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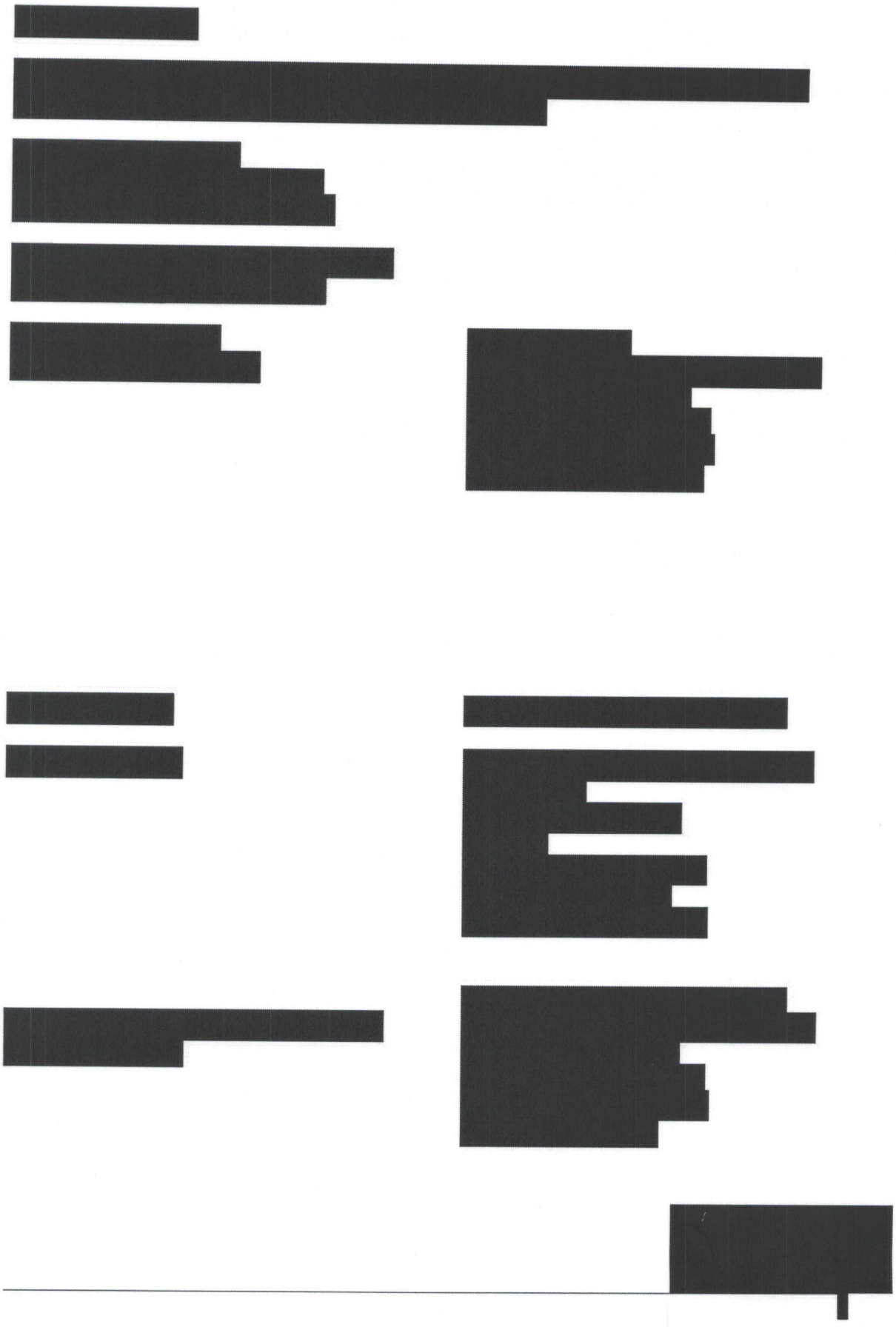

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1.0 TRIAL SYNOPSIS

Title	A Phase Ib/II Trial of Interleukin-2 in Combination with Pembrolizumab for Patients with Unresectable or Metastatic Melanoma
Abbreviated Title	Pembrolizumab + IL-2
Trial Phase	Ib/II
Sites	[redacted]
Clinical Indication	Metastatic or unresectable melanoma
Trial Type	Interventional/Therapeutic
Type of control	None
Route of administration	IV
Trial Blinding	No
Trial Treatments	• Pembrolizumab 200mg IV Q3 weeks (flat dose) • IL-2 at 1 of 3 doses: 6,000, 60,000 or 600,000 IU/kg IV bolus Q 8H up to 14 doses at Weeks 4, 7, 16, 19, 28, and 31.
Treatment Groups	• Phase Ib Dose-escalation portion: Pembrolizumab 200mg IV Q3 weeks (flat dose) + IL-2 in escalating dose cohorts • Phase II: Pembrolizumab 200mg IV Q3 weeks (flat dose) + IL-2 at the maximum tolerated dose (MTD)
Study Design	• Pembrolizumab will be administered alone once as a loading dose, followed by concurrent administration of pembrolizumab and IL-2. • In the Phase Ib portion of the study, dose cohorts subjects will be treated with escalating doses of IL-2: 6,000 IU/kg, 60,000 IU/kg, or 600,000 IU/kg.

	• In the Phase II portion, patients will be treated with pembrolizumab and the MTD of IL-2. This will be a two-stage design for interim futility analysis based on response rate. • Patients who are benefitting from therapy may receive up to 3 courses (6 cycles) of IL-2. Patients will continue to receive pembrolizumab for up to 2 years.
Study Objectives Primary Secondary	• To characterize the safety of IL-2 in combination with pembrolizumab. • To characterize the efficacy of IL-2 in combination with pembrolizumab. • To characterize the safety of IL-2 in doses ranging up to the FDA-approved dose when administered in combination with pembrolizumab. • To characterize clinical endpoints, including overall survival and progression-free survival, 1- and 2-year survival rates. • To characterize immune parameters in the blood and tumor microenvironment and cellular and molecular features of the tumor tissue
Study Endpoints Primary Secondary	• Best objective response rate (BORR) according to RECIST v. 1.1, with the modification that progressive disease must be confirmed on a subsequent scan 4-6 weeks later. • Safety • Complete response rate • Progression-free survival • Overall survival at 1 and 2 years
Research Hypotheses	• Combination therapy will result in a higher response rate than that which is previously reported for pembrolizumab monotherapy. • Combination therapy [redacted]

[redacted]

	• Combination therapy will lead to clinical endpoints that are better than those reported for pembrolizumab or IL-2 monotherapy. • Response to combination therapy will be associated with immune parameters in the blood and tumor microenvironment and cellular and molecular features of the tumor tissue.
Inclusion Criteria	• Histologic or cytologic diagnosis of cutaneous melanoma, mucosal melanoma, or melanoma of unknown primary that is considered unresectable (Stage III) or metastatic (Stage IV). • Be willing and able to provide written informed consent/assent for the trial. • Be > 15 years of age on day of signing informed consent. • Have measurable disease evident on radiographs (preferred) or clinical examination. For this protocol, measurable disease is defined as at least one evaluable tumor that is at least 10 mm in longest dimension. • Have a performance status of 0 or 1 on the ECOG Performance Scale (See Appendix 11.1 for classification criteria). • Patients must have a brain MRI or CT (with and without contrast) that is free of active metastases. Metastases that have been treated with radiation or surgical resection, are stable for at least 4 weeks and do not require steroids are eligible. • Normal cardiac function. Patients who have a history of heart disease, or who are over the age of 50 years must have a normal cardiac stress test within the prior 90 days. • Normal lung function. Patients who have extensive pulmonary metastases or any chronic pulmonary disease history must have pulmonary function testing demonstrating FEV1 and FVC > 65% of predicted values. • Demonstrate adequate organ function (all screening labs should be performed within 10 days of treatment initiation): ○ ANC ≥ 1500/mcL ○ Platelets ≥ 100,000/mcL ○ Hemoglobin ≥ [redacted]

[redacted]

[redacted]

	○ Creatinine ≤ 1.5 x ULN or creatinine clearance ≥6 mL/min for subjects with creatinine levels > 1.5 x ULN ○ Serum total Bilirubin ≤ 1.5 X ULN or Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN. Patients with Gilbert's Syndrome must have a total bilirubin < 3.0 mg/dL. ○ AST/ALT ≤ 2.5 x ULN or ≤ 5 x ULN for patients with liver metastases ○ Albumin >2.5 mg/dL ○ INR/PT ≤1.5 X ULN unless subject is receiving anticoagulant therapy, as long as PT or PTT is within therapeutic range of intended use of anticoagulants ○ aPTT ≤1.5 X ULN unless subject is receiving anticoagulant therapy, as long as PT or PTT is within therapeutic range of intended use of anticoagulants • Female subject of childbearing potential should have a negative urine or serum pregnancy test. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. • Female subjects of childbearing potential must be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year. • Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy. • Subject meets institutional requirements for IL-2 therapy.
Exclusion Criteria	• Has primary ocular melanoma. • Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment. • Has a history [redacted] matory bowel disease [redacted]

	• Has received systemic immunosuppressive steroid therapy or any other form of systemic immunosuppressive therapy for treatment of prior immune-related adverse events or other indications within 7 days prior to the first dose of trial treatment. Exception: Physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency is not considered systemic immunosuppressive steroid therapy.
	• Has received previous high dose (≥600,000 IU/kg) IL-2 therapy. Any other prior therapy (in the adjuvant or the metastatic setting) is allowed, including immunotherapy, targeted therapy, chemotherapy, and experimental therapy.
	• Has a history of significant congestive heart failure or significant pulmonary disease
	• Has a known history of active TB (Bacillus Tuberculosis)
	• Hypersensitivity to pembrolizumab or any of its excipients, or a known history of hypersensitivity to IL-2 or any component of the formulation.
	• Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
	• Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.
	  ○ Note: Subjects with ≤ Grade 2 neuropathy and/or alopecia are exceptions to this criterion and may qualify for the study.
	  ○ Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
	• Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

[redacted]

	• Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability. • Has a history of inflammatory bowel disease. • Has past medical history autoimmune disease (e.g. Crohn's disease, Rheumatoid arthritis, etc.) that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). • Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis. • Has an active infection requiring systemic therapy. • Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator. • Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial. • Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment. • Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies). • Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected). • Has received a live vaccine within 30 days of planned start of study therapy.

[redacted]

Criteria for Evaluation: (Efficacy, safety, stopping rules, etc.)	• Efficacy will be based on tumor assessments at specified time points. RECIST v1.1 will be used, with a modification to add a requirement that progressive disease must be confirmed on a subsequent scan 4-6 weeks later. • Adverse events will be evaluated by NCI CTCAE, version 4.0.
Statistics:	Sample Size • The total sample size is 60 evaluable subjects (approximately 12 for Phase Ib and 48 for Phase II). We anticipate enrolling 62-65 patients in order to obtain 60 evaluable patients. A phase Ib Dose-escalation portion will be conducted to determine the MTD, followed by a two-stage Phase II study. Definition of Positive Primary Endpoint • We will deem this approach meritorious of further study if toxicity is acceptable and ○ If the BORR is 30% or more, or ○ If the complete response rate exceeds 20%, or ○ If the 1 year overall survival rate exceeds 80%. Subgroup Analysis of Primary Endpoint: • BORR will be analyzed by the following characteristics known or suspected to affect clinical outcomes: ○ PD-L1 positive vs. negative ○ B-RAF mutated vs. wild type ○ Prior treatment with checkpoint inhibitor vs. not ○ ECOG 1 vs. 0 ○ LDH elevated vs. normal ○ Metastases limited to skin, lymph nodes, and lungs vs. other distant metastases Analysis of Secondary Objectives • The frequency of AEs and SAEs will be recorded. In addition, data on the inpatient course will be summarized, including the duration of hospital [redacted]

	interventions (transfer to a higher level of care, use of vasopressor, or use of supplemental oxygen) will be summarized. • Clinical measures of efficacy will be described, including overall survival, progression-free survival, need for additional therapy. • Descriptive statistical will be used, except where otherwise specified. Continuous variables will be presented by summary statistics (such as mean, median, standard error and 90% CI) and the categorical variables by frequency distributions (i.e., frequency counts, percentages and 90% CI). Analysis of Exploratory Objectives • Evaluation of immunological responses will be primarily based on the breadth and magnitude of cellular responses. The frequency of tumor specific T cells and regulatory cells including CD4+ Tregs and effector CD8+ will be measured pre-treatment and various days post-treatment in the tumor, when possible, and peripheral blood. Treatment effect for each patient will be measured as paired differences between pre and post measurements of these parameters at various times. Transformation of the data will be performed if appropriate, e.g. log transformation, and hence treatment effect will be expressed on a log scale.
Correlative Studies	Tumor Microenvironment • PD-L1 staining • Frequency of effector CD8+ T cells • Frequency of CD4+FoxP3+ regulatory T cells Peripheral Blood • Analysis of lymphocyte and myeloid cell subpopulations using flow cytometry • Chemokine/cytokine measurements • Serum VEGF, fibronectin, and CRP levels • Melanoma antigen specific T cell responses and antibodies
Number of trial subjects	60-65

[redacted]

Estimated enrollment period	*24 months*
Estimated duration of trial	*36 months*
Duration of Participation	Up to 2 years

2.0 TRIAL DESIGN

2.1 Overview

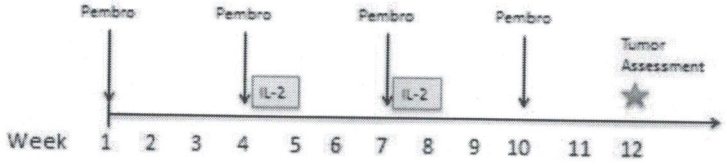
The major goal of this study is to explore the combination of pembrolizumab and IL-2 in advanced melanoma patients, many of whom will have had prior treatment with a PD-1 blocking antibody, which is now a standard of care as a first-line treatment option. The study will define a dose of IL-2 for combination therapy with pembrolizumab and will provide preliminary clinical response and safety data to appropriately design a prospective, randomized clinical trial comparing pembrolizumab + IL-2 to high dose IL-2 alone in a patient population that has received prior PD-1 inhibitor therapy.

Phase Ib. In the Phase Ib portion of the study, cohorts of patients will receive IL-2 in escalating doses (6,000, 60,000, and 600,000 IU/kg). Pembrolizumab will be administered alone once as a loading dose (200 mg flat dose), followed by concurrent administration of pembrolizumab (200mg IV Q3 weeks) and IL-2. Patients may receive up to 3 courses of IL-2. Patients will continue to receive pembrolizumab for up to 2 years.

Phase II. In the Phase II portion, patients will be treated with pembrolizumab (200mg IV Q3 weeks) and the maximum tolerated dose (MTD) of IL-2. As in the Phase Ib, pembrolizumab will be administered alone once as a loading dose, followed by concurrent administration of pembrolizumab (200mg IV Q3 weeks) and IL-2.

2.2 Trial Diagram/Schema

Course 1



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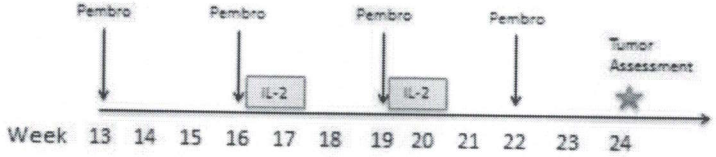

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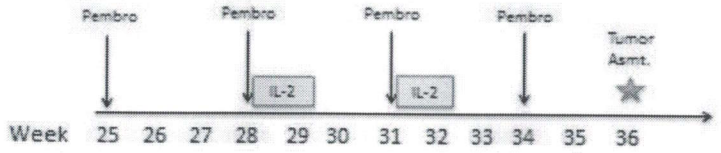
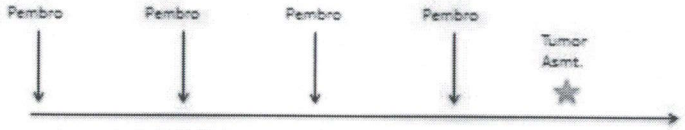
Course 3



Courses 4-9



3.0 OBJECTIVES & HYPOTHESISES

3.1 Primary Objectives & Hypotheses

3.1.1 Primary Objectives

- To characterize the safety of IL-2 in combination with pembrolizumab.
- To characterize the efficacy of IL-2 in combination with pembrolizumab.

[redacted]

3.1.2 Primary Hypothesis

- Combination therapy will be tolerable
- Combination therapy will be associated with a response rate >30%, which is greater than the expected response rate with IL-2 monotherapy.

3.2 Secondary Objectives & Hypotheses

3.2.1 Secondary Objectives

- To characterize additional clinical endpoints, including landmark overall survival, landmark progression-free survival, and complete response rate.

3.2.2 Secondary Hypothesis

- Combination therapy will lead to clinical outcomes that compare favorably with those reported for IL-2 monotherapy.

3.3 Exploratory Objectives

- To characterize immune parameters in the blood and tumor microenvironment and cellular and molecular features of the tumor tissue that correlate with response to combination therapy for study as potential predictive biomarkers.

4.0 BACKGROUND & RATIONALE

4.1 Background

4.1.1 Melanoma

Melanoma is a malignant cancer arising from melanocytes, cells that are derived from the neural crest and present throughout cutaneous and mucosal surfaces of the body. While melanoma may occur anywhere, the relationship between melanoma origins on sun-exposed regions and in juxtaposition to areas of chronic sun-damaged skin, has suggested that sunlight, and more specifically ultraviolet radiation, is the main environmental cause of cutaneous melanoma [1]. Other risk factors, however, have been identified and include geographical

location, ethnicity, skin type, eye color, personal and family history of melanoma and exposure to immune suppression. White Australians have the greatest risk of melanoma worldwide [2], and white populations have a 10-fold higher risk of developing melanoma compared to Black, Asian, or Hispanic populations, and this may be related to the degree of skin pigmentation and potential for protecting the skin from severe sun damage [3]. Within the white populations, a fair skin type, red or blonde hair color, and blue eyes are associated with a greater risk of developing melanoma. Approximately 5 to 10 % of all cutaneous melanomas occur in families with hereditary melanoma predisposition (familial melanoma). Approximately 40 to 60% of cutaneous melanoma tumor cells harbor mutations in the *BRAF* gene that result in constitutive activation of downstream signaling through the RAF-MEK-MAPK pathway [4, 5]. Most (about 90%) of these mutations result in substitution of glutamic acid for valine at codon 600 (BRAF V600E). Additional gene mutations have been identified in melanoma cells, including *Ras, MEK, c-Kit, PTEN*, and various genes encoding cyclin-dependent kinases. These mutations have become important targets for therapeutic intervention.

There were an estimated 76,250 new cases of invasive melanoma in 2012, making melanoma the fifth most common cancer in men and the sixth most common cancer in women in the United States (U.S.) [6]. In addition, there were 9,180 deaths related to melanoma in 2012 and the mortality rate has been increasing slightly despite the appearance of several new treatment regimens. Globally, the incidence of melanoma is increasing rapidly and a 270% increase between 1973 and 2002 has been documented in the U.S. This increase is the most rapid of any cancer with the exception of lung cancer in women [7]. The incidence of melanoma among children rose about 2% per year over the same time period, and the bulk of pediatric melanoma cases (77%) were diagnosed in adolescents age 15-19 [8]. The median age of melanoma diagnosis is 40 and this makes melanoma one of the worst types of cancer with respect to number of productive years of life lost.

Melanoma is characterized by a predictable growth pattern in which new primary tumors or pre-existing dysplastic nevi become transformed and begin to enlarge, the so-called horizontal growth phase. At this time patients may present with the complaint of a mole increasing in size and the growth may be associated with pruritus, hemorrhage, changes in size, shape and color. If the tumor is not excised, a vertical growth phase ensues in which melanoma cells may penetrate through the papillary dermis to the reticular dermis and cells can enter subdermal lymphatic vessels and spread to regional draining lymph nodes (Stage III). Localized melanoma that has not spread beyond the initial site is highly curable with wide local surgical excision being the major method of treatment. Melanoma that has spread to regional lymph nodes may be curable with wide excision of the primary tumor and removal of any involved regional lymph nodes [9]. Sentinel lymph nodes biopsy is an important adjunct to primary management and identifies regional nodal metastasis. Subsequent management depends on biologic features of the primary melanoma, as well as the clinical and pathologic features of the sentinel node disease, if any. At present, complete lymphadenectomy is the standard of care for nodal involvement but some investigators have suggested that single, micrometastatic sentinel nodes may be managed with less extensive approaches. Adjuvant therapy is limited to interferon-alfa although numerous immunotherapy and targeted therapy strategies are in clinical development.

[redacted]

Melanoma that has spread to distant sites (Stage IV) is infrequently curable with standard therapy, although long-term survival was occasionally reported after surgical resection, especially of solitary metastases, and with some immunotherapy regimens [10]. Prior to 2011 the only approved treatment agents for metastatic melanoma were dacarbazine, an alkylating chemotherapy agent, and recombinant interleukin-2, a cytokine and form of immunotherapy. Although some chemotherapy regimens produced objective responses, these were usually in a small subset of patients and the responses were usually short-lived. For example, dacarbazine or temozolomide (an oral analogue of dacarbazine) achieved a 7 to 12% objective response rate in metastatic melanoma patients but an objective response did not appear to be associated with a survival beyond 6-9 months [11-14]. Response rates for interleukin-2 ranged between 10-20% [15-17], with a small proportion (about 6-7%) achieving durable long-term responses, but its administration requires specialized facilities and experienced staff.

In 2011, the U.S. Food and Drug Administration and other regulatory authorities approved two novel therapies for advanced melanoma: a BRAF inhibitor, vemurafenib (Zelboraf™, Genentech), and an immune stimulatory agent, ipilimumab (Yervoy™, Bristol Myers Squibb). The trials upon which approval for these agents were based demonstrated improved overall survival compared to control treatments. The pivotal vemurafenib study showed improved rates of overall and progression-free survival in patients with previously untreated metastatic melanoma with the *BRAF* V600E mutation who received vemurafenib versus standard dacarbazine [18]. Ipilimumab is a monoclonal antibody that blocks the cytotoxic T-lymphocyte antigen 4 (CTLA-4), which is expressed on the surface of activated T cells and results in T cell non-responsiveness. This T cell checkpoint provides a homeostatic mechanism that prevents uncontrolled T cell activation and autoimmunity. In cancer, activated T cells may be prematurely deactivated and CTLA-4 blockade reverses this resulting in persistence of activated T cells and clearance of tumor cells. The pivotal trial of ipilimumab showed an improvement in patients with HLA-A2*0201 genotype, previously treated metastatic melanoma as compared with a gp100 peptide vaccine [19]. Another trial showed improved survival for metastatic melanoma patients treated with ipilimumab and dacarbazine versus placebo and dacarbazine [20]. Ipilimumab has been associated with autoimmune events, which can be severe and life-threatening although algorithms using corticosteroid management are now widely available.

Since 2011 an additional two targeted therapy agents, dabrafenib (Taflinar™, GSK) and trametinib (Mekinist™, GSK), which target BRAF and MEK, respectively. These agents and vemurafenib are approved for the treatment of patients with metastatic melanoma whose tumors harbor a mutation of *BRAF*. Responses in the range of 50-70% have been reported but median duration of response is usually around 6-7 months when nearly universal resistance to treatment emerges. Treatment has been associated with several adverse effects, including skin hypersensitivity, fatigue, arthralgias and appearance of benign and malignant squamous cell cancers. Patients with a wild-type BRAF gene are not candidates for targeted therapy in melanoma.

In 2014, two new immunotherapy drugs were approved for the treatment of melanoma that both blocked binding of the programmed cell death 1 (PD-1) receptor on T cells, pembrolizumab (Keytruda™, Merck) [redacted]

PD-1 acts as a T cell checkpoint and normally inhibits T cell activation. The blockade of PD-1 prevents T cell exhaustion, promotes T cell activation and resulted in a 24-30% objective response rate in clinical trials. Although final overall survival data is pending for these agents, many patients experienced long-term responses and treatment was associated with similar autoimmune adverse events as seen with ipilimumab but at much lower frequency and fatigue was reported as the most common toxicity associated with both pembrolizumab and nivolumab.

4.1.2 Pembrolizumab

4.1.2.1 Pharmaceutical and Therapeutic Background

Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin (Ig) superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, Tregs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors, including melanoma. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found [redacted] inflammatory environments.

PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab (formerly MK-3475) is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has recently been approved in the United States for the initial treatment of patients with unresectable or metastatic melanoma, and is now a standard of care option for first-line treatment..

4.1.2.2 Preclinical and Clinical Trial Data

Preclinical

In the 1-month and 6-month toxicology study in cynomologus monkeys, MK-3475 administered once a week and once every other week respectively, intravenously up to 200 mg/kg resulted in no adverse treatment related effects. The exposure multiple based on a predicted $AUC_{0\text{-tau}}$ of 4464 µg.day/mL at the maximum anticipated human clinical dose of 10 mg/kg Q2W or Q3W is 15-fold at 200 mg/kg, the NOAEL for the 6-month monkey study. Additionally, in the tissue cross-reactivity study of MK-3475 with human and monkey tissues demonstrated the expected on-target staining of the membranes of mononuclear leukocytes in both species. Off-target cross-reactivity staining was also noted in both species but was limited to cytoplasm of various cell types/tissues and the stroma (extracellular connective tissue matrix), and was considered related to the experimental method artifacts, i.e. tissue processing for IHC, that are well recognized limitations of tissue cross-reactivity studies and, thus not considered toxicologically relevant.

No reproductive or developmental toxicity studies are planned with MK-3475. Therefore, inclusion of women of childbearing potential in clinical trials should be in accordance with the study protocol and applicable regulatory guidance (e.g., ICH M3(R2): Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals).

Clinical data

As of 18-Oct-2013, 1,000 patients have been treated with MK-3475 at several dose schedules, including 10 mg/kg every 2 weeks. MK-3475 has been generally well tolerated, as expected based on preclinical findings and other anti-PD-1 monoclonal antibodies. As of 18-Oct-2013 no serious infusions reactions have been reported in PN001, ho[redacted] since the potential exists in anti-PD-1 monoclonal

antibodies, investigators should be vigilant to this possibility. Less than 1% of patients thus far assayed had confirmed positive ADA samples and among these, no or no clear impact on exposure has been observed. There is no contraindication to further clinical investigation with MK-3475. Pharmacokinetics were as expected, based on MK-3475 being an IgG mAb and based on preclinical data, which support dosing once every 2 or 3 weeks. MK-3475 monotherapy induces an ORR of 25%/27% in patients with ipilimumab-exposed melanoma by central independent RECIST and oncology review/investigator assessed immune-related response criteria (irRC), respectively. MK-3475 monotherapy induces an ORR of 39%/43% in patients with ipilimumab-naive melanoma by central independent RECIST and oncology review/investigator assessed irRC, respectively. These responses are remarkably durable. The preliminary 1-year survival rate for patients, many of whom have had multiple therapies, including ipilimumab, who receive MK-3475 is 81%. MK-3475 monotherapy induces an ORR of 21%/24% in patients with previously-treated NSCLC by central independent RECIST/investigator assessed irRC, respectively, with these responses also remarkably durable.

Preliminary data suggest higher levels of PD-L1 expression in tumors of NSCLC are associated with increased activity (ORR 67% by investigator assessed irRC/ 57% by central independent RECIST); additional data are required to define the optimal PD-L1 cut point. The most commonly reported treatment emergent AEs experienced are fatigue (43.8%), nausea (26.7%), cough (25.3%), pruritus (24.6%), diarrhea (22.3%) and rash (21.5%). Immune-related adverse events were reported in 21.4% of melanoma patients; most of these events (15.8%) were considered drug-related by the investigator. The most commonly reported, immune-related adverse events across the dose-schedules are rash (3.2%), pruritus (2.9%), vitiligo (2.9%), hypothyroidism (2.7%), arthralgia (2.2%), diarrhea (2.2%), and pneumonitis (1.9%). Review of the overall benefit:risk ratio of MK-3475 favors enrollment of eligible patients into clinical trials of MK-3475. The preliminary data suggest that a dose of MK-3475 at 2 mg/kg Q3W is appropriate for patients with melanoma.

4.1.3 Interleukin-2

4.1.3.1 Pharmaceutical and Therapeutic Background

In the late 1970's, it was shown that human peripheral blood lymphocytes exposed to IL-2 resulted in the generation of lymphocytes (lymphokine-activated killer, LAK, cells) capable of lysing fresh autologous tumors *in vitro* [21]. This observation was followed by *in vitro* data demonstrating regression of pulmonary metastases from transplanted murine sarcoma and B16 melanoma tumor cells in mice injected with IL-2-stimulated lymphocytes [22]. Subsequent studies showed the ability of directly administered, high-dose IL-2 to generate LAK cells in mice, and to mediate regression of established metastatic deposits, although a strong dose-response relationship was not observed [23].

After performing phase I studies confirming the safety of IL-2 and the adoptive transfer of LAK cells, a pilot study of the combination in the treatment of advanced cancer was published in 1985 [24]. Rosenberg et [redacted] with a variety of refractory tumors,

including 7 with melanoma. Partial responses were seen in 11 of the 25 patients (7 of 11 had melanoma), and complete tumor regression was seen in one patient with metastatic melanoma. Encouragingly, the responses seemed to be durable. Lotze et al. described the treatment of 10 patients with metastatic cancer with high-dose bolus IL-2 alone [25]. Three of the six patients with melanoma had objective disease regression, while no responses were seen in those patients with colorectal or ovarian cancer. Biopsy of regressing lesions revealed a marked lymphocytic infiltrate. Subsequently, the same group published data collected in the treatment of 157 patients with either single-agent high-dose IL-2 or IL-2 plus autologous transfer of LAK cells [26]. Of the 106 patients treated with combination therapy, 21.6% had an objective response including 7.5% who had complete responses. Meanwhile, 46 patients were treated with IL-2 alone; one patient (2.1%) had a CR, and 10.8% had partial responses, for an overall response rate of 13%. In both cohorts, complete responses were of prolonged duration.

The mechanism of anti-tumor activity with high-dose IL-2 is not completely understood but recent data has suggested a correlation of therapeutic response with CD4+FoxP3+ regulatory T cell (Treg) frequency, pre-treatment serum biomarkers (e.g. VEGF, fibronectin) and host gene polymorphisms supporting a role for immune-mediated tumor rejection [27-29]. In addition to stimulating the effector T-cells, IL-2 also stimulates Tregs, particularly at low levels. The preferential expansion of Tregs may inhibit tumor-specific immunity although the impact of low dose Il-2 in the context of PD-1 blockade is unclear. Low dose IL-2 is less toxic than high-dose IL-2, but as monotherapy has also been less effective [30, 31].

4.1.3.2 Preclinical and Clinical Trial Data

A series of clinical trials investigating the efficacy of single-agent high-dose IL-2 were performed between 1985 and 1993, at 22 institutions including the Surgical Branch of the National Cancer Institute and elsewhere. Rosenberg et al. evaluated 409 consecutive patients with melanoma or renal cell cancer treated with intravenous bolus IL-2 (720,000 IU/kg every eight hours, up to 14 doses over 5 days) at the National Cancer Institute from 1985 to 1996 [32]. In an updated analysis of this cohort through the fall of 1996, with follow-up ranging from 3 to 11 years, the overall response rate was 16%, including 17 complete responses (6%) [32]. Of the melanoma patients who had a complete response, 83.3% remained in an ongoing continuous remission at the time of publication, from 70 to 148 months. In the extramural clinical trials, a total of 270 patients with metastatic melanoma were treated with IL-2 at doses ranging from 360,000 to 720,000 IU/kg, intravenously over 15 minutes every 8 hours for up to 14 consecutive doses over five days as tolerated, with maximal supportive care including vasopressors [17]. A second treatment cycle was administered after 6 to 9 days of rest, with further course given every 6 to 12 weeks in stable or responding patients. Median duration of response was not reached at time of analysis for those achieving a complete response, and was nearly 6 months for those with partially-regressed disease. Responses were seen in all sites of disease and in patients with heavy tumor burden. Median survival for the total group was 11.4 months, and with a median follow-up of more than 5 years, nearly half the responding patients were still alive, with 15 having survived more than 5 years. On the basis of these studies, and particularly the extended duration of observed comple[redacted] Drug administration approved the

use of high-dose bolus IL-2 for the treatment of metastatic melanoma in 1998. Further follow-up on these pivotal studies suggested that patients can achieve durable long-term benefit from IL-2. After a median follow-up time for surviving patients that exceeded 7 years, the median duration of response for 43 responding patients and the 26 patients with partial responses in the pivotal IL-2 trials remained unchanged at 8.9 and 5.9 months, respectively [17]. Response durations ranged from 1.5 to > 122 months and disease progression had not been observed in any patient who was responding as of the last report or in any patient responding for longer than 30 months [17].

In these early trials, the most severe toxicities were related to a vascular leak syndrome that resembled the manifestations of septic shock. Sixty-four percent of patients experienced hypotension, while 1% suffered grade 4 hypotension. Other severe toxicities included mental status changes, tachyarrhythmia, and respiratory events, but these were rare, occurring in less than 4% of patients. Nausea, vomiting, and diarrhea were common, but were not life-threatening. Elevations of serum creatinine and bilirubin were frequent but did not lead to chronic organ dysfunction. Infections were seen in 15% of all patients, with bacterial sepsis due to *Staphylococcus aureus* leading to 6 treatment-related deaths. In 1990, antibiotic prophylaxis became standard practice during IL-2 therapy and treatment-related mortality decreased significantly [33]. There are now well established treatment guidelines for the prevention and management of high-dose IL-2-related toxicity [34]. Since the approvals of the immune checkpoint inhibitors, IL-2 is mostly being used as a salvage regimen and is not frequently used as a first-line therapy.

4.2 Rationale

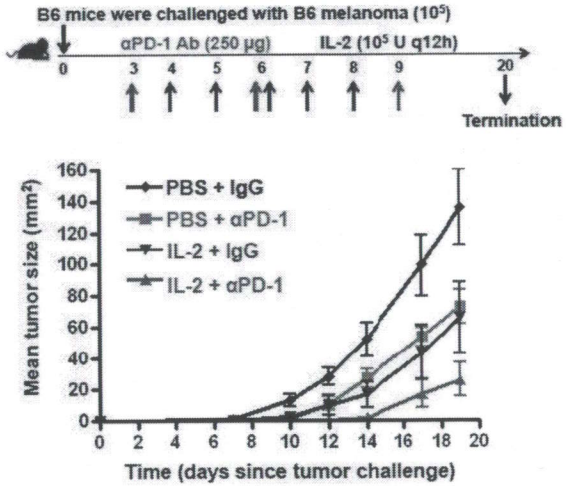
4.2.1 Rationale Selected Subject Population

Melanoma is the 5th most prevalent cancer in the United States and accounts for approximately 5 percent of all skin cancers. However, melanoma is responsible for 80 percent of all skin cancer related deaths. The median overall survival for patients with metastatic disease is approximately 6-12 months, although this may be shifting with new available systemic therapy. Recent studies with combination T cell checkpoints suggest an enhanced therapeutic response with two drugs although toxicity was also increased [35]. Thus, a high priority has been placed on testing combination immunotherapy regimens and those already demonstrating durable survival should be of the highest priority for clinical investigation.

In 1998 high-dose bolus IL-2 was approved for melanoma and induces objective responses in 15-20% of patients [17]. In 2011, the anti-CTLA-4 monoclonal antibody ipilimumab was approved based on randomized Phase III data demonstrating a survival benefit when compared to peptide vaccine therapy with a response rate of approximately 10% [19]. Two additional checkpoint inhibitors, pembrolizumab and nivolumab have been approved by the U.S. Food and Drug Administration for the treatment of metastatic melanoma since 2014, each with a response rate of approximately 25-40%. As monotherapy, each drug is only effective in a fraction of the treatment population, so better therapeutic strategies, including combinations of ef[redacted].

[redacted]

IL-2 + αPD-1 Combination Immunotherapy



Clinical data with high-dose IL-2 with ipilimumab suggest that combination with a checkpoint inhibitor is safe and effective.

- The combination of IL-2 and ipilimumab has been demonstrated to be tolerable in a Phase I/II study of 36 patients [37]. Most of the patients in this small study received the standard dose of 3 mg/kg ipilimumab in combination with high-dose IL-2. There were expected toxicities related to IL-2 and well as Grade 3 and 4 immune-related adverse events in 14% of patients, which were attributed to ipilimumab. All patients recovered from these toxicities without sequelae.

- At the time of first publication, the overall response rate was 22% (14% partial responses and 8% complete responses). With continued follow-up, patients demonstrated late improvements in their responses. The overall response rate increased to 25%, and most notably, the rate of complete response increased to 17% [38].

[redacted]

- Ongoing clinical trials are investigating high dose IL-2 and ipilimumab concurrently (NCT02203604) and sequentially (NCT01856023). Other trials are investigating tumor-infiltrating lymphocytes with IL-2 and anti-PD-1 sequentially (NCT02500576) and concurrently (NCT01993719).

- Analysis of registry data has documented survival in over 50 patients who were treated with high dose IL-2 following immune checkpoint blockade [39]. According to data collected in the IL-2 observational registry "PROCLAIM", IL-2 given before or after checkpoint inhibitor as standard of care was not associated with increased incidence of severe or unexpected toxicities (*Cytokine Working Group teleconference, unpublished data, manuscript in preparation*).

- IL-2 and pembrolizumab have both individually been demonstrated to be effective in metastatic melanoma and are FDA-approved for this indication. Their side effect profiles are partially overlapping, and given the experience to date combining IL-2 with ipilimumab, which is more toxic than pembrolizumab, the combination of pembrolizumab and IL-2 is expected to be safe and effective.

This trial uses intermittent IV bolus dosing of IL-2 because it is the current standard and the pharmacokinetics are more reliable than subcutaneous administration.

4.2.3 Rationale for Dose Selection of IL-2

This study will test the safety of escalating doses of IL-2 doses that spans two orders of magnitude, starting with a low dose and escalating upwards The threshold of IL-2 for T-cell activation varies widely among individuals and cell types. Given that biologic phenomena have a threshold effect and do not have a linear and predictable dose-response curve, a high dose of IL-2 may not be required for efficacy. In contrast, low doses of IL-2 have been reported to preferentially expand Tregs and this could limit efficacy. While Treg expansion has generally been associated with suppression of anti-tumor immunity, the full impact of low-dose IL-2, especially when administered in combination with PD-1 blockade, is unknown.

The trial will explore a low dose (6,000 IU/kg) of IL-2 based on preclinical data [36]. Very low dose IL-2 (6,000 IU/kg) is appealing because the toxicity is expected to be lower and it may make combination therapy more generalizable (i.e. outpatient treatment, community settings). There is limited data supporting the efficacy of intermediate-dose (60,000 IU/kg) IL-2 in renal carcinoma [40], but it has not been effective as monotherapy in melanoma. The trial will test high-dose IL-2 (600,000 IU/kg) because this is the most effective and widely used dose. This trial uses intermittent IV bolus dosing of IL-2 because it is the current standard and the pharmacokinetics are more reliable than subcutaneous administration.

4.2.4 Rationale for Dose Selection of Pembrolizumab

A flat dose of pembrolizumab will be administered with IL-2 in doses ranging up to high-dose IL-2 at 600,000 IU/kg, which is the FDA-approved dose.

An open-label Phase I trial (Protocol 001) was conducted to evaluate the safety and clinical activity of single agent MK-3475. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule is sufficient for target engagement and clinical activity.

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

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication.

The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The choice of the 200 mg Q3W as an appropriate dose for fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 [redacted]

with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

4.2.5 Rationale for Efficacy Endpoints

The primary endpoint is the best objective response rate (BORR) by RECIST v1.1 with a confirmatory scan, as indicated. Radiographic response to therapy has been a reliable surrogate endpoint in the high-dose IL-2 literature, as patients who have complete and partial responses have improved overall survival on average compared with those who have stable or progressive disease. The use of BORR as a surrogate endpoint decreases the length of the trial and provides sufficient evidence of activity of the combination of drugs. In addition, landmark analysis of progression-free and overall survival will be determined as these are also valid endpoints in this population.

4.2.6 Rationale for Biomarker Endpoints

4.2.6.1 Peripheral Blood

Given the high short-term toxicity of IL-2 and the low frequency of responses, various parameters in the blood have been explored as predictive biomarkers. High serum VEGF, fibronectin [28], and CRP [41] have been negatively correlated with clinical responses to IL-2. Select blood proteins as well as cytokine profiles will be examined in this study. On-treatment effects such as increases in the effector T cell/regulatory T cell ratio, and decreases in amount of circulating regulatory T cells have been previously reported to correlate with therapeutic activity and will be explored in this study as well.

4.2.6.2 Tumor Microenvironment

It is hypothesized that the combination of pembrolizumab and IL-2 will induce tumor-specific immunity, and lead to long-term T cell memory and inhibition of CD4+CD25+ regulatory T cells in the tumor microenvironment, as well as increased infiltrates of effector CD8+ and NK lymphocytes into the tumor. Further, elevated levels of tumor-associated PD-L1 expression have been correlated with better clinical responses to PD-1 blockade therapy. Therefore, expression of PD-L1 and PD-L2 will be assayed (QualTek Laboratories assay). The immune cells in the tumor microenvironment will be phenotyped and quantified using flow cytometry. Tumor DNA and

[redacted]

RNA will be probed for general mutation load and for defined mutations, such as NRAS, particular single nucleotide polymorphisms, INF gamma pathway signature genes using NanoString profiling [42].

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Histologic or cytologic diagnosis of cutaneous melanoma, mucosal melanoma or melanoma of unknown primary.

5.1.2 Subject Inclusion Criteria

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

1. Histologic or cytologic diagnosis of cutaneous melanoma, mucosal melanoma, or melanoma of unknown primary that is considered unresectable (Stage III) or metastatic (Stage IV).
2. Be willing and able to provide written informed consent/assent for the trial.
3. Be ≥ 15 years of age on day of signing informed consent.
4. Have measurable disease evident on radiographs (preferred) or clinical examination. For this protocol, measurable disease is defined as at least one evaluable tumor that is at least 10 mm in longest dimension.
5. Have a performance status of 0 or 1 on the ECOG Performance Scale (See Appendix 11.1 for classification criteria).
6. Patients must have a brain MRI or CT (with and without contrast) that is free of active metastases. Metastases that have been treated with radiation or surgical resection, are stable for at least 4 weeks and do not require steroids are eligible.
7. Normal cardiac function. Patients who have a history of heart disease, or who are over the age of 50 years must have a normal cardiac stress test within the prior 90 days.

[redacted]

8. Normal lung function. Patients who have extensive pulmonary metastases or any chronic pulmonary disease history must have pulmonary function testing demonstrating FEV1 and FVC > 65% of predicted values.

9. Demonstrate adequate organ function as defined in Table 1,

Table 1. Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN. Patients with Gilbert's Syndrome must have a total bilirubin < 3.0 mg/dL.
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	≥2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

10. Female subject of childbearing potential should have a negative urine or serum pregnancy test. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required [redacted]

11. Female subjects of childbearing potential must be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

12. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

13. Subject meets institutional requirements for IL-2 therapy.

5.1.3 Subject Exclusion Criteria

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

1. Has primary ocular melanoma.

2. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.

3. Has received systemic immunosuppressive steroid therapy or any other form of systemic immunosuppressive therapy for treatment of prior immune-related adverse events or other indications within 7 days prior to the first dose of trial treatment. Exception: Physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency is not considered systemic immunosuppressive steroid therapy.

4. Has received previous high dose (≥600,000 IU/kg) IL-2 therapy. Any other prior therapy (in the adjuvant or the metastatic setting) is allowed, including immunotherapy, targeted therapy, chemotherapy, and experimental therapy.

5. Has a history of significant congestive heart failure or significant pulmonary disease

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

7. Hypersensitivity to pembrolizumab or any of its excipients, or a known history of hypersensitivity to IL-2 or any component of the formulation.

[redacted]

8. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

9. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

   - Note: Subjects with ≤ Grade 2 neuropathy and/or alopecia are exceptions to this criterion and may qualify for the study.

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

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

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

12. Has a history of inflammatory bowel disease.

13. Has past medical history of autoimmune disease (e.g. Crohn's disease, Rheumatoid arthritis, etc.) that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs).

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

15. Has an active infection requiring systemic therapy.

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

17. Has known psychiatric or substance abuse disorders that would [redacted] the requirements of the trial.

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

19. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

20. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

21. Has received a live vaccine within 30 days of planned start of study therapy.

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

5.2 Trial Treatments

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

Table 2 Trial Treatment

Drug	Dose/ Potency	Dose Frequency	Route of Administration
Pembrolizumab	200 mg flat dose	Q3W	IV infusion
IL-2	6,000 IU/kg	Q8H	IV bolus
	60,000 IU/kg		
	600,000 IU/kg		

[redacted]

5.2.1 Pembrolizumab

5.2.1.1 Treatment Setting and Timing

Trial treatment should be administered after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment should be administered on Day 1 of each indicated week, but may be administered up to 7 calendar days before or after the scheduled Day 1 due to administrative reasons (± 7 day window).

Pembrolizumab will be given in the outpatient setting during study visits that do not contain IL-2 treatment. When the visit includes hospitalization for IL-2 administration, pembrolizumab may be given in the inpatient setting. On days when both drugs are given, IL-2 administration should commence **1-8 hours after completion of the pembrolizumab infusion**.

5.2.1.2 Dosing

All subjects will be treated with pembrolizumab given at a flat dose of 200 mg IV every 3 weeks per Trial Flow Chart. The flat dose will be used whether given in combination with IL-2 or given as monotherapy.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

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

5.2.1.3 Pembrolizumab Monotherapy

Subjects who do not tolerate IL-2 will be permanently discontinued from IL-2 and will finish the treatment period on pembrolizumab monotherapy (200 mg IV Q 3 weeks until the end of the treatment period, which is defined as 2 calendar years from the date of enrollment), provided that treatment is not discontinued earlier to due unacceptable toxicity or significant progression of disease. The subject does not need to continue to meet all eligibility criteria to continue to receive treatment.

[redacted]

5.2.1.4 Discontinuation of Pembrolizumab for patients with confirmed CR

Subjects who achieve a complete response (CR) will continue to receive pembrolizumab Q 3 weeks until 1) the CR is confirmed, and 2) they have received treatment for 6 months (defined as 24 ± 3 weeks) from the date of the first instance of unconfirmed CR. If both criteria are met, the subject will have the option to discontinue pembrolizumab treatment. These subjects should have Safety Assessments with clinical and laboratory evaluation **Q 6 weeks and tumor assessments will continue to be Q 12 weeks** per the trial flow chart (Section 6.0). If the tumor assessments during the remainder of the 2 year study period show reoccurrence of disease while off treatment, the patient may resume treatment on the trial. The maximum active treatment period is 2 years including treatment breaks.

5.2.2 IL-2

5.2.2.1 Treatment Setting and Timing

All doses of IL-2 will be administered in the inpatient setting. IL-2 will be given intravenously (IV) every 8 hours for up to 14 doses in each cycle. The 8 hour dosing is a guideline and doses may be delayed or omitted per investigator discretion and/or institutional guideline (no strict window).

IL-2 will be administered according to standard institutional guidelines and in accord with current clinical practice guidelines for IL-2 administration [34]. Concomitant medications must be reviewed prior to each cycle of IL-2.

> *Antihypertensive medication*: Patients with a history of hypertension who are taking concomitant outpatient antihypertensive medications must discontinue these medications 48H prior to admission. Upon discharge from the hospital to home, patients should resume their antihypertensive medications (other than betablockers) during the week between cycles, usually starting 48 hours after discharge. If patients are planning additional IL-2 treatment they should not re-start betablockers. Examples of betablockers include: metoprolol, carvedilol, nebivolol, labetolol, sotalol, propranolol, oxprenolol, pindolol, penbutolol, and acebutolol.

Supportive concomitant medications are necessary during IL-2 therapy to decrease toxicity. A prophylactic antibiotic, such as oxacillin, must be administered to prevent catheter-related infections during the hospitalization. Special precautions should be made when using the following medications with IL-2: psychotropic drugs, nephrotoxic medications, cardiotoxic medications, and contrast media. Benzodiazepines, sleeping aides, and haldoperidol are sometimes indicated as supportive medications. Indomethacin is typically given every 6-8 hours during IL-2 treatment to manage fever if the creatinine remains below 3.0 mg/dL, but other nephrotoxic medications should be avoided if possible, especially the use of IV contrast media, which should be avoided for two weeks following IL-2 therapy.

Typically, 2 cycles of IL-2 make up a course of IL-2. The duration of a cycle is the duration of hospitalization (approximately 3-7 days).

Admission for IL-2 will occur at Weeks 4, 7, 16, 19, 28, and 31 as per the Study Flow Chart in Section 6.0. IL-2 may not be given earlier or later than the alotted window (±7 days). A minimum rest period of 9 days is required in between admissions to the hospital. If an admission for IL-2 is moved up or delayed, the pembrolizumab will be moved up or delayed as well to be given on the same day as the IL-2.

On days when pembrolizumab and IL-2 are scheduled to be administered together, pembrolizumab should be administered first, followed by IL-2 administration, which should commence **1-8 hours** after the completion of pembrolizumab infusion.

The following should be done daily during IL-2 administration: neurologic assessment, complete blood count, blood chemistries, chest x-ray, vital signs, pulse oximetry, weight, and fluid intake and output.

5.2.2.2 Dosing of IL-2 in the Phase Ib Portion

Patients in the Phase Ib portion of the study will be assigned to a dose cohort of IL-2 upon study entry.

Level	Dose of IL-2 (IV bolus Q 8 hrs)	Dose of pembrolizumab
1	6,000 IU/kg	200 mg
2	60,000 IU/kg	200 mg
3	600,000 IU/kg	200 mg

5.2.2.3 Dosing of IL-2 in the Phase II portion

All subjects will be treated with the MTD of IL-2. If no MTD is reached in the Phase Ib portion, the 600,000 IU/kg dose will be called the MTD.

[redacted]

5.2.2.4 Calculation of IL-2 Dose

Calculate Total Dose as follows: Desired dose of IL-2 in IU/kg X Patient body weight in kg = IL-2 dose in IU.

Based on the investigator's discretion, IL-2 dose can be calculated using the actual or ideal body weight.

Calculate Rate of Infusion as follows: Infusion volume in ml ÷ 15 minutes = rate of infusion in ml/min.

5.2.2.5 Determining Number of Courses of IL-2

Subjects who experience an SAE of Special Interest (see Section 7.2.1.4) during IL-2 therapy or other significant IL-2-related toxicity in the treating physician's opinion should be discontinued from IL-2. Subjects may decline additional IL-2. Subjects in whom IL-2 is discontinued for these reasons should be treated with pembrolizumab monotherapy Q 3 weeks.

Subjects who achieve SD or an unconfirmed/confirmed PR should repeat the course of IL-2 and, at the discretion of the treating investigator, and may receive up to 3 courses of IL-2 in combination with pembrolizumab. For example, subjects who have regressing lesions not meeting RECIST criteria for PR (classified as SD) would be expected to continue IL-2 and pembrolizumab Q3 weeks, provided that toxicity is acceptable. All protocol treatment (IL-2 and pembrolizumab) should continue until CR is achieved or removal from study. Subjects who achieve an unconfirmed or confirmed CR should be discontinued from IL-2.

5.2.3 Duration of Participation

Subjects will remain on study for up to 2 years. Subjects who are benefitting from therapy (SD/PR/CR) as judged by the treating investigator may continue on active treatment with pembrolizumab for up to 2 years.

5.3 Treatment Allocation

In the Phase Ib portion of the study, accrual will start with the lowest dose of IL-2 (6,000 IU/kg IV Q8 hours) with a cohort size of 3 subjects and proceed to higher doses. Please see Section 8 for dose escalation procedure.

In the Phase II expansion cohort, all subjects will be treated with the MTD of IL-2 according to the same schedule with pembrolizumab.

There will be no randomization or within-subject dose escalation.

[redacted]

5.4 Dose Modification/Withholding

5.4.1 Dose Modifications of Pembrolizumab

No dose reductions of pembrolizumab are allowed.

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment.

Pembrolizumab must be withheld (not delayed) for drug-related toxicities and severe or life-threatening AEs as per Table 3 below. See Section 5.4 and Events of Clinical Interest Guidance Document for supportive care guidelines and management recommendations, including use of corticosteroids.

If criteria for resuming treatment are met, pembrolizumab treatment should resume at the next scheduled treatment timepoint (3 weeks later), or be permanently discontinued as per Table 3 below.

Although no dose delays for toxicity are allowed, an administrative delay within the allotted window of ±7 days is allowed as per the Trial Flow Chart (Section 6.0). The next dose should be given when is it is due according to the Trial Flow Chart with the goal of maintaining a consistent treatment schedule across all patients.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the study PI or co-PI. The reason for interruption should be documented in the patient's study record.

Table 3. Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General instructions:

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

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		

[redacted]

AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• 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[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		

[redacted]

All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		
1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. **NOTE:** For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM). *Please refer to Section5.6 Rescue Medications and Supportive Care for additional information on toxicity management.*				

[redacted]

5.4.2 Dose Modifications of IL-2

No dose reductions or dose escalations of IL-2 are allowed (other than the use of ideal body weight for dose calculations, which is permitted. See Section 5.2.2).

Cycles of IL-2 may not be delayed beyond the window allotted in the Study Flow Chart in Section 6.0 (±7 days).

Delays and omissions of the individual doses of IL-2 within a cycle are allowed. Dose delays will be administered according to investigator's judgment. Table 4 is provided as a guide for treating investigators (reproduced from the Proleukin package insert with permission).

Table 4. IL-2 Dose Holding and Restarting Guidelines for Drug-Related Adverse Events

Body System	Hold dose for	Subsequent doses may be given if
Cardiovascular	Atrial fibrillation, supraventricular tachycardia or bradycardia that requires treatment or is recurrent or persistent Systolic bp <90 mm Hg with increasing requirements for pressors Any ECG change consistent with MI, ischemia or myocarditis with or without chest pain; suspicion of cardiac ischemia	Patient is asymptomatic with full recovery to normal sinus rhythm Systolic bp ≥90 mm Hg and stable or improving requirements for pressors Patient is asymptomatic, MI and myocarditis have been ruled out, clinical suspicion of angina is low; there is no evidence of ventricular hypokinesia
Respiratory	O2 saturation <90%	O2 saturation >90%
Nervous	Mental status changes, including moderate confusion or agitation	Mental status changes completely resolved
Body as a Whole	Sepsis syndrome, patient is clinically unstable	Sepsis syndrome has resolved, patient is clinically stable, infection is under treatment
Urogenital	Serum creatinine >4.5 mg/dL or a serum creatinine of ≥4 mg/dL in the presence of severe volume overload, acidosis, or hyperkalemia Persistent oliguria, urine output of <10 mL/hour for 16 to 24 hours with rising serum creatinine	Serum creatinine <4 mg/dL and fluid and electrolyte status is stable Urine output >10 mL/hour with a decrease of serum creatinine >1.5 mg/dL or normalization of serum creatinine
Digestive	Signs of hepatic failure including encephalopathy, increasing ascites, liver pain, hypoglycemia Stool guaiac repeatedly >3-4+	All signs of hepatic failure have resolved Stool guaiac negative
Skin	Bullous dermatitis or marked worsening of pre-existing skin condition, avoid topical steroid therapy	Resolution of all signs of bullous dermatitis

[redacted]

IL-2 will be permanently discontinued for any grade ≥ 4 hematological or ≥ 3 non-hematological adverse events that do not resolve to ≤ grade 2 within 7 days of completing IL-2 treatment if the side effect is definitely related to IL-2. This will be considered an IL-2-related SAE (see Section 7.2.1.2), and the patient will not receive further IL-2. The patient may continue on study with pembrolizumab monotherapy at the discretion of the treating investigator.

5.4.1 Inpatient visits (both drugs scheduled to be given):

In the event that a patient is experiencing a significant pembrolizumab-related adverse event at the time that inpatient admission for IL-2 is scheduled (with ±7 day window), the scheduled admission/therapy will be omitted (not delayed) until the pembrolizumab-related adverse event resolves to Grade 1 or less. Both drugs may be given at the next regularly scheduled timepoint.

If the following pembrolizumab-related adverse events are present, both drugs should be withheld, including:

- Any ≥ Grade 2 non-skin related adverse event (including ECIs/irAEs), except for isolated laboratory abnormalities
- Any ≥ Grade 3 laboratory abnormality
- Any adverse event, laboratory abnormality or intercurrent illness that, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued dosing.

If these adverse events resolve to Grade 1 or less, treatment can be resumed at the next regularly scheduled timepoint. If there are questions about a specific patient, the investigator may contact the study PI for further discussion.

5.5 Concomitant Medications/Vaccinations (allowed & prohibited)

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

5.5.1 Acceptable Concomitant Medications

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

All concomitant medications received within 28 days before the first dose of trial treatment and during trial treatment should be recorded.

See Section 5.2.2.1. for more detailed information on concomitant medications specifically during the hospitalization for IL-2 therapy.

5.5.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy other than pembrolizumab and IL-2
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the study PI or co-PI.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

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

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

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below and in greater detail in the ECI guidance document. Where appropriate, these guidelines include the use of oral or intravenous

treatment with corticosteroids as well as additional anti-inflammatory agents (i.e. infliximab) if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the investigator is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (as outlined in the ECI guidance document). Refer to Section 5.4 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Suggested conditional procedures, as appropriate, can be found in the ECI guidance document.

- **Pneumonitis**:
  - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
  - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
  - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

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

  - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
  - For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.
  - For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

[redacted]

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

    - For **T1DM** or **Grade 3-4** Hyperglycemia
        - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
        - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis**:

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

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

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

- **Hepatic**:
    - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
        - Treat with IV or oral corticosteroids
    - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours

[redacted]

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

- **Renal Failure or Nephritis**:
  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3-4** events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Management of Infusion Reactions: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Table 5 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab.

Table 5 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion);	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS	No subsequent dosing

[redacted]

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

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

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 7.2.5-Reporting of Pregnancy