Official Title:	A Phase 1b/II Trial of Interleukin-2 in Combination With Pembrolizumab for Patients With Unrespectable or Metastatic Melanoma
NCT number:	02748564
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and Lactation to Merck. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.7.3 Use in Pregnancy

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

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to T[redacted]nd followed as described above and in Section 7.2.5.

5.7.4 Use in Nursing Women

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

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.6.

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression
- Unconfirmed disease progression plus clinical deterioration
- Unacceptable adverse experiences as judged by the treating investigator
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject

[redacted]

[redacted]

- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed study treatment
- Administrative reasons

The Follow-up procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.5 Visit Requirements. After the end of treatment, each subject will be followed for 90 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.2.1.1).

Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.9 Subject Replacement Strategy

Subjects in the Phase Ib portion of the study who are not evaluable for toxicity will be replaced.

Subjects in the Phase II portion who are not evaluable for response will be replaced. See section 8.4 for definition of evaluable for response.

Sixty (60) evaluable subjects will be accrued. A maximum of up to 65 patients may be enrolled (up to 5 replacements). Subjects who are screen failures do not count towards accrual.

5.10 Criteria for Early Trial Termination

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

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

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

[redacted]

6.0 TRIAL FLOW CHART

Table 6. Study Flow Chart

Trial Period:	**Screening**	**Treatment (Weeks)**						**Safety Follow-up[j]**	**Long-Term Follow-up**
Treatment Cycle/Title:	Study Screening Visit(s)	Course 1:	1	4	7	10	12	(90 days after last dose of rx)	Survival Follow-Up Q12 weeks
		Course 2:	13	16	19	22	24		
		Course 3:	25	28	31	34	36		
		Courses 4-9:	Q3	Q3	Q3	Q3	Q12		
Scheduling Window (Days):	-28*		± 7	± 7	± 7	± 7	± 7	±14	± 28
Informed Consent	X								
Inclusion/Exclusion Criteria, including pulmonary function and cardiac stress testing when appropriate	X								
Demographics and Medical History	X								
Prior and Concomitant Medication Review	X		X	X	X	X		X	
Pembrolizumab Administration[a]			X	X	X	X			
IL-2 Administration[b]				X[b]	X[b]				
Review Adverse Events	X		X	X	X	X		X	
Physical Examination[c]	X		X	X	X	X		X	
Vital Signs and Weight[d]	X		X	X	X	X		X	
ECOG Performance Status	X		X	X	X	X		X	
CBC with Differential, Comprehensive Serum Chemistry Panel (D. Bili if T.Bili > ULN), Magnesium, Phosphorus[e]	X		X[e]	X	X	X		X	
Amylase, and Lipase, T3, Free T4, TSH, Uric Acid, LDH[e]	X		X		X			X	
PT/INR, aPTT, UA, CXR, EKG[f]	X			X[f]	X[f]				
Pregnancy Test – Urine or Serum β-HCG[g]	X			X	X			X	
Correlative Studies Blood Collection			X[k]						
Tumor Assessment[h]	X						X		
Tumor Tissue Collection[i]	X[i]		X[i]						
Post-study disease status and anticancer therapy status									X
Survival Status									X

Footnotes

[redacted]

* All screening assessments within 28 days of Day 1 of treatment, unless otherwise noted. Brain MRI for screening may be performed up to 90 days prior to the first dose of trial treatment if there is no evidence of brain metastases. Subjects with known, 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.

a. Pembrolizumab may be discontinued for patients who have achieved a confirmed CR and have received treatment for 6 months following CR per Section 5.2.1.4.
b. Concomitant medications must be reviewed prior to each cycle of IL-2. A prophylactic antibiotic, such as oxacillin, must be administered to prevent catheter-related infections during the hospitalization. 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. In the dose-escalation portion of the study, subjects will be treated in escalating dose cohorts of IL-2 (See Section 5.2.2 for dose levels). IL-2 administration should commence 1-8 hours after completion of the pembrolizumab infusion. IL-2 may be omitted in Courses 2 and 3 if patient has achieved an unconfirmed or confirmed CR, if IL-2 was associated with significant toxicity in the treating physician's opinion, or if patient declines additional IL-2.
c. Full physical examination is required at screening visit. Directed physical examination is required at all other time points.
d. Current or baseline weight can be used for calculation of IL-2 dose at the discretion of the investigator for calculation of IL-2 dose as long as current weight does not differ from baseline weight by >10%.
e. Labs on Week 1 do not need to be repeated if screening labs were performed within 14 days of the start of treatment. These labs may be repeated at the discretion of the treating investigator in the week following IL-2 to monitor any abnormalities that were seen during IL-2 treatment.
f. PT/INR, PTT, urinalysis (UA), chest x-ray (CXR) and electrocardiogram (EKG) are required at baseline and on admission for IL-2 (or within 7 days prior) but are not required at every pembrolizumab treatment visit. These items can be omitted in patients no longer receiving IL-2. CT chest may replace CXR at baseline.
g. Pregnancy test is required only in women of childbearing potential (WOCBP). WOCBP are those who have not been surgically sterilized or have not been free from menses for > 1 year.
h. Tumor assessment may be performed by imaging and/or clinical evaluation. Additional tumor assessments may need to be performed to confirm CR, PR or PD. See Section 7.1.3 for full details.

[redacted]

i. Tumor tissue will be collected at baseline and at Week 13 (± 14 days). Submission of tissue is strongly encouraged but optional. At baseline, fresh tumor tissue is strongly preferred, but archival tissue may be submitted instead. Approximately $1cm^3$ is requested, or as much as is feasible. Patients are encouraged to submit tissue at Week 13 whether they are continuing on study or discontinuing treatment. See Appendix 11.5 for processing and shipping details.

j. The mandatory Safety Follow-Up Visit should be conducted 90 days (±14 days) after the last dose of trial treatment, or before the initiation of a new anti-cancer treatment, whichever comes first.

k. Blood collection for correlatives to be drawn pre-dose every 12 weeks at the start of each Course (week 1, 13, 25, 37 and then every 12 weeks). Pre-dose collection can be drawn at time of other labs. Repeat draw is not required if scheduled treatment is delayed for toxicity.

7.0 TRIAL PROCEDURES AND ASSESSMENTS

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

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

For minors, according to local legislation, one or both parents or a legally acceptable representative must be informed of the study procedures and must sign the informed consent form approved for the study prior to clinical study participation. The explicit wish of a minor, who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

Minors who are judged to be of an age of reason must also give their written assent.

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

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

The informed consent will contain specific information about the trial therapy, the trial population, and follow-up requirements.

[redacted]

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.2 Eligibility

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

7.1.1.3 Medical History

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

Cardiac and Pulmonary History

Patients over the age of 50 must have a cardiac stress test without evidence of reversible ischemia at baseline (within 90 days). A cardiac stress test should be performed on a patient regardless of age who has possible cardiac symptoms or is considered to be at high risk by the treating investigator. Any method of stress (exercise, pharmacologic) is acceptable. The test must include imaging with either ultrasound (stress echocardiogram) or nuclear medicine imaging.

Patients with a history of chronic lung disease or heavy smoking should have PFT's performed during screening.

7.1.1.4 Prior and Concomitant Medications Review

Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial.

Treatment for the disease for which the subject has enrolled in this study will be recorded separately. Any prior use of checkpoint inhibitor (e.g. ipilimumab, pembrolizumab, nivolumab, PD-L1 inhibitor) should be documented.

Concomitant Medications

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

[redacted]

7.1.1.5 Disease Details and Treatments

The investigator or qualified designee will obtain prior and current details regarding disease status. The BRAF mutational status on each subject should be documented and recorded as mutated-V600E, mutated-other, wild type, or not available. Prior therapies should be documented. Any prior use of checkpoint inhibitors (e.g. ipilimumab, pembrolizumab, nivolumab, or PD-L1 inhibitors) should be documented.

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

7.1.1.6 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 90 days after the last dose of trial treatment, the Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

7.1.1.7 Assignment of Subject Number

The coordinating site will assign each screened patient a subject number.

7.1.1.8 Trial Compliance (Medication/Contraception/Other)

The investigator or qualified designee will review trial compliance regarding medication, contraception, scheduled assessments, other.

7.1.2 Clinical Procedures/Assessments

All clinical procedures/assessments will be performed according to the Trial Flow Chart (Section 6.0).

7.1.2.1 Adverse Event (AE) Monitoring

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

For subjects receiving treatment with pembrolizumab all AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs); see the separate ECI guidance document in Appendix regarding the identification, evaluation and management of potential irAEs.

[redacted]

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

7.1.2.2 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening. A full physical exam includes at least these systems: General, HEENT, Neck, Cardiovascular, Respiratory, Abdominal, Lymph nodes, Musculoskeletal, Extremities, Neurological, Psychiatric, and Skin. When clinically appropriate based on disease location, symptoms, or comorbidities, it may also include ophthalmologic eye exam, breast exam, genitourinary exam, and/or rectal exam.

7.1.2.3 Directed Physical Exam

During the treatment portion of the study, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

7.1.2.4 Vital Signs, Height and Weight

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

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 11.1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

7.1.3 Tumor Imaging and Assessment of Disease

All tumor assessments will be performed according to the Trial Flow Chart (Section 6.0). If a patient discontinues treatment for any reason other than progression, tumor assessments will be done every 12 weeks (± 14 days) until Week 49.

7.1.3.1 Methods of Tumor Assessment

The preferred imaging modality is CT scan. Other modalities (MRI, PET-CT, ultrasound, endoscopy, laparoscopy, cytology, histology) may be used as adjuncts. If there is a compelling reason to do PET/CT scans or MRI (e.g. patient has allergy to iodinated contrast), the PI should be contacted for permission.

All measurements should be taken and recorded in metric notation using a ruler or calipers. The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is

[redacted]

preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam. Combinations of clinically measurable and radiographically measurable are permissible. For example, the patient may have dermal lesions that are most accurately measured by clinical evaluation with a ruler or calipers, and lymph nodes that are most accurately measured on CT scan.

Cytology and histology may be helpful to differentiate a complete response from a partial response.

7.1.3.2 RECIST version 1.1

The primary set of response criteria for this trial is RECIST v1.1 [43]. See Appendix 11.3 for criteria for complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD).

RECIST v1.1 will be modified for this trial. To account for tumor pseudo-progression that can sometimes occur with immunotherapy, it is required that RECIST PD be confirmed on a subsequent assessment performed 4-6 weeks later (see Section 7.1.3.4 for details).

7.1.3.3 Evaluation of Best Overall Response (BOR)

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

7.1.3.4 Confirmation of PD

Allowing patients to continue treatment despite the initial radiologic progression takes into account the observation that some patients with melanoma can have a transient tumor flare in the first few months after start of immunotherapy with subsequent disease response.

The minimal criteria must be met to continue treatment in patients with radiological PD. Such criteria may include the following:

1. No symptoms or signs (including worsening of laboratory values) indicating disease progression
2. No decline in ECOG performance status or symptomatic clinical deterioration
3. No evidence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

If a patient does not meet all of the requirements above, the patient should be removed from trial immediately for unconfirmed PD with clinical demise. Every [redacted]

document the objective progression even after discontinuation of treatment. Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time (not evaluated by confirmatory scan) should be reported as "symptomatic clinical deterioration."

For patients who are clinically well and meet the criteria above, the patient may remain on treatment at the discretion of the investigator, and imaging should be repeated no less than 4 weeks but no more than 6 weeks later (4-6 weeks).

If the repeat assessment demonstrates CR, PR, or SD (relative to baseline) as per RECIST v1.1, treatment may be continued as per treatment calendar.

If the repeat assessment shows demonstrates PD (relative to baseline or the nadir tumor burden, whichever is smaller) as per RECIST v1.1, treatment will be discontinued. The development of confirmed PD and/or the development of symptomatic clinical deterioration constitutes confirmed progressive disease. In the case of confirmed progressive disease, study treatment should be discontinued.

7.1.3.5 Confirmation of PR or CR

The subject's first instance of a PR or CR should be confirmed on a repeat assessment no less than 4 weeks later (4-6 weeks); however, it is acceptable to delay the repeat assessment until the next scheduled interval imaging study (12 weeks ± 7 days) at the discretion of the treating investigator, or if the patient prefers not to have an extra CT scan for this purpose.

A biopsy of any residual lesion may be used to confirm a CR at the discretion of the treating investigators.

7.1.3.6 Determining the date of progression or response

For all patients who experience disease progression on study, the date noted for disease progression is the time of the scan when it was originally determined, and not the later date of the confirmatory scan.

For all patients who experience complete or partial on study, the date noted for disease response is the time of the scan when it was originally determined, and not the later date of the confirmatory scan.

7.1.4 Tumor Tissue Collection and Correlative Studies Blood Sampling

7.1.4.1 Tumor Tissue Collection

Tumor tissue will be collected at baseline and at Week 13 (± 14 days). Submission of tissue is strongly encouraged but optional. At baseline, fresh tumor tissue is strongly preferred, but archival tissue may be submitted instead. Approximately 1cm^3 is requested, or as much as is feasible. Patients are encouraged to submit tissue at Week 13 whether they are continuing on study or discontinuing treatment. The tumor biopsy tissue will be analyzed for the following:

[redacted]

immunophenotype of myeloid and lymphoid cells, PD-L1 and PD-L2 expression by tumor cells (Qualtek), antigen-specific T-cells, intracellular cytokines and effector molecules, and gene expression analysis (NanoString). See Section 11.5 for processing and shipping details.

7.1.4.2 Correlative Studies Blood Sampling

Research blood samples will be collected at Weeks 1, 13, 25 and 37 and then every 12 weeks. See Appendix 11.5 for processing and shipping details.

7.1.5 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 6.

[redacted]

Table 7 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal*	Total triiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	*results are noted)*	Free thyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or bicarbonate)*	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		
	Amylase		
	Lipase		

† Urine or serum pregnancy test on women of childbearing potential only.

‡ If considered standard of care in your region.

[redacted]

[redacted]

Laboratory tests should be performed by the local laboratory (no centralized labs). Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.6 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. If the subject is willing to adhere to follow-up procedures, all assessments listed in the Safety Follow-up and Long-term Follow-up columns in the Trial Flow Chart in Section 6.0 should be completed and recorded until withdrawl of consent or death, so that data can be analyzed in accordance with the intent to treat principle.

7.1.7 Visit Requirements

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

7.1.7.1 Screening

Subjects will be screened for eligibility. The inclusion and exclusion criteria will be reviewed at the Screening visit(s). Eligible subjects will be enrolled before treatment start after verification of fulfilling all inclusion criteria without matching any exclusion criterion. All requirements must be completed no more than 4 weeks prior to start of treatment.

7.1.7.2 Treatment Period

The treatment period is divided into 4 courses. Each course consists of 12 weeks. Courses 1-3 may include IL-2 therapy, for a maximum of three courses of IL-2 per patient depending on tolerance and response. Course 4 consists of pembrolizumab monotherapy for all subjects.

On-Treatment Safety Assessments/Treatment visits

Safety will be evaluated for all treated patients using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (http://ctep.cancer.gov/reporting/ctc.html). Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, physical examinations, and clinical laboratory tests. Subjects who are not willing to adhere to the study calendar should be removed from active treatment and enter survival follow-up mode.

7.1.7.3 Post-Treatment Visits

If a patient does not receive any assigned protocol treatment, follow-up data will not be collected. However, the reason for not starting protocol treatment must be documented on the off treatment form.

[redacted]

Safety Follow-Up

The mandatory Safety Follow-Up Visit should be conducted 90 ±14 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur in the 90 days following last study treatment (but before the initiation of a new anti-cancer treatment) should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first.

Subjects who are taken off treatment for reasons other than progressive disease may remain on study and complete study requirements until the end of the 2 year study period. Subjects should complete on-study tumor assessments at the scheduled timepoints despite discontinuing therapy until they initiate new anti-cancer treatment or withdraw their consent.

The end of on-study pembrolizumab treatment is defined as 2 calendar years from the date of enrollment. Following the end of the study, the investigator may choose to continue pembrolizumab off-study in stable/responding patients at his/her discretion.

Long-term Follow-up

7.1.7.3.1.1 Subsequent Anti-Cancer Therapy Status

For subjects who discontinue trial treatment for a reason other than disease progression, every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death. At the end of the treatment period, the investigator may choose to continue pembrolizumab off-study at his/her discretion. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated. In-person visits are not required. Once new anti-cancer therapy has been initiated the subject will be followed for survival only.

7.1.7.3.1.2 Survival Follow-up

All subjects will be followed for survival. The study team should make contact with the subject every 12 weeks (starting after the EOT/Safety follow-up visit) to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first. Telephone visits and electronic communications are permissible if in-person visit are inconvenient. Indirect contact through another medical provider (e.g. a local medical oncologist's office, family physician's office, or hospice) is acceptable. This should be documented with dated documentation (such as laboratory results or an office note) or a research note created by the study team. The date of death should be recorded. The on-line Social Security Death Index may be used to verify the date of death.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laborator[redacted]

symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the study drugs is also an adverse event.

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

Study drug(s) includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by [redacted].

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

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

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

All adverse events will be recorded from the time the consent form is signed through 90 days following cessation of treatment, or until the initiation of subsequent therapy, whichever comes first. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.

All adverse events of grade 2-5 must be recorded in the eCRF in OnCore. Adverse events of grade 1 need not be captured in the database unless the grade 1 AE is determined to be intolerable and/or leads to a change in dose or schedule, or the treating investigator wishes it to be reported in the database.

7.2.1 Immediate Reporting of Adverse Events

7.2.1.1 Serious Adverse Events

A serious adverse event (SAE) is any adverse event occurring at any dose or during any use of the study drug(s) that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;

[redacted]

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

* Common and expected toxicities related to IL-2 administration will not be considered reportable SAEs.

7.2.1.2 SAE Reporting to [redacted]

Any SAE, or follow-up to a SAE, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to the study drug(s), must be reported within 24 hours to Sponsor-Investigator (report to [redacted].

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the study drug(s) that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately [redacted]

SAE reports and any other relevant safety information are to be forwarded to the [redacted]

A [redacted]

[redacted] up for outcome.

7.2.1.3 SAE Reporting to Prometheus

[redacted]

[redacted]

[redacted]

Common and expected toxicities related to IL-2 administration will not be considered reportable SAEs. For guidance on common and uncommon toxicities expected with IL-2, investigators may refer to recent IL-2 guidelines [34]. During IL-2 administration, only SAEs of Special Interest will be considered reportable.

IL-2 Related SAEs of Special Interest must be reported within 24 hours of the investigator's knowledge of the event.

An IL-2 Related SAE of Special Interest is an SAE that occurs during IL-2 treatment or within 14 days after IL-2 treatment, and is defined by any of the following:

- Any grade 3 or greater toxicity that does not improve to grade 1 or better within 1 week
  - Exceptions: grade 3 arthralgia/myalgias, grade 3 fatigue, and grade 3 amylase or lipase elevation, which should all be considered non-serious AEs.
- Any reportable ECI (See Appendix 11.4 and full length ECI Guidance Document)
  - Exception: grade 3 skin AE that improves to grade 1 or better within 1 week.
- Hypotension with systolic BP<80 and not responsive to fluid resuscitation and/or vasopressors
- Pulmonary edema requiring intubation
- Pneumonitis (Grade 3 or 4)
- Renal dysfunction requiring dialysis
- Grade 4 cardiac dysrhythmia or Grade 2 or 3 dysrhythmia not easily controlled with medical management
- Myocardial ischemia (Grade 3 or 4) or infarction or symptomatic myocarditis
- Pericardial tamponade
- Bowel ischemia or perforation
- Life threatening sepsis
- Severe altered mental status or coma
- Any other severe or life-threatening toxicity which, in the opinion of the treating investigator, would preclude further treatment with IL-2.

Any AE that meets any of the criteria above should be reported as an IL-2 Related SAE of Special Interest to the IRB, Merck, and Prometheus using the above SAE reporting procedures.

7.2.1.5 Events of Clinical Interest

[redacted]

[redacted]

[redacted]

[redacted] Study drug(s), as defined in Section 7.2.4 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

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

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

1. Additional adverse events:

A separate guidance document has been provided entitled "Event of Clinical Interest Guidance Document". This document can be found in Appendix and provides guidance regarding identification, evaluation and management of ECIs and irAEs.

ECIs (both non-serious and serious adverse events) identified in this guidance document from the date of first dose through 90 days following cessation of treatment, or 90 days after the initiation of a new anticancer therapy, whichever is earlier, need to be reported [redacted]

[redacted] er etiologic causes. If no other cause is found, then it is assumed to be immune-related.

NOTE: **Hypophysitis**

Hypophysitis is defined as presumed inflammation of the pituitary gland based on clinical, laboratory and imaging data. For this protocol, hypophysitis should be recorded as an AE as "Endrocrine disorders – Other (hypophysitis)" if 2 or more of the following CTCAE terms co-occurring in the same subject: adrenal insufficiency, hypothyroidism, and hypogonadism.

[redacted]

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

7.2.2 Recording AEs During Inpatient Hospitalization for Study Therapy

Events of the inpatient course should be documented, including detailed information about AEs.

The study team may choose to summarize the information in the Discharge Summary or in a Research Note using the following template:

Summary of Research Data from Inpatient Hospitalization

- What was duration of hospital stay (in days)? _____
- How many doses of IL-2 did the patient receive? _____
- Did the patient require any of the following during this admission?
    a. Transfer to a higher level of care? Yes/No
    b. Vasopressor therapy? Yes/No
    c. Supplemental oxygen? Yes/No
    d. Ventilator? Yes/No
- List all AE's during the hospitalization with highest grade, start and stop dates, and attribution.

AE	Grade	Start Date	Stop Date	Attribution
1.				
2.				
3.				
4.				
5.				
6.				
7.				
8.				
9.				
10.				

7.2.3 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

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

[redacted]

Table 8 Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of The study drug(s) that:	
	†**Results in death**; or	
	†**Is life threatening**; or places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new cancer; (that is not a condition of the study) or	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Study drug(s) to be discontinued?	
Relationship to test drug	Did the Study drug(s) cause the adverse event? The determination of the likelihood that the Study drug(s) caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Study drug(s) and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Study drug(s) caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Study drug(s) such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Study drug(s)? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Study drug(s) (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Study drug(s) discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Study drug(s); or (3) the trial is a single-dose drug trial); or (4) Study drug(s)(s) is/are only used one time.)

[redacted]

	Rechallenge	Was the subject re-exposed to the Study drug(s) in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Study drug(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE STUDY DRUG(S), OR IF REEXPOSURE TO THE STUDY DRUG(S) POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Study drug(s) or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following		**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Study drug(s) relationship).**
Yes, there is a reasonable possibility of Study drug(s) relationship.		There is evidence of exposure to the Study drug(s). The temporal sequence of the AE onset relative to the administration of the Study drug(s) is reasonable. The AE is more likely explained by the Study drug(s) than by another cause.
No, there is not a reasonable possibility Study drug(s) relationship		Subject did not receive the Study drug(s) OR temporal sequence of the AE onset relative to administration of the Study drug(s) is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)

7.2.4 Definition of an Overdose for This Protocol and Reporting of Overdose to [redacted]

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

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

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

[redacted]

7.2.5 Reporting of Pregnancy and Lactation to [redacted]

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial completing the trial, or 90 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

[redacted]

7.2.6 Sponsor Responsibility for Reporting Adverse Events

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

[redacted]

8.0 STATISTICAL ANALYSIS PLAN

8.1 Summary

Subjects with advanced melanoma will be treated with pembrolizumab (200 mg IV Q 3 weeks) beginning at Week 1 and escalating doses of IL-2 (6,000, 60,000, or 600,000 IU/kg) beginning at Week 4. In the Phase Ib dose-escalation 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. If DLT is reached in 0 out of 3 subjects, sequential dose escalation will proceed to the intermediate and high doses (60,000 and 600,000 IU/kg, respectively), also using a minimum cohort size of 3 subjects." Based on the data from the Phase Ib dose-escalation portion, the maximum tolerated dose (MTD) will be determined. If no MTD is reached, 600,000 IU/kg will be considered the MTD. The Phase II will be a two-stage design, H1=30%, H0=17%, two-stage design for futility analysis. The primary endpoint is the best objective response rate (BORR).

8.2 Phase Ib Escalation Procedure

The study will use a Semi-Bayesian modified toxicity probability interval (mTPI) method for Phase I dose escalation portion[44]. The starting cohort size will be 3 patients, but the method can handle varying cohort size when real data have different cohort sizes.

Subjects will be enrolled to the Phase Ib portion of the trial starting with Cohort 1 (Table). Subjects will be followed for 6 weeks to monitor for dose-limiting toxicity (DLT).

The following table displays the escalation/de-escalation/stay/ decisions using the set-up: maximum number of patients at a given dose =18, true probability of toxicity pT=0.3, and the higher and lower ends of the equivalence interval =0.05.

The required sample size is 9 - 18 subjects. There will be no within-patient dose escalation.

Number of patients treated at current dose

Number of dose limiting toxicities (DLTs)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	D	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E
2		DU	D	S	S	S	S	S	S	S	E	E	E	E	E	E	E	E
3			DU	DU	D	S	S	S	S	S	S	S	S	S	S	E	E	E
4				DU	DU	DU	D	D	S	S	S	S	S	S	S	S	S	S
5					DU	DU	DU	DU	DU	D	S	S	S	S	S	S	S	S
6						DU	DU	DU	DU	DU	DU	D	S	S	S	S	S	S
7							DU	DU	DU	DU	DU	DU	DU	D	S	S	S	S
8								DU	DU	DU	DU	DU	DU	DU	DU	DU	D	S
9									DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
10										DU	DU	DU	DU	DU	DU	DU	DU	DU
11											DU	DU	DU	DU	DU	DU	DU	DU

	12												DU	DU	DU	DU	DU	DU	DU
	13													DU	DU	DU	DU	DU	DU
	14														DU	DU	DU	DU	DU
	15															DU	DU	DU	DU
	16																DU	DU	DU
	17																	DU	DU
	18																		DU
					E = Escalate to the next higher dose S = Stay at the current dose D = De-escalate to the next lower dose U = The current dose is unacceptably toxic MTD = 30% Epsilon1 = 0.05 Epsilon2 = 0.05									

8.3 Phase II Two-Stage Design

The phase II will be a two-stage Simon's minimax design with up to n=48 patients to test H0=17% versus H1=30% at alpha=0.10 and power=0.80with an interim futility analysis when n1=23 patients response data are available. If 3 or fewer responses are observed during stage 1, then the trial is stopped early. When the trial continues to completion of all 48 patients, if 12 or more responses are observed, we then reject H0=17%. We will also estimate the BORR with a 95% confidence interval, which will be compared to the well-documented IL-2 RR of 16-17% to justify or forgo a randomized trial comparing the combination to IL-2 alone.

8.4 Definitions of Terms

8.4.1 Definition of evaluable for response

A subject is evaluable for response if he/she received at least 1 dose of IL-2 and at least 1 dose of pembrolizumab, and completed at least 1 on-study response assessment.

8.4.2 Definition of evaluable for toxicity

A subject is evaluable for toxicity if he/she received at least 1 dose of IL-2 and at least 1 dose of pembrolizumab.

8.4.3 Definition of DLT

Dose limiting toxicity (DLT) is defined by the following criteria:

[redacted]

Any Grade 4 or 5 toxicity that is possibly, probably, or definitely attributable to the study agent or agents and occurs during the first 6 weeks from the initiation of study treatment constitutes a DLT.

EXCEPTIONS: The following Grade 4 toxicities are expected with high-dose IL-2 treatment and tend to reverse with holding IL-2 treatment and providing supportive care measures, including intubation, vasopressors and anticoagulants. The following Grade 4 exceptions do not constitute a DLT:

- Venous access complication. Grade 4 is defined as Embolic event including pulmonary embolism or life-threatening thrombus.
- Hypotension. Grade 4 is defined as Life-threatening and urgent intervention indicated.
- Urine output decreased. Grade 4 is defined as Anuria (<240 ml in 24 hr)
- Pulmonary edema. Grade 4 is defined as Life-threatening respiratory compromise; urgent intervention or intubation with ventilatory support indicated. Pulmonary edema requiring intubation for < 72 hours is acceptable.
- Cytokine release syndrome. Grade 4 is defined as Life-threatening consequences requiring pressor or ventilatory support.

Any Grade 3 toxicity constitutes a DLT if it meets all of the following parameters:

1. toxicity is possibly, probably, or definitely attributable to the study agent or agents, and
2. toxicity occurs during the first 6 weeks from the initiation of study treatment, and
3. toxicity does not resolve to grade 2 or less within 14 days of onset.

In addition to the above criteria, DLT is also defined by any of the following treatment-emergent contraindications to IL-2:

- Sustained ventricular tachycardia (≥5 beats)
- Cardiac arrhythmias not controlled or unresponsive to management
- Chest pain with ECG changes, consistent with angina or myocardial infarction
- Cardiac tamponade
- Intubation for >72 hours
- Renal failure requiring dialysis >72 hours
- Coma or toxic psychosis lasting >48 hours
- Repetitive or difficult to control seizures
- Bowel ischemia/perforation
- GI bleeding requiring surgery
- Life-threatening hypersensitivity to IL-2 or any component of the Proleukin formulation.

A grade 3 laboratory abnormality without clinical symptomatology does not define a DLT. Specific examples include:

[redacted]

- amylase elevation without epigastric pain and vomiting
- hyperbilirubinemia and transaminitis without abdominal pain or tenderness
- electrolyte abnormalities, including acidosis, hypomagnesemia, hypocalcemia, hypokalemia, hypophosphatemia and hyponatremia without arrhythmias or muscle weakness
- hematologic abnormalities, including lymphopenia, neutropenia, anemia and thrombocytopenia

These are examples of expected laboratory abnormalities that occur during treatment with high-dose IL-2 which are expected to resolve with holding IL-2 treatment and providing supportive care.

More than half of patients experience transient grade 3 toxicities during treatment with high-dose IL-2, which justifies this strict definition of a DLT.

8.4.4 Definition of DLT observation period

Subjects will be monitored for dose-limiting toxicity (DLT) for the first 6 weeks after the initiation of study treatment. AEs that occur after that time will not be considered DLTs.

8.5 Justification of Sample Size

The sample size is 60 evaluable subjects. We anticipate enrolling 62-65 patients in order to obtain 60 evaluable patients.

Approximately 9-18 patients will be treated in the Phase Ib portion of the trial.

Approximately 48 patients will be required for the Phase II, two-stage design with H1=30%, H0=17%, for futility analysis. Phase Ib subjects treated at the MTD will be included in the two-stage futility analysis; these subjects will be included in the determination of the Phase II primary endpoint.

8.6 Analysis of Primary Objectives

8.6.1 Intent to Treat Analysis

If the subject is willing to adhere to follow-up procedures, all assessments listed in the Safety Follow-up and Long-term Follow-up columns in the Trial Flow Chart in Section 6.0 should be completed and recorded until withdrawal of consent or death, so that data can be analyzed in accordance with the intent to treat principle.

[redacted]

8.6.2 Phase Ib

The primary endpoint of the Phase Ib will be the toxicity/MTD. If no MTD is reached, the 600,000 IU/kg dose will be called the MTD. The coordinating center will communicate the determination of the MTD via an electronic memo to all participating sites. At that time, the Phase II portion will open to accrual.

8.6.3 Phase II

The Primary Objective is to characterize the efficacy of the IL-2 in combination with pembrolizumab using the primary endpoint of BORR as per RECIST v1.1. BORR will be calculated in the overall study population and in subpopulations that have and have not received prior therapy with checkpoint inhibitor.

There will be a subset analysis of RR in lung vs. melanoma subjects, as well a PD-1 naïve vs. PD-1 refractory. PD-1 refractory is defined as having received prior treatment with PD-1/PD-L1 containing antibodies in the adjuvant or metastatic setting We estimate 75% of the potential subjects will have received treatment with a checkpoint inhibitor prior to study entry. The BORR will be analyzed by prior treatment status.

8.6.3.1 Definition of Positive Primary Endpoint

We assume that objective response rate for high dose IL-2 alone is no greater than 16-17%. Therefore if the effect of adding pembrolizumab to high-dose IL-2 were 30% or better, this would be a clinically meaningful treatment option in this population, which is expected to be largely (75%) pembrolizumab refractory.

It is not known if the efficacy of IL-2 is affected by prior immune checkpoint blockade, but based on the available data the response rate is expected to be similar. In a prospectively collected registry study of melanoma and renal cell carcinoma patients who received PD-1 inhibitor or ipilimumab prior to treatment with HD IL-2, the RR to HD IL-2 was 17.7% or 9/51 patients [45]. In a similar but smaller study of patients who received PD-1 inhibitor prior to treatment with HD IL-2, the response rate was 8.3% or 1/12 patients [46]. In general, in-class cross-resistance with immunotherapy agents is not observed, and therefore, this justifies the inclusion of both checkpoint-naïve and checkpoint-refractory patients in this protocol.

The objective response rate for pembrolizumab refractory population is difficult to estimate because the effectiveness of rechallenging with pembrolizumab is unknown. For purposes of this study it will be estimated to be 10% in the truly refractory population. Patients who have received prior treatment with PD-1 inhibitors and derived clinical benefit may be expected to have a higher response rate, which has also not been studied, but can be estimated to be 40% based on a rechallenge study of ipilimumab [47].

A total of approximately 50 patients treated at the MTD of IL-2 + pembrolizumab will allow us to estimate a point estimate of the BORR and 95% confidence interval (CI) as below:

[redacted]

If the BORR is	The 95% CI will be +/-	Limits of 95% CI will be
20%	11.3%	(8.9 – 31.3%)
30%	13.0%	(17.0 – 43.0%)
40%	13.9%	(26.1 – 53.9%)
50%	14.1%	(35.9 – 64.1%)

We will deem this approach meritorious of further study in a randomized trial of the combination versus pembrolizumab alone 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%.

8.6.3.2 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

8.7 Analysis of Secondary Objectives

The secondary objectives are to characterize the safety of IL-2 in doses ranging up to the FDA-approved dose when administered in combination with pembrolizumab, and to characterize clinical endpoints, including overall survival, progression-free survival, 1- and 2-year survival.

The frequency of AEs and SAEs will be recorded. In addition, data on the inpatient course will be summarized, including the duration of hospital stay (in days), and the need for select 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).

[redacted]

8.8 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 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.

8.9 Early Stopping Rule for Toxicity

There will be two planned interim analyses for consideration of early trial termination. The DSMB will evaluate the toxicity data after the first 15 patients are enrolled and again after the first 35 patients are enrolled. If there are >2/15 or >4/35 patients with DLTs or SAEs of Special Interest, the study will be placed on hold for consideration of termination or an amendment to increase the safety of the trial. The DSMB has the authority to halt accrual to the study at any time for concerns over unacceptable toxicity or unacceptable rates of death.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF DRUGS

9.1 Pembrolizumab

9.1.1 Investigational Product - Pembrolizumab

Merck will provide pembrolizumab. Participating sites will receive shipments of pembrolizumab directly from [redacted]

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

Clinical Supplies will be provided by [redacted]s summarized below:

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

To request drug supply of pembrolizumab, use the Merck **Drug Request Form**.

9.1.2 Packaging and Labeling Information

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

[redacted]

9.1.3 Clinical Supplies Disclosure

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

9.1.4 Storage and Handling Requirements

The drug product must be stored under refrigerated conditions (2°C - 8°C). The drug product after reconstitution with sterile water for injection and the liquid drug product are a clear to opalescent solution which may contain proteinaceous and extraneous particulates. The reconstituted lyophilized product and the liquid product are intended for IV administration. The reconstituted drug product solution or the liquid drug product can be further diluted with normal saline in IV containers made of polyvinyl chloride (PVC) or non-PVC material. Reconstituted vials should be immediately used to prepare the infusion solution in the IV bag and the infusion solution should be immediately administered. If not used immediately, vials and/or IV bags may be stored at 2-8 °C for up to a cumulative time of 20 hours. If refrigerated, the vials and/or IV bags should be allowed to equilibrate to room temperature prior to subsequent use. MK-3475 solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes room temperature storage of reconstituted or liquid DP solution in vials, room temperature storage of infusion solution in the IV bag and the duration of infusion.

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

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

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

9.1.5 Returns and Reconciliation

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

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

9.2 IL-2

9.2.1 Supply

IL-2 (Aldesleukin, Proleukin®) is a commercially available product (Prometheus) and is on-label for metastatic melanoma. IL-2 will be obtained through the commercial supply.

9.2.2 Storage, Preparation, and Administration of IL-2

Reconstituted IL-2 should be further diluted with 5% Dextrose, USP. Do not mix with saline containing solutions. Reconstituted IL-2 may be diluted as necessary in volumes of 50 ml to 500 ml with 5% Dextrose, USP. When diluted for IV administration in 5% Dextrose Injection, USP, in a plastic bag (e.g. Viaflex, manufactured by Travenol Laboratories, Inc.,) IL-2 is chemically stable for 48 hours at refrigerated and room temperatures, 2-30°C. Intact vials are stored in the refrigerator (2-8°C) protected from light. Each vial bears an expiration date.

For doses at 600,000units/kg:

Reconstituted IL-2 should be further diluted with 5% Dextrose, USP. Do not mix with saline containing solutions. Reconstituted IL-2 may be diluted as necessary in volumes of 50 ml to 500 ml with 5% Dextrose, USP to maintain a concentration between 0.03 mg/mL and 0.07 mg/mL (490,000 units/ml to 1,145,000 units/ml). When diluted for IV administration in 5% Dextrose Injection, USP, in a plastic bag (e.g. Viaflex, manufactured by Travenol Laboratories, Inc.,) IL-2 is chemically stable for 48 hours at refrigerated and room temperatures, 2-30°C. Intact vials are stored in the refrigerator (2-8°C) protected from light. Each vial bears an expiration date.

For doses at 60,000 units/kg

Concentrations of Proleukin below 0.03 mg/mL and above 0.07 mg/mL (below 490,000 units/ml and above 1,145,000 units/ml) have shown increased variability in drug delivery. Dilution and delivery of Proleukin outside of this concentration range requires compounding with 0.1% albumin (for example, 1 ml of 5% albumin added to 50 ml D5W bag before adding Aldesleukin (IL-2) (48).

For doses at 6,000 units/kg

Concentrations of Proleukin below 0.03 mg/mL and above 0.07 mg/mL (below 490,000 units/ml and above 1,145,000 units/ml) have shown increased variability in drug delivery. Dilution and delivery of Proleukin outside of this concentration range requires compounding with 0.1% albumin (for example, 0.5 ml of 5% albumin added to 25 ml D5W bag before adding Aldesleukin (IL-2) (48).

9.2.3 IL-2 Formulation/Reconstitution: IL-2

Formulation/Reconstitution: IL-2 (Aldesleukin, Proleukin®), please see the Investigators Brochure for the complete pharmaceutical package insert) is a commercially available product (Prometheus).

The medication is provided as a lyophilized powder and a vial of medication is reconstituted with 1.2mg of Sterile Water for Injection, USP, and the resultant concentration is 18 million IU/ml.

Diluent should be directed against the side of the vial to avoid excess foaming. Swirl contents gently until completely resolved.

Do not shake.

Since vials contain no preservative, reconstituted solution should be used within 8 hours.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

Subjects' identities, names or any identifying characteristics will not be disseminated in publications, nor made public. The data forms will be de-identified, meaning that the patients identifying information will be matched to the research number, in a separate file.

10.2 Compliance with Financial Disclosure Requirements

The Principal Investigator and Sub-Investigators must comply with applicable federal, state, and local regulations regarding reporting and disclosure of conflict of interest. Conflicts of interest may arise from situations in which financial or other personal considerations have the potential to compromise or bias professional judgment and objectivity. Conflicts of interest include but are not limited to royalty or consulting fees, speaking honoraria, advisory board appointments, publicly-traded or privately-held equities, stock options, intellectual property, and gifts.

[redacted]

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated

[redacted]

Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

[redacted]

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the

Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives [redacted]

regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms. The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

10.4 Issues with Minors

For minors, according to local legislation, one or both parents or a legally acceptable representative must be informed of the study procedures and must sig[redacted]

form approved for the study prior to clinical study participation. The explicit wish of a minor, who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

Minors who are judged to be of an age of reason must also give their written assent.

10.5 Compliance with Trial Registration and Results Posting Requirements

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

10.6 Quality Management System

10.6.1 Data Safety Monitoring Board

The Rutgers Cancer Institute Human Research Oversight Committee is responsible for annual data and safety monitoring of investigator initiated phase I and II, therapeutic interventional studies that do not have an independent Data Safety Monitoring Board (DSMB). The primary focus of the HROC is review of safety data, toxicities and new information that may affect subject safety or efficacy. Annual safety reviews includes but may not be limited to review of safety data, enrollment status, stopping rules if applicable, accrual, toxicities, reference literature, and interim analyses as provided by the sponsor-investigator. The HROC in concert with the Quality Assurance Monitoring Team oversees the conduct of Rutgers CINJ cancer-related, sponsor-investigator therapeutic intervention and prevention intervention studies that do not have an external monitoring plan, ensuring subject safety and that the protocol is conducted, recorded and reported in accordance with the protocol, standing operating procedures (SOPs), Good Clinical Practice (GCP), and applicable regulatory requirements.

10.6.2 Monitoring

[redacted]

[redacted]

[redacted] trial network that has conducted over 50 cytokine-based clinical trials over the past 20 years. All sites have high-dose IL-2 experience and must commit to accrual of at least 10 patients each year. Thus, the members of the CWG represent a group of national experts on the clinical use of IL-2. The CWG has an established monthly teleconference to discuss protocol status, subject accrual adverse events and other aspects of each trial.

10.7 Registration

[redacted]

- Registration: Any subject that has signed the consent will be entered into OnCore. A copy of the consent will be uploaded into the Documents section.

- Enrollment: Once eligibility has been confirmed, the completed, signed and dated eligibility checklist subjects will be enrolled through OnCore. A sequence number (subject study ID) will be generated at the time of enrollment, this is the point the patient is considered on study. Participating centers will upload source documents for baseline and screening assessments into OnCore.

Patients will <u>not</u> start protocol treatment prior to registration.

Trial treatment should begin within 10 days of registration or as close as possible to the date on which treatment is allocated/assigned. [redacted]

10.8 Data Management

10.8.1 Study Documentation

Study documentation includes but is not limited to source documents, case report forms, monitoring logs, appointment schedules, study team correspondence with sponsors or regulatory bodies/committees, and regulatory documents that can be found in the DCI-mandated "Regulatory Binder", which includes but is not limited to signed protocol and amendments, approved and signed informed consent forms, FDA Form 1572, CAP and CLIA laboratory certifications, and clinical supplies receipts and distribution records.

Source documents are original records that contain source data, which is all information in original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents include but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial. When possible, the original record should be retained as the source document. However, a photocopy is acceptable provided that it is a clear, legible, and an exact duplication of the original document.

10.8.2 Case Report Forms (CRFs)

The electronic CRF stored in Oncore® will be the primary data collection document for the study. The CRFs will be updated in a timely manner following acquisition of new source data. Only the key personnel delegated on the delegation of authority log are permitted to make entries, changes, or corrections in the CRF.

An audit trail will be maintained automatically by the electronic CRF management system. All users of this system will complete user training, as required or appropriate per regulations.

10.8.3 Data Management Procedures and Data Verification

Users of the electronic CRF will have access based on their specific roles in the protocol.

Completeness of entered data will be checked automatically by the eCRF system, and users will be alerted to the presence of data inconsistencies. Additionally, the data manager and project manager will cross-reference the data to verify accuracy. Missing or implausible data will be highlighted for the PI requiring appropriate responses (i.e. confirmation of data, correction of data, completion or confirmation that data is not available, etc.).

The database will be reviewed and discussed prior to database closure, and will be closed only after resolution of all remaining queries. An audit trail will be kept of all subsequent changes to the data.

10.8.4 Study Closure

Following completion of the studies, the PI will be responsible for ensuring the following activities:

- Data clarification and/or resolution

- Accounting, reconciliation, and destruction/return of used and unused study drugs

- Review of site study records for completeness

- Shipment of all remaining laboratory samples to the designated laboratories

10.9 Data Safety Monitoring Plan

[redacted]

[redacted]