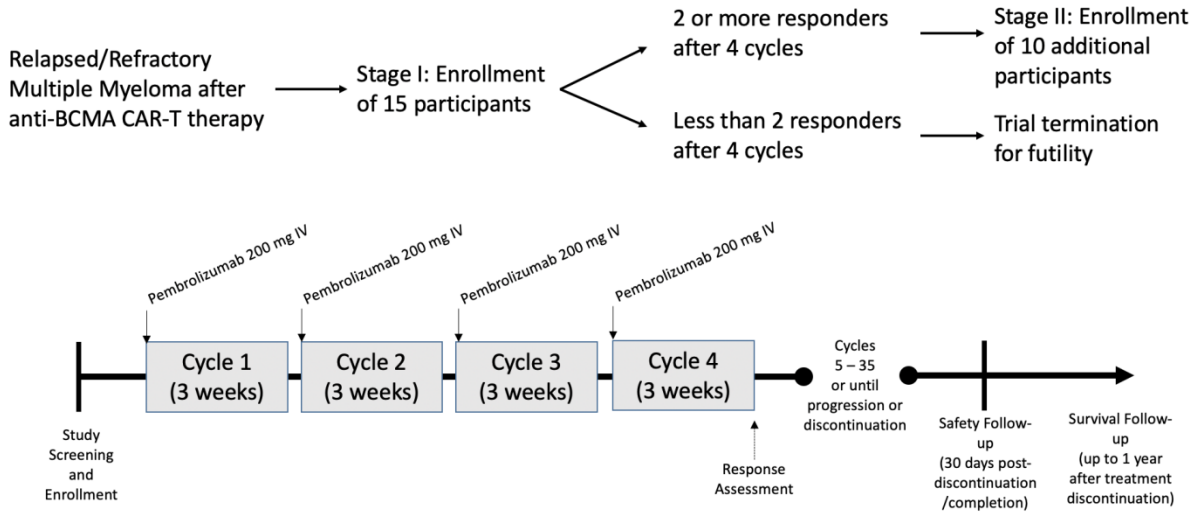

Figure 1 Trial Schema

3.2 Sample Size

Participants with relapsed or refractory MM after anti-BCMA CAR-T therapies will be included in this study. We anticipate enrolling 25 - 27 participants to allow for the possibility of 10%

participant dropout before receiving pembrolizumab therapy or during the response evaluation period.

- Stage 1: 15 participants will be accrued. The trial will be terminated at Stage 1 if 0 or 1 response is observed; otherwise, it will continue to Stage 2.
- Stage 2: 10 more patients will be accrued (for a total of 25 patients). We will reject the null hypothesis if 6 or more responses are observed in 25 patients.

If a participant is enrolled but does not receive any doses of pembrolizumab, the participant may be replaced.

If a participant is enrolled and receives less than 4 cycles of therapy and discontinues therapy or withdraws from the study for reasons other than disease progression, the participant will not be evaluated for the primary efficacy endpoint and will be replaced. However, all participants who receive at least one dose of pembrolizumab will be included in the safety analysis for adverse events (including those that received < 4 cycles of therapy).

3.3 Eligibility Criteria

3.3.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Male/female participants who are 18 years of age or older on the day of signing informed consent with histologically confirmed diagnosis of multiple myeloma will be enrolled in this study.

2. Ability to understand a written informed consent document, and the willingness to sign it or a legally acceptable representative (if applicable).

3. Have an Eastern Cooperative Oncology Group (ECOG) performance status <2 (Karnofsky >60%, see Appendix 1). Evaluation of ECOG is to be performed within 7 days prior to the start of study treatment.

4. The effects of pembrolizumab on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception detailed in Appendix 3 for the duration of study participation and 120 days after last administration of study treatment.

   (See Appendix 3 for more details) Female participants are eligible if not pregnant, not breastfeeding, and one of the following:

   a) Not a WOCBP as defined in Appendix 3

   OR

   b) WOCBP who agrees to follow contraceptive guidance in Appendix 3 during treatment period and at least 120 days following last dose of study treatment

   Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

   Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 120 days after last

administration of study treatment. Men should also refrain from donating sperm during this period.

5. Participants must have either

    a. progressive disease after prior anti-BCMA CAR-T therapy and have not started another systemic anti-cancer therapy following progression after anti-BCMA CAR-T therapy. Patients who received localized radiotherapy alone for symptomatic relief of progressive disease following anti-BCMA CAR-T will be allowed.

    OR

    b. stable disease as best hematologic response after at least 30 days post anti-BCMA CAR-T infusion.

    Progression after anti-BCMA CAR-T is defined by International Myeloma Working Group (IMWG) criteria:

    a) Increase of > 25% from lowest response value in any one or more of the following:

        i. Serum M-component and/or (the absolute increase must be > 0.5 g/dL)

        ii. Urine M-component and/or (the absolute increase must be > 200 mg/24 h)

        iii. Only in patients without measurable serum and urine M-protein levels; the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL

        iv. Bone marrow plasma cell percentage: the absolute percentage must be > 10%

        and/or:

    b) Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas

        and/or:

    c) Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder

    Stable disease is defined by IMWG criteria: Not meeting criteria for sCR, CR, VGPR, PR, or PD (see Appendix 6)

6. Time from date of anti-BCMA CAR-T infusion to date of first administration of pembrolizumab (study drug) must be ≥ 30 days. In order to be eligible for this study, participants must not be candidates for treatment regimens known to provide clinical benefit in MM as assessed by the treating physician and must have previously received

or are intolerant to a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody.

7. Diagnosis of symptomatic multiple myeloma defined as: clonal bone marrow plasma cells >10% or biopsy-proven bony or extramedullary plasmacytoma and any one or more of the following CRAB features and myeloma-defining events:

    a) Hypercalcemia: serum calcium >0.25 mmol/L (>1mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11mg/dL)

    b) Renal insufficiency: creatinine clearance <40 mL per minute or serum creatinine >177 micromol/L (>2mg/dL)

    c) Anemia: hemoglobin value of >20g/L below the lowest limit of normal, or a hemoglobin value <100g/L

    d) Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET/CT. If bone marrow has <10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement

    e) Any one or more of the following biomarkers of malignancy:

        i. 60% or greater clonal plasma cells on bone marrow examination

        ii. Serum involved / uninvolved free light chain ratio of 100 or greater, provided the absolute level of the involved light chain is at least 100 mg/L

        iii. More than one focal lesion on MRI that is at least 5mm or greater in size

8. Active and measurable disease, defined by serum paraprotein (M-protein) $\geq$ 0.5 g/dL, 24-hour urine Bence Jones protein of $\geq$200 mg, or abnormal serum free light chain ratio with involved light chain of $\geq$10 mg/dL (100 mg/L).

9. Have adequate organ function as defined in the following table (Table 3.3.1). Specimens must be collected within 10 days prior to the start of study treatment.

Table 3.3.1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥500/μL [a, b]
Platelets	≥25 000/μL [a, b]
Hemoglobin	≥8.0 g/dL [a, b]
Renal	
Creatinine OR Measured or calculated[c] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN

AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal.

[a] Growth factor and/or transfusion support is permissible to stabilize participant prior to study treatment if needed.

[b] No lower limit if cytopenia is related to bone marrow involvement.

[c] Creatinine clearance (CrCl) should be calculated per institutional standard.

Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

3.3.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. A WOCBP who has a positive urine pregnancy test within 72 hours prior to study treatment initiation (see Appendix 3). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

   Note: in the event that 72 hours have elapsed between the screening pregnancy test and the first dose of study treatment, another pregnancy test (urine or serum) must be performed and must be negative in order for subject to start receiving study medication.

2. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti PD L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX 40, CD137).

3. Has received prior systemic anti-cancer therapy including investigational agents within 4 weeks prior to study treatment initiation.

   Note: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Participants with ≤Grade 2 neuropathy may be eligible.

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

4. Has received anti-BCMA CAR-T infusion < 30 days prior to study treatment initiation.

5. Has received subsequent systemic anti-cancer therapy following anti-BCMA CAR-T therapy. Participants who received localized radiotherapy alone for symptom control following anti-BCMA CAR-T therapy will be allowed to participate.

6. Has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette-Guerin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed. SARS-COV-2 vaccines are generally mRNA-based or viral vector vaccines (replication-incompetent) and are allowed.

7. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study intervention.

   Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.

8. Has a diagnosis of primary immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.

9. Has an active second malignancy requiring treatment, unless potentially curative treatment has been completed with no evidence of malignancy for 2 years. Participants with the following low-risk or non-invasive malignancies will be allowed:

   a. Basal cell carcinoma of the skin

   b. Squamous cell carcinoma of the skin

   c. Carcinoma in-situ of the cervix

   d. Carcinoma in-situ of the breast

   e. Superficial bladder cancer

   f. Incidental histologic finding of prostate cancer (T1a or T1b using the TNM [tumor, nodes, metastasis] clinical staging system) or prostate cancer that is curative or considered very-low or low risk in which observation is reasonable.

   g. Other in-situ cancers

   Note: The time requirement does not apply to participants who underwent successful definitive resection of basal cell carcinoma of the skin, squamous cell carcinoma of the skin, superficial bladder cancer, in situ cervical cancer, or other in-situ cancers

10. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, i.e., without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable, and without requirement of steroid treatment for at least 14 days prior to first dose of study intervention.

11. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.

12. 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 (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment and is allowed.

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

14. Has an active infection requiring systemic therapy. Prophylactic antibiotics/antivirals are allowed.

15. Has a known history of Human Immunodeficiency Virus (HIV) infection.

16. Has known active Hepatitis B virus infection (defined as Hepatitis B [HBV] DNA detected or Hepatitis B surface antigen [HbsAg] positive) or known active Hepatitis C virus infection (defined as Hepatitis C [HCV] RNA qualitative detected). Subjects who have been vaccinated against hepatitis B (positive for hepatitis B surface antibody [HBsAB]) who are negative for other markers of prior hepatitis B infection (e.g., Hepatitis B core antibody [HBcAb] negative) are eligible. Subjects with past exposure or known history of hepatitis B infection (e.g., HBcAb positive) are eligible for the study provided that they are negative by assessment for HBV DNA and HbsAg. Subjects with a history of hepatitis C infection (defined as detectable HCV antibody) are eligible as long as they have a negative HCV viral load.

17. Has a known history of active TB (Bacillus Tuberculosis).

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

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

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

21. Has had a history of allogenic bone marrow/tissue/solid organ transplant.

22. Has unmeasurable disease by serum/urine testing (oligo-secretory or non-secretory multiple myeloma).

23. Has diagnosis of Waldenstrom's disease, light chain amyloidosis, or POEMS disease.

24. ECOG performance status ≥ 2.

3.4 Inclusion of Women and Minorities

3.4.1 Eligibility of Women and Minorities

Individuals of any sex/gender, race, or ethnicity are eligible for this study.

3.4.2 Recruitment of Minority Groups

The study recruitment strategy aims to achieve representation of minority groups that reflects the demographics of the affected population in the catchment area.

3.5 Inclusion Across the Lifespan

3.5.1 Age Range of Participants

Individuals ages 18 and over are eligible for this study. Children are excluded from the study because the disease/condition does not occur regularly in children.

3.5.2 Study Design/Recruitment Considerations Related to Age Groups

The study design and recruitment strategy aim to achieve representation of age groups that reflect the demographics of the affected population.

3.6 Duration of Treatment

In the absence of treatment delays due to adverse events (AEs), treatment may continue for up to 2 years or until:

- Disease progression resulting in discontinuation of the study treatment;
- Inter-current illness that prevents further administration of treatment;
- Unacceptable adverse event(s);
- Participant decides to withdraw from the study;
- Significant participant non-compliance with protocol;
- If the participant meets an exclusion criterion (either newly developed or not previously; or, recognized) that precludes further study participation
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the investigator.

3.7 Duration of Follow Up

Participants will be followed for a minimum of 30 days after last treatment or removal from study, or until death, whichever occurs first. Participants removed from study for unacceptable treatment or study-related adverse event(s) will be followed until resolution or stabilization (as determined by the investigator) or until initiation of new anti-cancer therapy, whichever occurs first.

After completing the follow-up period, participants will be followed every 12 weeks (+/- 14 days) to assess for survival/anti-cancer therapy status for up to 1 year after treatment completion or discontinuation. If possible, these visits will be done via video appointment or telephone follow-up.

Long term/Survival Follow-up visits are only required for patients who have either completed 35 cycles of therapy or have discontinued treatment for reasons other than disease progression and have not yet started treatment with another anti-cancer therapy.

Participants who experienced confirmed disease progression or start a new anticancer therapy will be taken off study. Efforts will be made to contact these participants for survival follow-up by telephone every 12 weeks (± 14 days) to assess for survival status until death, withdrawal of consent, or the end of the trial, whichever occurs first for up to one year after treatment discontinuation.

3.8 Primary Completion

The expected primary completion date is 30 months after the study opens to accrual.

3.9 Study Completion

The expected study completion date is 42 months after the study opens to accrual.

4 Investigational Products

4.1 Description, Supply, and Storage of Investigational Products

4.1.1 Pembrolizumab

Classification

Pembrolizumab is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 149 kDa.

Mechanism of Action

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response.

Metabolism

Pembrolizumab is catalyzed into small peptides and single amino acids via general protein degradation, but it does not rely on metabolism for clearance.

Contraindications

None.

Formulation, Appearance, Packaging, and Labeling

Pembrolizumab, manufactured by Merck, is supplied as a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for intravenous infusion. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP.

Supplies will be labeled in accordance with regulatory requirements.

Availability

Pembrolizumab is being obtained as commercial supply provided by Merck.

Storage and handling

Pembrolizumab is stored at the UCSF investigational pharmacy.

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.

Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake.

Side Effects

Complete and updated adverse event information is available in the Investigational Drug Brochure (IB) and/or product package insert.

4.2 Accountability Records for Investigational Product

UCSF Investigational Drug Services (IDS) will manage drug accountability records for UCSF study supply of investigational product(s).

4.3 Ordering Investigational Product

UCSF will obtain pembrolizumab directly from Merck.

4.4 Returns and Reconciliation

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

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

5 Treatment Plan

5.1 Dosage and Administration

Treatment will be administered on an outpatient basis.

Trial interventions should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed in the Trial Flow Chart (Fig. 1, Section 3.1). Trial interventions may be administered up to 3 days before or after the scheduled Day 1 of each cycle after Cycle 1 if needed for administrative reasons.

Pembrolizumab 200 mg will be administered as 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.

Table 5.1 Regimen Description

Investigational Product	Premedication; precautions	Dose	Route	Schedule	Cycle Length
Pembrolizumab	N/A	200 mg	Intravenous	Day 1 of each 3-week cycle	3 weeks (21 days)

Trial intervention should begin as close as possible to the date on which intervention is allocated/assigned. The treatment is planned for a maximum of 35 cycles or until progression of disease/dose-limiting toxicities.

At least two doses of tocilizumab per patient must be available on site prior to dosing of pembrolizumab.

5.2 Dose Modifications and Dosing Delays

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 are critical to reducing 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. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 5.2-1. Additional guidelines for toxicity management for cytokine release syndrome and neurotoxicity are outlined in Sections 5.2.1 and 5.2.2 respectively.

Table 5.2-1 Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab

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

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1 – 2 mg/kg prednisone or equivalent) followed by taper Add prophylactic antibiotics for opportunistic infections	Monitor participants for signs and symptoms of pneumonitis Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1 – 2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood, or mucus in stool with or without fever) and bowel perforation (i.e., peritoneal signs and ileus) Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Grade 4 or recurrent Grade 3	Permanently discontinue		
AST or ALT elevation or Increased Bilirubin	Grade 2 [a]	Withhold	Administer corticosteroids (initial dose of 0.5 – 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
	Grade 3 [b] or 4 [c]	Permanently discontinue	Administer corticosteroids (initial dose of 1 – 2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New-onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	Initiate insulin replacement therapy for participants with T1DM Administer anti-hyperglycemic in participants with hyperglycemia	Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	Treat with non-selective beta-blockers (e.g., propranolol) or thioamides as appropriate	Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3, or 4	Continue	Initiate thyroid replacement hormones (e.g., levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders
Nephritis and renal dysfunction: grading according to increased	Grade 2	Withhold	Administer corticosteroids (prednisone 1 – 2 mg/kg or equivalent) followed by taper	Monitor changes in renal function
	Grade 3 or 4	Permanently		

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
creatinine or acute kidney injury		discontinue		
Myocarditis	Grade 1 or 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All Other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e].		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

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

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

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

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM)

[e] Events that require discontinuation include but are not limited to: Guillain-Barre Syndrome, encephalitis, Stevens-Johnson Syndrome, and toxic epidermal necrolysis.

Dose modification and toxicity management of infusion reactions related to pembrolizumab

Table 5.2-2 Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise, dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug intervention	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4:	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	No subsequent dosing

Life-threatening; pressor or ventilatory support indicated	is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug intervention.	
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

5.2.1 Dose modification for cytokine release syndrome (CRS)

For participants who develop cytokine release syndrome grades 1-3 after pembrolizumab, further doses of pembrolizumab will be held until CRS completely resolves. Once CRS has fully resolved, the clinical investigator may resume pembrolizumab 200 mg every 3 weeks. Pembrolizumab will be discontinued for participants who develop grade 4 CRS or any grade 3 CRS that does not resolve to Grade ≤ 1 or baseline within 48 hours with tocilizumab therapy and/or best medical care.

Guidelines for the management of patients who develop CRS, including the use of tocilizumab, are outlined in Section 6.4.4.1.

5.2.2 Dose modification for immune-effector cell-associated neurotoxicity (ICANS)

For participants who develop immune-effector cell-associated neurotoxicity grades 1-3 after pembrolizumab, further doses of pembrolizumab will be held until symptoms resolve. Once ICANS has fully resolved, the clinical investigator may resume pembrolizumab 200 mg every 3 weeks. Pembrolizumab will be discontinued for participants who develop grade 4 ICANS or any grade 3 ICANS that does not resolve to Grade ≤ 1 or baseline within 48 hours with steroids, tocilizumab therapy, and/or best medical care.

Guidelines for the management of patients who develop ICANS, including the use of tocilizumab and steroids, are outlined in Section 6.4.4.2.

5.2.3 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.

5.3 Stopping Rules

Fifteen evaluable participants will be enrolled in the first stage of the Simon two-stage trial. If 0 or 1 responses according to IMWG criteria are noted in these initial 15 participants, then the trial will be stopped for futility.

6 Study Procedures and Schedule of Events

The study-specific procedures and assessments are detailed in this section and outlined in the Study Calendar – Section 6.1.

Screening assessments must be performed within 28 days prior to the first dose of investigational product unless otherwise noted. Any results falling outside of the reference ranges may be repeated at the discretion of the investigator.

All on-study visit procedures are allowed **a window of ± 3 days** unless otherwise noted. Treatment or visit delays for public holidays, public health emergencies, or weather conditions do not constitute a protocol violation.

6.1 Study Calendar

Period/ Procedure	**Screening**	**Treatment Cycles (every 3 weeks)**						**End of Treatment**	**Safety Follow-up**	**Long-term Follow-up[1]**
Study Day/Visit Day	**-28 to -1**	**C1 D1**	**C1 D8 (+/- 3)**	**C2 D1 (+/- 3)**	**C3 D1 (+/- 3)**	**C4 D1 (+/- 3)**	**C5+ D1 (+/- 3)[2]**	**(+/- 21)**	**30 days (+/- 5) post-EOT**	**Every 12 weeks (+/- 14) post safety follow-up**
Study Treatment/Drug Administration										
Pembrolizumab		X		X	X	X	X			
Administrative Procedures										
Informed consent	X									
Clinical Assessments										
Physical exam [3, 4]	X	X	X	X	X	X	X		X	
Medical history	X									
Vital signs [4]	X	X	X	X	X	X	X		X	
Concomitant medications [4]	X	X	X	X	X	X	X	X	X	X
AE assessment	X	X	X	X	X	X	X	X	X	X
Performance status [4]	X	X	X	X	X	X	X		X	
Post-treatment anticancer therapy status									X	X
Survival/Long-term Follow-up									X	X

Period/ Procedure	Screening	Treatment Cycles (every 3 weeks)						End of Treatment	Safety Follow-up	Long-term Follow-up[1]
Study Day/Visit Day	**-28 to -1**	**C1 D1**	**C1 D8 (+/- 3)**	**C2 D1 (+/- 3)**	**C3 D1 (+/- 3)**	**C4 D1 (+/- 3)**	**C5+ D1 (+/- 3)[2]**	**(+/- 21)**	**30 days (+/- 5) post-EOT**	**Every 12 weeks (+/- 14) post safety follow-up**
Laboratory Assessments										
Hematology [4, 5]	X	X	X	X	X	X	X		X	
Chemistry [4, 6]	X	X	X	X	X	X	X		X	
Thyroid Function [4, 7]	X	X		X	X	X	X		X	
Tumor marker assessment: Urinalysis [8]	X						X[11]	X[11]		X[11]
Pregnancy test [4, 9]	X	X		X	X	X	X			
Tumor marker assessment: Serum protein and immunofixation electrophoresis (SPEP/SPIE) and serum-free light chains (FLC) [4, 10]	X	X					X	X		X
Lymphocyte subsets [4]		X					X[12]			
Tissue Collection/ Biopsy										
Bone marrow biopsy [11]							X			

[1] Follow-up visits will occur every 12 weeks, up to 1 year after treatment completion or discontinuation. Follow-up visits are only required for patients who have either completed 35 cycles of therapy or have discontinued treatment for reasons other than disease progression and have not yet started treatment with another anti-cancer therapy.

[2] Up to total of 35 cycles.

[3] Full physical exam at screening visit; directed physical exam at all other time points at which a physical exam is indicated

[4] Assessments to be performed before study treatment administration. Labs can be drawn up to 3 days prior to study treatment administration.

[5] Including CBC with differential and platelet count

[6] Including alkaline phosphatase (ALP), ALT/AST, total bilirubin, calcium, phosphorus, (BUN), creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate, uric acid, LDH, fasting lipid panel (LDL, total cholesterol, triglycerides),

[7] Including T3, FT4, and TSH

[8] 24-hour UPEP/UPIE will be obtained on all participants at screening. For participants that do not have measurable serum M-protein (M-protein < 1 g/dL) but measurable urine M-protein (M-protein ≥ 200 mg/24 hours) at screening, subsequent 24-hour UPEP/UPIE will be collected on C5D1 and then every 4 cycles thereafter to assess response. For participants with measurable serum M-protein (M-protein ≥ 1g/dL) and urine M-protein (M-protein ≥ 200 mg/24 hours), additional 24-hour UPEP/UPIE after screening will only be obtained at suspected achievement of sCR, CR, VGPR, PR, and PD to confirm IMWG response criteria. For participants with measurable serum M-

protein and unmeasurable urine M-protein (M-protein ≤ 200 mg/24 hours), additional 24-hour UPEP and UPIE after screening will only be obtained at suspected achievement of sCR, CR, VGPR, and PD to confirm IMWG response criteria.

[9] For women of child-bearing potential. Urine or serum HCG must be negative within 72 hours of treatment administration.

[10] Serum protein and immunofixation electrophoresis and serum-free light chains for disease assessment will be checked on C5D1 and then subsequently every 4 cycles thereafter for response assessment

[11] To confirm CR, bone marrow biopsy is only required for participants who have serologic markers consistent with complete response (disappearance of serum and urine M-protein on electrophoresis for patients with measurable M-protein at treatment initiation or normalization of the free light chain ratio for those with elevated free light chain markers but unmeasurable M-protein at treatment initiation).

[12] Lymphocyte subsets will be checked on C5D1 only

6.2 Participant Registration

A written, signed, informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

All participants consented to the study will be registered in OnCore®, the UCSF Helen Diller Family Comprehensive Cancer Center Clinical Trial Management System (CTMS). The system is password protected and meets HIPAA requirements.

6.3 Schedule of Procedures and Assessments

6.3.1 Pretreatment Period

6.3.1.1 Screening Assessments

The Screening procedures and assessments must be completed within 28 days of initiating study treatment.

- Clinical Assessments
  - Documentation of disease assessment:
    - Disease assessment: Disease assessment and responses will be assessed by serum and urine biomarkers including serum protein and immunofixation electrophoresis (SPEP/SPIE), 24-hour urine protein, and immunofixation electrophoresis (UPEP/UPIE), and serum-free light chain (FLC). The IMWG (International Myeloma Working Group) uniform response criteria will be used to assess disease response and progression[46]. See Appendix 6.
  - Full physical examination
    - 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.
  - Complete medical history
  - Vital signs
    - The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment, and at treatment discontinuation as specified in the Trial Flow Chart (Fig. 1, Section 3.1). Vital signs should include temperature, pulse, respiratory rate, weight, and blood pressure. Height will be measured at screening only.
  - Prior and Concomitant medication review
    - Prior medication review: The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before starting the trial. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

        - Concomitant medication review: The investigator or qualified designee will record medication, if any, taken by the participant during the trial.
    - AE assessment
        - The investigator or qualified designee will assess each participant to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 5.0. For CRS and ICANS, AEs will be graded and recorded according to the ASTCT consensus criteria (see Appendix 4 and 5).

          Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

          Please refer to Section 8.3 for detailed information regarding the assessment and recording of AEs.
    - Performance status
        - The investigator or qualified designee will assess ECOG status (see Appendix 1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.
- Laboratory Assessments
    - Hematology labs - CBC with differential and platelet count
    - Blood chemistry assessment, including: Alkaline phosphatase (ALP), aspartate aminotransferase/alanine aminotransferase (ALT/AST), total bilirubin, calcium, phosphorus, blood urea nitrogen (BUN), creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate, uric acid, lactate dehydrogenase (LDH), fasting lipid panel (low-density lipoprotein [LDL], total cholesterol, triglycerides)
    - Thyroid function tests - thyroid-stimulating hormone (TSH), free thyroxine (FT4)
    - Pregnancy Test - For women of child-bearing potential. Urine or serum HCG must be negative within 72 hours of treatment administration.
    - Disease assessment: Disease assessment and responses will be assessed by serum and urine biomarkers including serum protein and immunofixation electrophoresis (SPEP/SPIE), 24-hour urine protein, and immunofixation electrophoresis (UPEP/UPIE), and serum-free light chain (FLC). The IMWG (International Myeloma Working Group) uniform response criteria will be used to assess disease response and progression[46]. See Appendix 6.
        - SPEP/SPIE, 24-hour UPEP/UPIE, and FLC will be performed at screening to ensure measurable disease. These studies are to be performed within 28 days prior to the date of receiving treatment.
        - Tumor marker assessments: Urinalysis
        - Tumor marker assessments - Serum protein and immunofixation electrophoresis (SPEP/SPIE) and serum-free light chains (FLC).

6.3.2 Treatment Period

6.3.2.1 Study Procedures, Cycle 1, Day 1

- Study Treatment/Drug Administration
  - Administration of 200 mg of pembrolizumab given intravenously
- Clinical Assessments
  - Directed physical exam
    - The investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.
  - Vital signs
  - Concomitant medications
  - AE assessment
  - Performance status
- Laboratory Assessments (to be done prior to study drug administration)
  - Hematology
  - Chemistry
  - Thyroid function
  - Pregnancy test (for women of childbearing potential)
  - Lymphocyte subsets by flow cytometry
  - Disease assessment:
    - 24-hour UPEP/UPIE measurements will be obtained depending on the participant's disease status at screening:

      Participants who have measurable disease by SPEP/SPIE (M-protein ≥ 1 g/dL) and by 24-hour UPEP/UPIE (≥ 200 mg/24 hours) at screening will undergo a 24-hour UPEP/UPIE at time of suspected sCR, CR, VGPR, PR, and progressive disease.

      Participants with measurable disease by SPEP/SPIE (M-protein ≥ 1 g/dL) but no measurable 24-hour UPEP/UPIE (< 200 mg/24 hours) at screening will undergo a 24-hour UPEP/UPIE at time of suspected sCR, CR, VGPR, and progressive disease to confirm IMWG response criteria.

      Participants with measurable disease by 24-hour UPEP/UPIE (≥ 200 mg/24 hours) but not by SPEP/SPIE (M-protein < 1 g/dL) at screening will undergo a 24-hour UPEP/UPIE at C5D1, every 4 cycles thereafter while on study treatment, at treatment discontinuation and/or progression, and every 12 weeks during follow-up for patients who remain on study.

      Participants with only measurable disease by FLC and without measurable disease by SPEP/SPIE and UPEP/UPIE at screening will undergo 24-hour UPEP/UPIE at time of suspected sCR, CR, VGPR, and progressive disease.

      For participants who develop serologic markers consistent with a complete response (disappearance of serum and urine M-protein on

electrophoresis for patients with measurable M-protein at treatment initiation or normalization of the free light chain ratio for those with elevated free light chain markers but unmeasurable M-protein at treatment initiation), a bone marrow biopsy is required to confirm IMWG complete response.

For patients with extramedullary disease on study enrollment, imaging (PET/CT, CT, or MRI) is recommended to confirm IMWG response for patients who achieve at least a hematologic partial response. Imaging is also recommended if there is clinical concern for progressive disease.

- Tumor marker assessment: Serum protein and immunofixation electrophoresis (SPEP/SPIE) and serum-free light chains (FLC)

6.3.2.2 Study Procedures Cycle 1, Day 8 (+/- 3 days) (Safety follow-up visit)

- Clinical Assessments
  - Directed physical exam
  - Vital signs
  - Concomitant medications
  - AE assessment
  - Performance status
- Laboratory Assessments
  - Hematology
  - Chemistry

6.3.2.3 Study Procedures Cycle 2, Day 1

- Study Treatment/Drug Administration
  - Administration of 200 mg of pembrolizumab given intravenously
- Clinical Assessments
  - Directed physical exam
  - Vital signs
  - Concomitant medications
  - AE assessment
  - Performance status
- Laboratory Assessments (to be done prior to study drug administration)
  - Hematology
  - Chemistry
  - Thyroid function
  - Pregnancy test (for women of childbearing potential)

6.3.2.4 Study Procedures Cycle 3, Day 1

- Study Treatment/Drug Administration

- Administration of 200 mg of pembrolizumab given intravenously
- Clinical Assessments
  - Directed physical exam
  - Vital signs
  - Concomitant medications
  - AE assessment
  - Performance status
- Laboratory Assessments (to be done prior to study drug administration)
  - Hematology
  - Chemistry
  - Thyroid function
  - Pregnancy test (for women of childbearing potential)

6.3.2.5 Study Procedures Cycle 4, Day 1

- Study Treatment/Drug Administration
  - Administration of 200 mg of pembrolizumab given intravenously
- Clinical Assessments
  - Directed physical exam
  - Vital signs
  - Concomitant medications
  - AE assessment
  - Performance status
- Laboratory Assessments (to be done prior to study drug administration)
  - Hematology
  - Chemistry
  - Thyroid function
  - Pregnancy test (for women of childbearing potential)

6.3.2.6 Study Procedures Cycle 5 and every following cycle (every 3 weeks) for up to 35 cycles, Day 1

- Study Treatment/Drug Administration
  - Administration of 200 mg of pembrolizumab given intravenously
- Clinical Assessments
  - Directed physical exam
  - Vital signs
  - Concomitant medications
  - AE assessment
  - Performance status

- Laboratory Assessments (to be done prior to study drug administration)
    - Hematology
    - Chemistry
    - Thyroid function
    - Pregnancy test (for women of childbearing potential)
    - Lymphocyte subsets by flow cytometry (for Cycle 5, Day 1 only)
    - Disease assessment:
        - Tumor marker assessment: urinalysis – 24-hour UPEP/UPIE (Cycle 5, Day 1, if clinically indicated, repeat every 4 cycles thereafter)
        - Tumor marker assessment: Serum protein and immunofixation electrophoresis (SPEP/SPIE) and serum-free light chains (FLC) (Cycle 5, Day 1, if clinically indicated, repeat every 4 cycles thereafter)

      For participants who achieve serologic markers consistent with complete response (disappearance of serum and urine M-protein on electrophoresis for patients with measurable M-protein at treatment initiation or normalization of the free light chain ratio for those with elevated free light chain markers but unmeasurable M-protein at treatment initiation) after 4 cycles of therapy, a bone marrow biopsy will be obtained to evaluate for complete response (CR) according to IMWG criteria.
- Tissue Collection/Biopsy
    - Bone marrow biopsy (only needed if serologic markers consistent with CR)

6.3.3 End-of-Treatment Study Procedures

To be completed within 21 days of the last administration of pembrolizumab.

- Clinical Assessments
    - Concomitant medications
    - AE assessment
- Laboratory Assessments
    - Disease assessment:
        - Tumor marker assessment: urinalysis 24-hour UPEP/UPIE (if clinically indicated)
        - Tumor marker assessment: Serum protein and immunofixation electrophoresis (SPEP/SPIE)

In participants who discontinue study treatment, SPEP/SPIE, FLC, and 24-hour UPEP/UPIE (for participants being monitored by 24-hour UPEP/UPIE due to unmeasurable SPEP/SPIE or if disease progression is suspected) should be performed at the time of treatment discontinuation (±3-week window).

For participants who discontinue study treatment without documented disease progression and who do not withdraw from the study, every effort should be made to continue monitoring their disease status by lab markers at least once every 3 months until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first for up to one year.

Participants who develop progression of disease and/or start subsequent anti-cancer treatment may be taken off study and will not require further disease assessments.

6.3.4 Safety Follow-Up

Participants will be followed at 30 days (+/- 5 days) after discontinuing study treatment. The following procedures will be performed at Follow Up visit:

- Clinical Assessments
    - Directed physical exam
    - Vital signs
    - Concomitant medications
    - AE assessment
    - Performance status
    - Post-treatment anticancer therapy status
        - The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a participant initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 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 participant may be taken off study.
    - Survival/long-term follow-up
- Laboratory Assessments
    - Hematology
    - Chemistry
    - Thyroid function

6.3.5 Long Term/Survival Follow-up

After completing the follow-up period, participants will be followed every 12 weeks (+/- 14 days) to assess for survival/anti-cancer therapy status for up to 1 year after treatment completion or discontinuation. If possible, these visits will be done via video appointment.

Long term/Survival Follow-up visits are only required for patients who have either completed 35 cycles of therapy or have discontinued treatment for reasons other than disease progression and have not yet started treatment with another anti-cancer therapy.

The following procedures will be performed at each Long-Term/Survival Follow-Up visit:

- Clinical Assessments
    - Concomitant medications
    - AE assessment
    - Post-treatment anticancer therapy status
    - Survival/long-term follow-up
- Laboratory Assessments (review of markers if indicated)
    - Tumor marker assessment: urinalysis – 24-hour UPEP/UPIE (if clinically indicated)

- Tumor marker assessment: Serum protein and immunofixation electrophoresis (SPEP/SPIE) and serum FLC (free light chains)

Participants who experienced confirmed disease progression or start a new anticancer therapy will be taken off study. Efforts will be made to contact these participants for survival follow-up by telephone every 12 weeks (± 14 days) to assess for survival status until death, withdrawal of consent, or the end of the trial, whichever occurs first for up to one year after treatment discontinuation.

6.4 Use of Concomitant Medications

6.4.1 Concomitant Medications / Vaccinations (Allowed & Prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

6.4.2 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. This includes supportive care measures such as antimicrobial/antiviral prophylaxis and intravenous immunoglobulin therapy for hypogammaglobulinemia. All concomitant medication will be recorded on the case report form (CRF) including all prescriptions, over the counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days prior to the first dose of trial intervention and up to 30 days after the last dose of trial intervention should be recorded. Concomitant medications administered after 30 days after the last dose of trial intervention should be recorded for SAEs and events of clinical interest (ECIs) as defined in Section 8.3.

6.4.3 Prohibited Concomitant Medications

Participants are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
  - For participants with a history of breast cancer, the use of endocrine therapy for breast cancer prevention (e.g. selective estrogen receptor modulators and aromatase inhibitors) is allowed.
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy EXCEPT: localized radiation for symptomatic relief may be allowed at the investigator's discretion during the screening phase of the trial and for isolated sites (field of radiation covers ≤ 5% of the total bone marrow) of symptomatic disease during the treatment phase assuming no evidence of systemic progression

and participants are deemed to be deriving clinical benefit from study treatment as assessed by study investigator.

- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed. SARS-COV-2 vaccines are generally mRNA-based or viral vector vaccines (replication-incompetent) and are allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. All treatments that the Investigator considers necessary for a participant's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care.

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, the Sponsor, and the participant. There are no prohibited therapies during the Post-Treatment Follow-up Phase.

6.4.4 Rescue Medications & Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2 [Table 5.2-1]. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

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

Given that pembrolizumab may reactivate anti-BCMA CAR-Ts, there is a theoretical risk for development of cytokine release syndrome (CRS). CRS is a well-known side-effect of CAR-T therapies and is characterized by systemic inflammation, fever, and organ dysfunction due to immune activation. Clinical manifestation of CRS includes high fevers, hypotension, tachypnea, hypoxia, confusion, fatigue, nausea, vomiting, headache, evidence of disseminated intravascular coagulation, and macrophage activation syndrome. The etiology of CRS is thought to be secondary to increased inflammatory cytokines and activation of T-lymphocytes,

macrophages, and endothelial cells. These factors are important for activation and clonal expansion of CAR-T therapies and thus some degree of CRS is to be expected with CAR-T therapy. However, in some cases, the over-activation of immune responses may be associated with significant organ dysfunction, and thus therapies, including anti-inflammatory and anti-cytokine therapies, may be needed to modulate the degree of immune activation.

At least two doses of tocilizumab per patient must be available on site prior to dosing of pembrolizumab.

6.4.4.1 Cytokine Release Syndrome Management

For patients treated with CAR-T therapies, significant CRS can occur in more than one-half of patients, with the frequency of significant CRS depending on the underlying disease process and specific CAR-T product. In the treatment of MM, a CRS rate of 76% was observed in a phase I study of bb2121, an anti-BCMA CAR-T product, with the majority of events being grade 1 or 2 (70%); 6% were grade 3 events with no grade 4 or higher events observed[1]. Similar findings were observed in other early phase anti-BCMA CAR-T studies[47,48]

Management of cytokine release syndrome has involved the selective use of anti-cytokine therapies and anti-inflammatories for those patients with moderate to severe CRS. For patients with mild CRS (grade 1-2), supportive care alone with antihistamines, antipyretics, intravenous fluids, and close monitoring may be sufficient. For patients with moderate to severe CRS (grade 3 or higher; certain grade 2 cases), additional measures may be needed including: tocilizumab (anti-IL-6 receptor antibody), anakinra (IL-1 receptor antagonist), and/or dexamethasone. Given the success of tocilizumab in modulating severity of CRS, patients with moderate to severe CRS should be treated with tocilizumab first if supportive measures alone are unable to control the CRS. Tocilizumab is given as weight-based dose of 8 mg/kg intravenously at time of clinical instability, with the decision to administer and the timing individualized on a case-by-case basis with close consultation between the principal investigator (PI) and/or clinical investigators on the study. In severe cases or for those cases refractory to tocilizumab, additional therapies may be needed including: additional doses of tocilizumab, dexamethasone, or other anti-inflammatory/cytokine therapies.

Common indications for tocilizumab include any of the following:

- Hemodynamic instability despite intravenous fluids, especially if requiring vasopressor support
- Worsening respiratory status, including increasing oxygen requirements and/or need for high-flow oxygen, face mask, or mechanical ventilation.
- Any other significant deterioration thought to be secondary to CRS despite medical management.
- Patients with CRS should also undergo evaluation for infection and other causes for fevers and organ dysfunction. Patients should be closely monitored and may need admission to an intensive care unit depending on the clinical situation.
- Grading of CRS utilizes the ASTCT consensus criteria[49]. Refer to Appendix 4 for details.

6.4.4.2 Immune-effector Cell-associated Neurotoxicity Syndrome

Given that pembrolizumab may re-activate anti-BCMA CAR-T cells, there is a theoretical risk for development of immune-effector cell-associated neurotoxicity syndrome (ICANS).

Similar to CRS, ICANS is a well-described toxicity of CAR-T therapy and is also considered to be a result of excessive immune activation. Clinical symptoms include: altered levels of consciousness, impairment of cognitive function, aphasia, seizures, and cerebral edema. The typical onset of neurologic toxicity is usually within several days after onset of CRS but may occur independently of CRS. In the phase I study of the anti-BCMA CAR-T bb2121, 14 patients (42%) reported neurologic toxic effects, with 13 patients (39%) incurring grade 1 or 2 toxicities and 1 patient (3%) having grade 4 toxicity[1]. Similar rates were observed in early phase studies of other anti-BCMA CAR-T therapies[47,48].

Treatment for ICANS depends on severity of presentation. The ASTCT criteria are useful for risk-stratifying patients (refer to Appendix 5)[49]. In general, patients with Grade 1 toxicity can be treated with supportive care and close monitoring (including frequent neurologic exams and assessment). Patients with Grade 2 or higher toxicity may require IV steroids, with dexamethasone 10 mg IV q6-12 hours as a standard front-line therapy. The use of other anti-inflammatories, including tocilizumab may be considered, especially if there is concurrent CRS. Additional workup including neuroimaging, electroencephalogram, and pupillometry may be indicated. Other supportive measures may include the addition of antiepileptics and in severe cases, transfer to the intensive care unit. Ultimately, each case of ICANS will be assessed and treated on a case-by-case basis, and any interventions to address ICANS, including the use of steroids, is acceptable when deemed medically appropriate by the treating physician in close consultation between the principal investigator (PI) and/or clinical investigators on the study.

6.5 Dietary Restrictions

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

6.6 Participant Discontinuation Criteria

When a participant discontinues 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 should be followed in accordance with the safety requirements outlined in Section 8.3.

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

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in the subsequent sections.

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

- The participant or participant's legally acceptable representative requests to discontinue study treatment.
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment.
- Unacceptable adverse experiences/dose-limiting toxicities including:
    - Grade 3 or higher immune-related AE that warrant discontinuation as outlined in Table 5.2-1

  - Grade 3 or higher infusion reaction as outlined in Table 5.2-2
  - Grade ≥ 3 CRS not responsive to tocilizumab therapy and/or best medical care after 72 hours or grade 4 CRS
  - Grade ≥ 3 ICANS not responsive to best medical care after 72 hours or grade 4 ICANS
  - Recurrent grade 2 pneumonitis
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, placed the participant at unnecessary risk from continued administration of study treatment.
- The participant has a confirmed positive serum pregnancy test
- Noncompliance with study treatment or procedure requirements
- The participant is lost to follow-up
- Completion of 35 treatments (approximately 2 years) with pembrolizumab
- Administrative reasons

6.7 Participant Withdrawal from Study

Participants who withdraw prior to completion of the trial should be encouraged to complete all applicable activities scheduled for the final study visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.3.

A participant must be withdrawn from the study if the participant or the participant's legally acceptable representative withdraws consent from the study.

A participant may also be withdrawn from the study for the following reasons:

- Progressive disease
- Start of new anti-cancer therapy
- Noncompliance with study treatment or procedure requirements
- The participant is lost to follow-up
- Investigator decision

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specified details regarding procedures to be performed at the time of withdrawal from the study are outlined in Section 6.3.3.

6.8 Participant Replacement Strategy

If a participant is enrolled but does not receive any doses of pembrolizumab, the participant may be replaced.

If a participant is enrolled and receives less than 4 cycles of therapy and discontinues therapy or withdraws from the study for reasons other than disease progression, the participant will not be evaluated for the primary efficacy endpoint and will be replaced. However, all participants who receive at least one dose of pembrolizumab will be included in the safety analysis for adverse events (including those that received < 4 cycles of therapy).

6.9 Clinical Criteria for Early Trial Termination

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

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to participants
4. Plans to modify or discontinue the development of the study drug

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

7 Reporting and Documentation of Results

7.1 Evaluation of Efficacy: Antitumor Effect – Hematologic Tumors

Measurement of antitumor effect will be primarily through tumor markers (SPEP/SPIE, FLC, UPEP/UPIE, and bone marrow biopsy [where applicable]) as per International Myeloma Working Group (IMWG) Uniform Response Criteria. Only participants that complete at least 4 cycles of therapy or have progressive disease after at least one cycle of therapy will be included in the analysis for the primary endpoint. See Appendix 6 for additional details.

7.1.1 Methods for Evaluation of Measurable Disease

For participants with measurable disease by M-protein (serum M-protein ≥ 1 g/dL), response criteria will be determined primarily by SPEP/SPIE. For participants with measurable disease by 24-hour UPEP/UPIE (≥ 200 mg/24 hours) but not by SPEP/SPIE (M-protein < 1 g/dL), response criteria will be determined primarily by UPEP/UPIE. For participants with only measurable disease by FLC and without measurable disease by SPEP/SPIE and UPEP/UPIE, response criteria will be determined primarily by FLC levels.

Participants will also undergo 24-UPEP/UPIE at certain time points depending on 24-hour UPEP/UPIE at screening.

- Participants who have measurable disease by SPEP/SPIE (M-protein ≥ 1 g/dL) and by 24-hour UPEP/UPIE (≥ 200 mg/24 hours) at screening will undergo a 24-hour UPEP/UPIE at time of suspected sCR, CR, VGPR, PR, and progressive disease.
- Participants with measurable disease by SPEP/SPIE (M-protein ≥ 1 g/dL) but no measurable 24-hour UPEP/UPIE (< 200 mg/24 hours) at screening will undergo a 24-hour UPEP/UPIE at time of suspected sCR, CR, VGPR, and progressive disease to confirm IMWG response criteria.
- Participants with only measurable disease by FLC and without measurable disease by SPEP/SPIE and UPEP/UPIE at screening will undergo 24-hour UPEP/UPIE at time of suspected sCR, CR, VGPR, and progressive disease.

For participants who develop serologic markers consistent with a complete response (disappearance of serum and urine M-protein on electrophoresis for patients with measurable M-protein at treatment initiation or normalization of the free light chain ratio for those with

elevated free light chain markers but unmeasurable M-protein at treatment initiation), a bone marrow biopsy is required to confirm IMWG complete response.

For participants with known soft tissue plasmacytomas or extramedullary disease on enrollment, imaging (PET/CT, CT, or MRI) is recommended to confirm IMWG response for patients who achieve at least a hematologic partial response. Imaging is also recommended if there is clinical concern for progressive disease.

7.1.2 Response Criteria

The primary endpoint is the overall response rate (ORR), defined as the proportion of patients achieving a partial response (PR) or better (including sCR, CR, and VGPR) after 4 cycles of pembrolizumab therapy. The response criteria are described below (see Appendix 6 for additional details) :

- Stringent complete response (sCR)
    - Requires achieving complete response (CR) defined below plus normal FLC ratio and absence of clonal plasma cells by immunohistochemistry or flow cytometry
- Complete response (CR)
    - *For patients with measurable serum or urine M-protein on enrollment:* negative immunofixation of serum and urine and < 5% plasma cells in the bone marrow is required
    - *For patients without measurable serum and urine M-protein levels on enrollment:* a normal FLC ratio (0.6 – 1.65) is necessary in addition to the above criteria
    - *For patients with known soft tissue plasmacytomas or extramedullary disease on enrollment*, disappearance of all soft tissue plasmacytomas is required to meet CR
- Very good partial response (VGPR)
    - *For patients with measurable serum or urine M-protein on enrollment:* detectable M-protein on immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-protein plus urine M-component < 100 mg/24 hours is required.
    - *For patients without measurable serum and urine M-protein levels on enrollment (only measurable disease is by serum FLC):* ≥ 90% decrease in the difference between involved and uninvolved free light chains is required.
- Partial response (PR)
    - *For patients with measurable serum and urine M-protein on enrollment:* ≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% to < 200 mg/24 hours are required.
    - *For patients with measurable serum but without measurable urine M-protein on enrollment:* ≥ 50% reduction of serum M-protein is required.
    - *For patients without measurable serum and urine M-protein levels on enrollment (only measurable disease is by serum FLC):* ≥ 50% decrease in the difference between involved and uninvolved free light chains is required (provided the

serum-free light chain assay shows involved level > 10 mg/dL and the serum-free light chain is abnormal).

- *For patients with known soft tissue plasmacytomas or extramedullary disease on enrollment*, ≥ 50% reduction in size of soft tissue plasmacytomas is required in addition to the above criteria.

- Stable Disease (SD)
  - Not meeting criteria for sCR, CR, VGPR, PR, or PD
- Progressive Disease (PD)

  Meeting one of the following criteria:
  - Increase of ≥ 25% from the lowest response value achieved in one or more of the following:
    - serum M-protein: absolute increase must be ≥ 0.5 g/dL)
    - Urine M-component (absolute increase must be ≥ 200 mg/24h)
    - *Only in patients without measurable serum and urine M-protein levels at enrollment:* the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL)
  - Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas
  - Development of hypercalcemia (corrected serum calcium 11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder.

7.1.3 Time to Event Definitions

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

Overall survival (PFS) is defined as the duration of time from start of treatment to time of death.

Time-to-next treatment (TNT) is defined as the duration of time from start of treatment to start of next line therapy.

7.2 Evaluation of Safety

The safety parameters for this study include all laboratory tests and hematological abnormalities, physical findings, and spontaneous reports of adverse events reported to the investigator by participants.

Toxicity will be assessed according to the ASTCT criteria for CRS and ICANS and NCI CTCAE version 5.0 for all other toxicities.

Safety analyses will be performed for all participants who receive at least one dose of pembrolizumab.

8 Safety Parameters

8.1 Definitions

8.1.1 Adverse Event (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.1.2 Serious Adverse Event (SAE)

An adverse event is considered *serious* if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
    - An adverse event is considered life-threatening if, in the view of either the investigator or sponsor, its occurrence places the participant at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
- Congenital anomaly/birth defect

Important medical events that may not result in death, are life-threatening or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.1.3 Unanticipated Problem (UP)

An unanticipated problem (UP) is any incident, experience, or outcome that meets all of the following criteria:

1) unexpected (in terms of nature, severity, or frequency) given (a) the research procedures are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being study;

2) related or possibly related to participation in the research; and

3) suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

Only a small subset of adverse events occurring in human subjects participating in research will meet these three criteria for an unanticipated problem. Furthermore, there are other types of incidents, experiences, and outcomes that occur during the conduct of human subjects research that represent unanticipated problems but are not considered adverse events. For example,

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

8.2 Classification of Adverse Events

8.2.1 Severity

Adverse events are graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

8.2.2 Attribution

Adverse events are given an assignment of attribution or relationship to the investigational agent(s) or study procedure. Attribution categories are:

- Definite – The adverse event is clearly related to the investigational agent(s) or study procedure.
- Probable – The adverse event is likely related to the investigational agent(s) or study procedure.
- Possible – The adverse event may be related to the investigational agent(s) or study procedure.
- Unrelated – the adverse event is clearly not related to the investigational agent(s) or study procedure.

8.2.3 Expectedness

An adverse event is considered unexpected if the nature, severity, or frequency of the event is not listed in the study protocol, product inserts, investigator brochure, or informed consent document.

8.3 Recording of Adverse Events

Refer to the Data Safety Monitoring Plan, located in Appendix 2.

8.4 Expedited Reporting

8.4.1 Reporting to the HDFCCC Data and Safety Monitoring Committee

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s) or to a study procedure, the UCSF PI or his/her designee must notify the DSMC Chair (or qualified alternate) within 1 business day of knowledge of the event. The contact may be by phone or e-mail.

8.4.2 Reporting to Institutional Review Board

The UCSF PI must report events to the IRB according to institutional guidelines.

8.4.3 Expedited Reporting to the FDA

If the study is being conducted under an IND, the Sponsor (or the Sponsor-Investigator) is responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting in accordance with federal regulations (21 CFR §312.32).

The Sponsor (or Sponsor-Investigator) must report in an IND safety report any suspected adverse reaction that is both serious and unexpected. The Sponsor needs to ensure that the event meets all three definitions:

- Suspected adverse reaction
- Unexpected
- Serious

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The timeline for submitting an IND safety report to FDA is no later than **15 calendar days** after the Investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)).

Any unexpected fatal or life-threatening suspected adverse reaction will be reported to FDA no later than **7 calendar days** after the Investigator's initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IND safety report will be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

8.4.4 Reporting to Industry Partners/External Collaborators

Selected nonserious and SAEs are also known as events of clinical interest (ECIs) and must be reported to Merck.

Events of clinical interest for this study include:

1. An overdose of pembrolizumab that is not associated with clinical symptoms or abnormal laboratory results. For purposes of this study, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated. If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

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

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

Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to Merck if the event is considered drug related.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to Merck within the time frames as indicated in Table 8.4.4.

Table 8.4.4 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation	Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period	Reporting Time Period: After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Merck:
Serious Adverse Event (SAE) including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine-related. (Follow ongoing to outcome)	Within 2 business days but no longer than 3 calendar days of learning of event
Pregnancy/ Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 2 business days but no longer than 3 calendar days of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential drug-induced liver injury (DILI) - require regulatory reporting	Not required	Within 2 business days but no longer than 3 calendar days of learning of event

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: [redacted]

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

8.5 Follow-up of Adverse Events

All participants who experience adverse events will be followed with appropriate medical management until resolved or stabilized, as determined by the investigator or until the initiation

of new anti-cancer therapy, whichever occurs first. For selected adverse events for which administration of the study drug/intervention was stopped, a re-challenge of the subject with the study drug/intervention may be conducted if considered both safe and ethical by the investigator.

8.6 Adverse Events Monitoring

Refer to the Data Safety Monitoring Plan, located in Appendix 2.

8.7 Pregnancy and Exposure during Breastfeeding

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

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

9 Statistical Considerations and Evaluation of Results

This study will utilize a Simon's two-stage design with 15 participants enrolled in stage I and 10 additional participants enrolled in stage II assuming that at least 2 or more participants achieve a treatment response after 4 cycles of therapy during stage I of the study. The primary endpoint will be overall response rate (partial response [PR] or better) after 4 cycles of therapy. A Bayesian toxicity monitoring design will be incorporated for ongoing safety analysis during the trial to pause enrollment if at any time the rate of grade 3 or higher non-hematologic adverse events exceeds 30%.

9.1 Sample Size Considerations

9.1.1 Sample Size and Power Estimate

The primary endpoint is the overall response rate (ORR), defined as the proportion of patients achieving a partial response (PR) or better after 4 cycles of pembrolizumab therapy. Simon's minimax two-stage design will be used to test the null hypothesis that the true ORR is 10% against a one-sided alternative that the true ORR is higher than 30%. The two-stage minimax design described below will have an 80% power to reject the null hypothesis that ORR is 10% at one-sided Type I error rate of 5%, assuming that the ORR is 30%.

Stage 1: 15 participants will be accrued. The trial will be terminated at Stage 1 if 0 or 1 response is observed; otherwise, it will continue to Stage 2. Response rate for Stage I will be determined based on patients who have completed at least 4 cycles of therapy or have progressive disease after at least one cycle of therapy; participants who withdraw or drop out due to toxicities before meeting these endpoints will not be used in the analysis of response and will be replaced.

Stage 2: 10 more patients will be accrued (for a total of 25 patients). We will reject the null hypothesis if 6 or more responses are observed in 25 patients.

Early stopping probability: Under this design, if the true response rate is 10%, the probability of stopping the trial early will be 55%.

We plan to enroll 25-27 participants to allow for the possibility of 10% participant dropout before receiving pembrolizumab therapy or during the response evaluation period.

9.1.2 Accrual Estimates

We anticipate enrolling approximately 12 – 15 patients a year. As an active clinical trial site and a center that offers commercial anti-BCMA CAR-T, we anticipate 30 to 50 patients to receive anti-BCMA CAR-T on a yearly basis; the majority of these patients will ultimately have disease progression, allowing for enrollment in this clinical trial.

9.2 Interim Analyses and Stopping Rules

The clinical trial will be stopped for futility if after the first stage of Simon two-stage trial (after fifteen evaluable participants enrolled), there are only zero or one participant who responds with PR or better according to IMWG.

There will also be monitoring for adverse events, specifically for non-hematologic grade 3 or higher adverse events. If at any point it is expected that the rate of grade 3 or higher non-hematologic AE exceeds 30%, enrollment will be paused for safety review by the HDFCCC data and safety monitoring committee, study sponsor, and study PI. If after this safety review is conducted and the study is deemed unsafe to continue, the study will be stopped.

Previous data suggested a severe grade 3-4 AE rate of around 15-20% in pembrolizumab monotherapy trials across various cancers[17,37–40]. These events would be expected to be 15-20% in this study irrespective of cause. Hence, we will render the study treatment tolerable in this population if the observed severe adverse event rate is <30%. We will report the toxicity and advise the providers regarding excessive toxicity and pause enrollment for a safety review if at any point it is expected that the rate of grade 3 or higher non-hematologic AE exceeds 30%. Moreover, the study will be stopped and the FDA will be informed if at any point it is expected that the rate of Grade 4 or higher adverse events (including Grade 4 CRS and treatment-related immunologic AEs) or any treatment-related death exceeds 30%. In this case, the FDA must approve the study's resumption prior to re-initiation of enrollment and study treatment.

Specifically, we will apply a Bayesian toxicity monitoring rule with Beta (0.6, 3.4) as the prior distribution. This means that our prior guess of the proportion of toxicity is 15%, and there is 90% chance that the rate of toxicity is 0.2%-48.9%. We will suspend enrollment if the posterior probability that the toxicity rate exceeds the threshold (30%) is 70% or higher and stop the study if the rate of Grade 4 or higher adverse events (including Grade 4 CRS and treatment-related immunologic AEs) or any treatment-related death meets these parameters. The monitoring will start from the first patient, and the decision rule for a safety pause/stop is as follows:

Pause if at any time:

# toxicity and death	Out of # patients
2	2
3	3-5
4	6-8
5	9-11
6	12-14
7	15-17
8	18-20
9	21-23
10	24-25

Study enrollment will also be paused for safety review if any participants encounter:

- Treatment-related death
- Grade 4 toxicity (excluding clinically insignificant/temporary laboratory abnormalities)
- Grade 4 CRS or Grade 3 CRS that does not resolve to Grade ≤ 1 or baseline within 48 hours
- Grade 4 ICANS or Grade 3 ICANS that does not resolve to Grade ≤ 1 or baseline within 48 hours

9.3 Analysis Plans

9.3.1 Primary Analysis (or Analysis of Primary Endpoints)

Participants that complete at least 4 cycles of therapy or have progressive disease after at least one cycle of therapy will be included in the analysis.

To account for the adaptive nature of Simon's two-stage design, final analyses for the primary endpoint will calculate the uniformly minimum variance unbiased estimator (UMVUE), p-value, and 95% CI for the proportion of patients achieving partial response (PR) or better after 4 cycles of pembrolizumab therapy. The calculation will be performed using R clinfun package (www.r-project.org).

9.3.2 Secondary Analysis (or Analysis of Secondary Endpoints)

Continuous data will be summarized using descriptive statistics such as means, medians, standard deviations, and ranges. Categorical data will be summarized using frequency counts and percentages. Graphical summaries of selected endpoints may also be presented.

Secondary Objective and Endpoints #1 - Safety and Tolerability Analysis: The safety population will consist of all participants who receive any amount of study treatment. Safety will be assessed by evaluation of AEs. The safety analyses will be performed using the safety population. Specific AEs will be counted once for each participant for calculating rates but will be presented in total in participant listings.

Secondary Objective and Endpoints #2 -Depth of Response

Point estimate and exact binomial confidence interval will be reported for the proportion of patients achieving PD (progressive disease), SD (stable disease), PR (partial response), VGPR (very good partial response), CR (complete response), and sCR (stringent complete response) for best-achieved response at any time during pembrolizumab therapy.

Secondary Objective and Endpoints #3 -Time to Event Outcomes

For overall survival (OS), participants who remain alive at the end of study follow-up will be censored at the time when they are known to be alive. For progression-free survival (PFS), participants without progression or death will be censored at the time of the last evaluable disease assessment, while participants without a disease assessment will be censored at the date of first study treatment received. OS and PFS will be summarized using the Kaplan-Meier (KM) method. The 12-months event-free probabilities, 25th percentile, median, and 75th percentile, along with their corresponding 95% confidence intervals, will be reported. Median duration of response among the responders will be reported along with 95% confidence intervals. Competing risks analysis will be performed for analyzing time to next treatment (TNT), with death as a competing event. For patients who are alive and do not receive the next line of therapy, TNT will be censored at the last study contact. Cumulative incidence function, along with 95% confidence intervals, will be reported for TNT.

9.3.3 Exploratory Analysis

For immunologic correlatives, analysis will be predominately descriptive. Lymphocyte counts (ALC, CD3, CD4, ad CD8 counts) may depicted graphically and changes for these endpoints pre- and post-pembrolizumab will be assessed and compared via paired t-test. Further exploratory analyses may include assessing whether changes in lymphocyte count and composition correlate with overall response rate.

10 Study Management

10.1 Pre-study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the PI will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to participants before any protocol-related procedures are performed on any participants.

The PI must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

The clinical investigation will not begin until either FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed, or the FDA has determined that the study is exempt from IND requirements.

10.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant-facing materials related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the IRB of record. Prior to obtaining IRB approval, the protocol must be approved by the Helen Diller Family Comprehensive Cancer Center Site Committee and by the Protocol Review Committee (PRC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

10.3 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the IRB -approved informed consent form prior to participation in any study-specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

10.4 Changes in the Protocol

Once the protocol has been approved by the IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the PI and approved by PRC and the IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to participants, an amendment may be implemented prior to IRB approval. In this circumstance, however, the PI must then notify the IRB according to institutional requirements.

10.5 Handling and Documentation of Clinical Supplies

The PI will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs at the site. The date, quantity, and batch or code number of the drug, and the identification of participants to whom the investigational product has been dispensed by participant number and initials will be included.

The PI shall not make the investigational product available to any individuals other than to qualified study participants. Furthermore, the PI will not allow the investigational product to be used in any manner other than that specified in this protocol.

10.6 Case Report Forms (CRFs)

The PI and/or designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study-specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. Study personnel will complete the CRFs; the PI will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the participant's medical records maintained by study personnel. All source documentation should be kept in separate research files for each participant.

In accordance with federal regulations, the PI is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The PI will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

The PI will be responsible for ensuring the accurate capture of study data. At study completion, when the CRFs have been declared to be complete and accurate, the database will be locked. Any changes to the data entered into the CRFs after that time can only be made by joint written agreement among the PI and the trial statistician.

All source documentation and CTMS data will be available for review/monitoring by the UCSF DSMC and regulatory agencies.

10.7 Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center DSMC will be the monitoring/auditing entity for this study. The UCSF DSMC will monitor or audit the study in accordance with the NCI-approved Data and Safety Monitoring Plan (DSMP). The DSMC will routinely review all adverse events and serious adverse events. The DSMC will review study-related activities to ensure that the study is conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). Significant results of the DSMC monitoring/auditing review will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as applicable. See Appendix 2 - Data and Safety Monitoring Plan.

10.8 Record Keeping and Record Retention

The PI is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The PI is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed participant consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

In accordance with FDA regulations, the PI shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication until 2 years after the investigation is discontinued and FDA is notified.

10.9 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the Sponsor-Investigator and collaborators.

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Appendix 1 Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity Fully active, able to carry on all pre-disease performance without restriction	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
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)	80	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self, unable to carry on normal activity or to do active 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	60	Requires occasional assistance, but is able to care for most of his/her needs
		50	Requires considerable assistance and frequent medical care
3	In bed > 50% of the time Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated Death not imminent
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair	20	Very sick, hospitalization indicated Death not imminent
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

Appendix 2 Data and Safety Monitoring Plan for a Phase II or III Institutional Trial

1. Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for auditing data quality and participant safety for all HDFCCC institutional clinical trials. A summary of DSMC activities for this trial includes:

- Semiannual auditing (depending on trial accrual)
- Review of serious adverse events
- Minimum of biennial regulatory auditing

2. Monitoring and Reporting Guidelines

Investigators will conduct a continuous review of data and participant safety at monthly site committee meetings where the results of each participant's treatment are discussed and documented in the site committee minutes.

All institutional Phase II and III therapeutic trials are audited on a semiannual basis, with all data from twenty percent of the enrolled participants audited by the DSMC Monitor/Auditor. The assigned DSMC Monitor/Auditor will review no more than a total of 10 participant charts during the course of auditing this trial. DSMC Monitor/Auditors will send a follow-up report to the study team within 20 business days after the auditing visit is complete for the PI and the study team to resolve all action items from this report within 20 business days. An abbreviated regulatory review (i.e., reviewing protocol and consent versions, SAEs, PVs, DOA logs, 1572 forms, etc.) will occur at each participant monitoring review; however, a full regulatory review will occur on a biennial basis by the DSMC for regulatory compliance.

Auditing of all enrolled participants in these trials will be complete after 20% of enrolled participants have been audited through five cycles of treatment. However, regulatory reviews of the trial, safety reviews (i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV) reviews), and audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.

3. Review and Oversight Requirements

3.1 Adverse Event Monitoring

All Grade 3-5 adverse events (AEs), whether or not considered to be expected or unexpected and whether or not considered to be associated with the use of the investigational agent(s) or study procedure, will be entered into OnCore®, UCSF's Clinical Trial Management System.

Adverse events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) as developed and revised by the Common Therapy Evaluation Program (CTEP) of the National Cancer Institute. Adverse events are further given an assignment of attribution or relationship to investigational agent or study procedure. Attribution categories are:

- **Definite** – The adverse event is clearly related to the investigational agent(s) or study procedure.
- **Probable** – The adverse event is likely related to the investigational agent(s) or study procedure.

- **Possible** – The adverse event may be related to the investigational agent(s) or study procedure.
- **Unrelated** – the adverse event is clearly not related to the investigational agent(s) or study procedure.

All Grade 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the Site Committee meetings. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and attribution assignment.

3.2 Serious Adverse Event Reporting

By definition, an adverse event is defined as a serious adverse event (SAE) according to the following criteria:

- Death.
- Life-threatening (i.e., results in an immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Permanent or significant disability/incapacity
- Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above.
- Event occurring in a gene therapy study.
- Event that changes the risk/benefit ratio of a study.
- Any other event the Principal Investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution.

Serious adverse event reporting will be in accordance with all IRB regulations. For trials conducted under an investigational new drug (IND) application, the SAE will be reported in accordance with Code of Federal Regulation Title 21 Part 312.32 and will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:

https://irb.ucsf.edu/adverse-event

Med Watch forms and information:

www.fda.gov/medwatch/getforms.htm

All serious adverse events are entered into OnCore®, as well as submitted to the IRB (per IRB guidelines). The SAEs are reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks. The date the SAE is sent to all required reporting agencies will be documented in OnCore®.

If the SAE involves a subject death and is determined to be possibly, probably, or definitely related to the investigational drug or any research-related procedure, the event must be reported to the DSMC Chair (or Vice-Chair) and DSMC Director within one business day.

3.3 Review of Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, the Principal Investigator will notify the DSMC via report at the time the increased rate is identified.

The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Investigator voluntarily holds enrollment or stops the study due to safety issues, the DSMC Chair (or Vice-Chair) and the DSMC Director must be notified within one business day and the IRB must be notified as per IRB reporting regulations.

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Appendix 3 Contraceptive Guidance and Pregnancy Testing

Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Refer to below for approved methods of contraception.

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

Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab, the participant will be immediately discontinued from study intervention(s). The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Merck within 2 working days if the outcome is a serious adverse experience (e.g. death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to Merck.

If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to Merck and followed as described in Section 8.7.

Breastfeeding

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, participants who are breastfeeding are not eligible for enrollment.

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
- A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception

or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.

- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

CONTRACEPTION REQUIREMENTS

Male Participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol defined time frame in Section 3.1.1:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table A3 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
  - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table A3 during the protocol-defined time frame in Section 3.1.1.

Table A3 Highly Effective Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*

• Combined (estrogen- and progestogen- containing) hormonal contraception [b, c]
  ○ Oral
  ○ Intravaginal
  ○ Transdermal
  ○ Injectable

• Progestogen-only hormonal contraception [b, c]
  ○ Oral
  ○ Injectable

Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only contraceptive implant [b, c] • Intrauterine hormone-releasing system (IUS) [b] • Intrauterine device (IUD) • Bilateral tubal occlusion
• Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP, and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
• Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly. b) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

Pregnancy Testing

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

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

Appendix 4 ASTCT Consensus Grading System for CRS

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or†		
Hypoxia	None	Requiring low-flow nasal cannula‡ or blow-by	Requiring high-flow nasal cannula‡, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

* Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

† CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

‡ Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

Appendix 5 ASTCT Consensus Grading System for ICANS

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness†	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings‡	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/ cerebral edema	N/A	N/A	Focal/local edema on neuroimaging§	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.
N/A indicates not applicable.

* A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

† Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

‡ Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

§ Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

Immune Effector Cell-Associated Encephalopathy (ICE) score

ICE
• **Orientation:** orientation to year, month, city, hospital: 4 points • **Naming:** ability to name 3 objects (eg, point to clock, pen, button): 3 points • **Following commands:** ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point • **Writing:** ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point • **Attention:** ability to count backwards from 100 by 10: 1 point

Score 10: no impairment

Score 7 – 9: consistent with Grade 1 ICANS

Score 3 – 6: consistent with Grade 2 ICANS

Score 0 – 2: consistent with Grade 3 ICANS

Score 0 due to patient unarousable and unable to perform ICE assessment, consistent with grade 4 ICANS

Appendix 6 IMWG Uniform Response Criteria

Response	IMWG criteria[46]
Stringent complete response (sCR)	CR as defined below plus normal FLC ratio and absence of clonal plasma cells by immunohistochemistry or flow cytometry
Complete response (CR)	Negative immunofixation of serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow. *For patients without measurable serum and urine M-protein levels at baseline*: a normal FLC ratio (0.6 – 1.65) is necessary in addition to the above criteria
Very good partial response (VGPR)	Serum and urine M-component detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-component plus urine M-component < 100 mg/24 hours *For patients without measurable serum and urine M-protein levels at baseline*: ≥90% decrease in the difference between involved and uninvolved free light chains
Partial response (PR)	≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% to < 200 mg/24 hours. *If serum and urine M-protein are not measurable*, a decrease ≥50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. *If serum and urine M-protein are not measurable*, and serum-free light assay is also not measurable, ≥ 50% reduction in bone marrow plasma cells is required in place of M-protein, provided baseline percentage ≥ 30%. In addition to the above criteria, if present at baseline, ≥50% reduction in the size of soft tissue plasmacytomas is also required.
Stable Disease (SD)	Not meeting criteria for CR, VGPR, PR, or PD
Progressive disease (PD)	Meeting one of the following criteria: 1) Increase of 25% from lowest response value in any of the following: a) serum M-protein (absolute increase must be ≥ 0.5 g/dL) b) Urine M-component (absolute increase must be ≥ 200 mg/24h) c) *Only in patients without measurable serum and urine M-protein levels*: the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL) d) *Only in patients without measurable serum and urine M-protein levels and without measurable disease by FLC levels*: bone marrow plasma cell percentage (absolute percentage must be ≥ 10%) 2) Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas 3) Development of hypercalcemia (corrected serum calcium 11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder.

All response categories (CR, sCR, VGPR, PR, and PD) require 2 consecutive assessments made at any time before the institution of any new therapy for confirmation; CR, sCR, VGPR, PR, and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For PD, serum M-component increases of more than or equal to 1 g/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL.

Appendix 7 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. Laboratory tests for hematology, chemistry, and others are specified in Table A7 below.

Participants will have laboratory evaluations (CBC, basic metabolic panel (BMP), liver function tests (LFT), uric acid, magnesium, thyroid function tests, β-hCG for WOCBP) prior to the administration of pembrolizumab for each cycle to ensure adequate organ function. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing.

Table A7 Laboratory Tests

Hematology	Chemistry	Other
Hematocrit	Albumin	Serum or urine β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Total triiodothyronine (T3)
WBC (total and differential)	Aspartate aminotransferase (AST)	Free thyroxine (T4)
Red Blood Cell Count	Carbon Dioxide	Thyroid-stimulating hormone (TSH)
Absolute Neutrophil Count	*(CO_2 or bicarbonate)*	Serum protein and immunofixation electrophoresis (SPEP/SPIE)
Absolute Lymphocyte Count	Uric Acid	Urine protein and immunofixation electrophoresis (UPEP/UPIE) – 24-hour collection
	Calcium	Free light chain assay (FLC)
	Chloride	Lymphocyte subsets
	Glucose	
	Phosphorus	
	Potassium	
	Sodium	
	Magnesium	
	Total Bilirubin	
	Direct Bilirubin	
	Total protein	
	Blood Urea Nitrogen	

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.