UPCI Protocol #: **15-114**

TITLE: A Phase II Study of High Dose Bolus IL2 in Patients with Inoperable Stage III or Stage IV Melanoma Who Have Failed Prior Anti-PD1 Immunotherapy: Efficacy and Biomarker Study

Coordinating Center: University of Pittsburgh Cancer Institute
5150 Centre Avenue, Pittsburgh, PA, 15232
Phone: 412 647-8587
Fax: 412 623-7862

Principal Investigator: Ahmad A. Tarhini, MD, PhD
Associate Professor of Medicine and Translational Science
University of Pittsburgh School of Medicine
UPMC Cancer Pavilion
5150 Centre Ave., 5th floor
Pittsburgh, PA 15232
Phone: 412-648-6578
Fax: 412-648-6579
E-mail: tarhiniaa@upmc.edu

Statistician: Yan Lin, Ph.D.
University of Pittsburgh Cancer Institute &
Biostatistics Dept, University of Pittsburgh

Study Chair Liaison: Amy Rose, RN BSN OCN
University of Pittsburgh Cancer Institute
5150 Centre Avenue
Third Floor
Pittsburgh, PA 15232
Phone: (412) 647-8587
Fax: (412) 623-7862
E-mail: kennaj@upmc.edu

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SCHEMA

This is a phase II study of high dose bolus interleukin-2 (HD IL2) in patients with advanced inoperable stage III or stage IV melanoma who have failed prior anti-PD1 immunotherapy.

The planned treatment consists of 3 courses (6 cycles) of HD IL-2. Response assessment will occur at the end of each course of therapy and patients without evidence of disease progression (RECIST v.1.1) or limiting toxicities will be offered additional courses of treatment of HD IL2 for a maximum of 3 courses.

	Course of HD IL2*							
	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8
HD IL-2 600,000 U/kg/dose IV Q8h x 5 days (max 14 doses)	X		X					
Response Assessment								X

*Local variations are allowed as per local site standard practice, patient recovery from adverse events and scheduling requirements.

Primary Objective: To determine the response rate (CR+PR) of HD IL2 in patients with inoperable stage III or stage IV melanoma who have either failed prior treatment with anti-PD1 immunotherapy (nivolumab or pembrolizumab) or who have demonstrated tumor progression following such therapy.

Secondary Objectives: (1) Evaluate the toxicities of HD IL2 in this patient population (CTCAE v.4). (2) Evaluate the progression free survival (PFS) and overall survival (OS). (3) Bank biological specimens for the future testing of laboratory correlative studies within the circulation and the tumor microenvironment (TME) to better understand the impact of HD IL2 in this setting.

The primary endpoint is (CR+PR) as assessed by RECIST criteria version 1.1. The total accrual goal is 45 patients.

Definitions:

1. A **cycle of IL-2**: eligible patients receive HD IL2 at 600,000 IU/kg IV every 8 hours for up to 14 doses. This constitutes one cycle of IL2.
2. Each **course** consists of 2 cycles of HD IL2 as follows: high-dose IL2 at 600,000 IU/kg is given IV every 8 hours for up to 14 doses (one cycle), followed by a rest period of 1-2 weeks and readmission for a second HD IL2 cycle for up to 14 doses (2^{nd} cycle).

3. Based on the occurrence of treatment-related toxicities and requirements for dose adjustments or delays, a patient may or may not receive the full planned treatment, but response assessment will continue to be carried out at the end of each course.

Patients will receive HD IL-2 following the institutional standard of care guidelines. Patients will receive a maximum of 3 courses (6 cycles; 1 course of IL2 = 2 cycles of IL2). Response assessment will be carried out at the end of each course. In the absence of disease progression by RECIST v.1.1, patients will be offered additional courses of therapy for a maximum of 3 courses (6 cycles).

ABBREVIATIONS

High dose bolus interleukin-2: HD IL-2
Complete response: CR
Overall survival: OS
Progression free survival: PFS
Partial response: PR
Pulmonary function tests: PFTs
Stable disease: SD
Tumor microenvironment: TME
University of Pittsburgh Cancer Institute: UPCI

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1. OBJECTIVES

1.1. Primary Objectives

- To determine the response rate (CR+PR) of HD IL-2 in patients with inoperable stage III or stage IV melanoma who have either failed prior treatment with anti-PD1 immunotherapy (nivolumab or pembrolizumab) or who have demonstrated tumor progression following such therapy.

1.2. Secondary Objectives

- Evaluate the toxicities of HD IL-2 in this patient population (CTCAE v.4).
- Evaluate the progression free survival (PFS) and overall survival (OS).
- Test laboratory correlative studies within the circulation and the tumor microenvironment (TME) to better understand the impact of HD IL2 in this setting.

2. BACKGROUND

2.1. Metastatic Melanoma

Annually, more than 8,000 patients are found to have metastatic melanoma presenting as a recurrence of an earlier primary melanoma, and this number closely approximates the annual number of deaths from this disease [1]. This statistic illustrates the lack of progress that has been made in the treatment of stage IV melanoma over the last several decades. Therapeutic approaches that have been studied in metastatic melanoma include chemotherapy, biochemotherapy, protein kinase inhibitors, nonspecific immune adjuvants, cancer-specific vaccines, cytokines, monoclonal antibodies, and specific immunostimulants [1]. Chemotherapy with single agent dacarbazine was the only US-FDA approved chemotherapy agent for metastatic melanoma. Immunological approaches later yielded the only US-FDA approved agent for metastatic disease in 30 years, high-dose bolus interleukin-2 (IL-2), based on prolonged durable responses in some patients with metastatic melanoma [2]. However, a lack of progress for several decades has recently changed dramatically, driven by a deepening understanding of melanoma biology and host immunology.[3, 4] This progress at the molecular levels has been translated into the clinic with new molecularly targeted agents (BRAF and MEK kinase inhibitors) and immune checkpoint modulators (CTLA4 and PD-1 blocking antibodies) that have made major improvements in disease control and the survival of patients with metastatic melanoma. First line therapy in patients with metastatic melanoma in practice currently primarily consists of immune checkpoint inhibitor or targeted kinase inhibitor therapy. Unfortunately, only a proportion of patients derive long term clinical benefits and the majority of patients eventually progress where there is a need for effective salvage systemic therapy. In this setting, there appears to be an important role of HD IL2 which is not well defined at this time. Therefore, participation of patients receiving salvage HD IL2 in clinical trials is presently the best strategy in order to define its clinical and biological impact in this setting and help guide the development of future salvage strategies.

2.2. High Dose Interleukin-2

IL-2 plays a central role in immune regulation as it affects the survival of key cells of the immune system that are responsible for the antitumor cytotoxicity of T-lymphocytes and natural-killer (NK) cells, and it has a cofactor role in the activation of B cells and macrophages [5]**.** The administration of IL-2 at high bolus IV doses once every eight hours was a regimen developed by the National Cancer Institute (NCI) based on animal models indicating that antitumor activity with this agent was dose-dependent [6-8]. Initial studies with HDB IL-2 utilized doses of 600,000-720,000 units/kg every 8 hours from days 1-5 (cycle 1) and days 15-19 (cycle 2) with a maximum of 14 doses per cycle or 28 doses per course (1 course = 2 cycles). Responding or stable patients were offered a second course of therapy 8-12 weeks later. IL-2 was administered either as a single agent or in combination with immunologically active cells, so-called adoptive immunotherapy. The latter technique utilized two types of immune cells: the lymphokine- activated-killer (LAK) cells and the tumor infiltrating lymphocytes (TIL). Eight clinical trials conducted between 1985 and 1993 and using the HDB IL-2 regimen described above, with or without LAK cells, were reviewed in a retrospective analysis. These trials had an enrollment of 270 patients with advanced metastatic melanoma [7-11]. In those studies that involved the concurrent administration of LAK cells, these cells were obtained using leukapheresis from patients during the rebound lymphocytosis that occurs following treatment and cessation of bolus IL-2 (days 8 to 12). LAK cells were then cultured in IL-2 for 3 to 4 days. These generated LAK cells were reinfused with IL-2 during the second cycle of IL-2 administration. The retrospective analysis of these trials with a follow-up through December 1998 along with a more recent update demonstrated an objective response rate of 16% with durable responses in 4% of patients [2, 10-12]. The median response duration was 8.9 months (range 4 to 106+ months). Twenty eight percent of the responding patients, including 59% of those patients who had achieved a complete response, have remained progression free at a median follow-up of 62 months. Furthermore, no patient who had responses longer than 30 months has relapsed, suggesting the possibility that these patients may be “cured”. The frequency of the responses was similar in patients with visceral metastases and/or large tumor burdens, but the responses were less in patients with poor performance status or those who had received prior systemic therapy. Based on these data, HDB IL-2 received approval by the US-FDA for the treatment of metastatic melanoma [11-13]. In addition to being logistically challenging, randomized studies have not shown superiority for IL-2 administered with LAK cells versus therapy with HD IL-2 alone [12-14]. Furthermore, a randomized phase III trial of CD8+ TIL given in combination with rIL-2 in metastatic renal cell carcinoma has been negative [13-15]. We have previously shown that HD IL2 is an active therapy for patients who progress on biochemotherapy; this observation has implications regarding the importance of dose intensity for IL-2 therapy [16]. Continuous infusion of IL-2 at intermediate dosage is a critical component of biochemotherapy regimens and it was previously unknown whether patients treated with biochemotherapy and failing to obtain response, or responding and then demonstrating progression, are capable of subsequently responding and benefiting clinically from the HD IL2 regimen.

2.3. Rationale

First line therapy in patients with metastatic melanoma in practice currently primarily consists of immune checkpoint inhibitor or targeted kinase inhibitor therapy. Unfortunately, only a proportion of patients derive long term clinical benefits and the majority of patients eventually progress where there is a need for effective salvage systemic therapy. In this setting, there appears to be an important role of HD IL2 which is not well defined at this time. Therefore, participation of patients receiving salvage HD IL2 in clinical trials is presently the best strategy in order to define its clinical and biological impact in this setting and help guide the development of future salvage strategies.

Immunologically, we expect that HD IL2 will be effective as salvage immunotherapy in patients in patients failing anti-PD1. In an animal model, IL2 was found to synergize with PD-L1 blockade in reinvigorating exhausted T cells [17]. This model showed that CD8+ T cell expansion and T cell function were upregulated in a regimen consisting of IL2 and anti-PD-L1.

Immunotherapy using checkpoint inhibitors represents a major advance in cancer therapy with an approach distinct from chemotherapy and targeted therapies. However, this new strategy of treatment is also associated with a unique spectrum of adverse events, mostly immune-related (irAEs), occurring via nonspecific immunologic activation that can sometimes be serious and even fatal [18]. Early recognition and management of these irAEs are of paramount importance for practicing clinicians in order to successfully and safely implement the use of these agents in routine clinical practice. These irAEs may have long term effects and it is not well understood how subsequent therapies may be affected by prior exposure to these agents. Therefore, it is important to define the safety of HD IL2 in this setting. Overall, we expect that HD IL2 will be safe in patients who failed prior anti-PD1 immunotherapy, primarily because anti-PD-1 and HD IL-2 have largely non-overlapping toxicities [11, 18].

3. PATIENT SELECTION

3.1. Eligibility Criteria

3.1.1. Patients must have histologically or cytologically confirmed metastatic melanoma. This includes AJCC stage IV or advanced/inoperable stage III. This also includes patients with a history of lower stage melanoma and subsequent recurrent metastatic disease that is either locally/regionally advanced/inoperable disease or distant metastases.

3.1.2. Patients must have measurable disease, according to RECIST version 1.1 [19]. See Section 10 for the evaluation of measurable disease.

3.1.3. Patients must be free of active brain metastasis by contrast-enhanced CT/MRI scans within 4 weeks prior to enrollment. If known to have prior brain metastases, these must have been adequately managed with standard of care radiation therapy, stereotactic radiosurgery or surgery prior to registration on the study.

3.1.4. A patient must have previously received anti-PD1 immunotherapy (nivolumab or pembrolizumab) and later experienced disease progression, within 3 months of registration on this study.

Patients must not have received systemic therapy or radiotherapy within the preceding 3 weeks. Patients must have recovered from adverse events from previous therapy by the time registration.
Patients must be at least 4 weeks from major surgery and have fully recovered from any effects of surgery, and be free of significant detectable infection prior to registration.

For patients who have received prior anti-CTLA4 monoclonal antibody therapy (ipilimumab or tremelimumab), there is a risk of bowel perforation with IL-2 therapy. Therefore, for these patients if they have a history of colitis or diarrhea during anti-CTLA4 monoclonal antibody therapy, it is recommended that they have a formal evaluation by a gastroenterologist and a colonoscopy/endoscopy should be considered to demonstrate the absence of active bowel inflammation before initiating IL-2 therapy on this protocol.

3.1.5. Age ≥ 18 years.

3.1.6. Life expectancy of greater than 3 months in the opinion of the investigator.

3.1.7. ECOG performance status 0 or 1 (Karnofsky ≥70%; see Appendix A).

3.1.8. Patients must have normal organ and marrow function as defined below:

-	leukocytes	≥3,000/mcL
-	absolute neutrophil count	≥1,500/mcL
-	platelets	≥100,000/mcL
-	total bilirubin	≤ 1.5 x institutional upper limit of normal
-	AST(SGOT)/ALT(SGPT)	≤2.5 X institutional upper limit of normal
-	creatinine	≤1.5 x institutional upper limit of normal
	OR	
-	creatinine clearance	≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal

3.1.9. Patients on full-dose anticoagulants (e.g., warfarin) with PT INR >1.5 are eligible provided that both of the following criteria are met:

a) The patient has an in-range INR (usually between 2 and 3) on a stable dose of oral anticoagulant or on a stable dose of low molecular weight heparin.

b) The patient has no active bleeding or pathological condition that carries a high risk of bleeding (e.g., tumor involving major vessels or known varices).

3.1.10. Pulmonary: FEV1 > 2.0 liters or > 75% of predicted for height and age. Pulmonary function tests (PFTs) are required for patients over 50 years old or with significant pulmonary or smoking history.

3.1.11. Cardiac: No evidence of congestive heart failure, symptoms of coronary artery disease, myocardial infarction less than 6 months prior to entry, serious cardiac arrhythmias, or unstable angina.

Patients who are over 40 years old or have had previous myocardial infarction greater than 6 months prior to study entry or have significant cardiac family history (CAD or serious arrhythmias) will be required to have a negative or low probability cardiac stress test (for example, thallium stress test, stress MUGA, stress echo or exercise stress test) for cardiac ischemia within 8 weeks prior to registration.

3.1.12. CNS: No history of cerebrovascular accident or transient ischemic attacks within the past 6 months from registration.

3.1.13. Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for at least 6 months after completion of study therapy. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

Women should not be lactating and, if of childbearing age, should have a negative pregnancy test (b-HCG test; serum or urine, minimum sensitivity 25 IU/L or equivalent units of b-HCG) within two week of registration in the study.

3.1.14. Ability to understand and the willingness to sign a written informed consent document.

3.2. Exclusion Criteria

3.2.1. Patients who have had systemic therapy for melanoma or radiotherapy within 3 weeks prior to registering on the study or those who have not recovered from adverse events due to agents administered more than 3 weeks earlier. Patients with a history of endocrinopathies (e.g. hypothyroidism, adrenal insufficiency, hypopituitarism) are eligible if they are stable on hormone replacement therapy.

3.2.2. Patients may not be receiving any other investigational agents.

3.2.3. Patients with active brain metastases should be excluded from this clinical trial except as noted above under section 3.1.3.

3.2.4. Patients with clinically significant cardiovascular or cerebrovascular disease:
- history of cerebrovascular accident or transient ischemic attack within past 6 months from registration.
- myocardial infarction, CABG or unstable angina within the past 6 Months from registration.
- New York Heart Association grade III or greater congestive heart failure (Appendix E), serious cardiac arrhythmia requiring medication, unstable angina pectoris within past 6 months from registration.
- clinically significant peripheral vascular disease within past 6 months from registration.

3.2.5. PT INR >1.5 unless the patient is on full-dose warfarin.

3.2.6. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.7. Patients who have other current malignancies are not eligible. Patients with other malignancies are eligible if they have been continuously disease free for > 2 years prior to the time of registration. Patients with prior history at any time of any in situ cancer, lobular carcinoma of the breast in situ, cervical cancer in situ, atypical melanocytic hyperplasia or melanoma in situ are eligible. Patients with prior history of basal or squamous skin cancer are eligible. Patients who have had multiple primary melanomas are eligible.

3.2.8. Patients must not have autoimmune disorders or conditions of immunosuppression that require current ongoing treatment with systemic corticosteroids (or other systemic immunosuppressants), including oral steroids (i.e., prednisone, dexamethasone) or <u>continuous use</u> of topical steroid creams or ointments or ophthalmologic steroids or steroid inhalers.

If a patient had been taking steroids, at least 2 weeks must have passed since the last dose. Patients stable on physiologic replacement doses of steroids or other forms of hormone replacement therapy are eligible.

3.3. Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1. General Guidelines

Eligible patients will be entered on study centrally at the Data Coordinating Center (DCC) at the University of Pittsburgh Cancer Institute (UPCI). All sites should e-mail the DCC at Melanoma_Team@upmc.edu to verify slot availabilities.

Following registration, patients should begin protocol treatment within 2 weeks. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The DCC should be notified of cancellations as soon as possible.

4.2. Registration Process

Once the signed informed consent has been obtained, all pretreatment evaluations have been performed, and patient's eligibility has been confirmed by the data coordinating center a patient will be entered on study.

To register a patient, the research nurse or data manager must complete the eligibility/registration form and contact the DCC at UPCI:

- E-mail a copy of the completed eligibility checklist, required pre-study tests (laboratory and pathology report), signed Informed Consent, and HIPAA authorization form to Melanoma_Team@upmc.edu.
- To complete the registration process, the data coordinating center coordinator will:

- Verify the eligibility
- Register the patient on study
- Assign a patient study number
- E-mail the confirmation of registration to the participating site

5. TREATMENT PLAN

5.1. Overall Treatment Plan

This is a phase II study of high dose bolus interleukin-2 (HD IL2) in patients with advanced inoperable stage III or stage IV melanoma who have prior anti-PD1 immunotherapy.

Definitions:

1. A cycle of IL-2: eligible patients receive HD IL2 at 600,000 IU/kg IV every 8 hours for up to 14 doses. This constitutes one cycle of IL2.

2. Each course consists of 2 cycles of HD IL2 as follows: high-dose IL2 at 600,000 IU/kg is given IV every 8 hours for up to 14 doses (one cycle), followed by a rest period of 1-2 weeks and readmission for a second HD IL2 cycle for up to 14 doses (2nd cycle).
3. Based on the occurrence of treatment-related toxicities and requirements for dose adjustments or delays, a patient may or may not receive the full planned treatment, but response assessment will continue to be carried out at the end of each course.

The planned treatment consists of 3 courses (6 cycles) of HD IL-2. Response assessment will occur at the end of each course of therapy and patients without evidence of disease progression (RECIST v.1.1) or limiting toxicities will be offered additional courses of treatment of HD IL2 for a maximum of 3 courses.

	Course of HD IL2*							
	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8
HD IL-2 600,000 U/kg/dose IV Q8h x 5 days (max 14 doses)	X		X					
Response Assessment								X

*Local variations are allowed as per local site standard practice, patient recovery from adverse events and scheduling requirements.

Patients will receive HD IL-2 following the institutional standard of care guidelines. Patients will receive a maximum of 3 courses (6 cycles; 1 course of IL2 = 2 cycles of IL2). Response assessment will be carried out at the end of each course. In the absence of disease progression by RECIST v.1.1, patients will be offered additional courses of therapy for a maximum of 3 courses (6 cycles).

Research biospecimens will be collected at the multiple time points as noted in section 8.1.1.

5.2. Aldesleukin (Interleukin-2) Administration

Aldesleukin (Interleukin-2, IL-2) will be administered on an inpatient basis. Reported adverse events and potential risks for aldesleukin are described in Section 7.

- Patients will receive a total of 6 cycles (1 cycle = 5 days) of IL-2 as described in section 5.1. A cycle of IL-2 may be delayed for up to 2 weeks in case of unresolved toxicity.

- Aldesleukin will be administered at 600,000 IU/kg IV bolus q 8 hours during

days 1-5 of each cycle (maximum 14 doses per 5 day cycle).

- As all institutions participating in this protocol have established and experienced high dose interleukin-2 programs, the administration of aldesleukin (at the protocol's specified dose and frequency) and the dose delay/discontinuation criteria during a cycle of IL-2 will follow the institutional standard of care guidelines. Useful guides are provided by:
    - Schwartzentruber DJ. J Immunother. 2001 Jul-Aug;24(4):287-93[20].
    - Janice P Dutcher, Douglas J Schwartzentruber, Howard L Kaufman, Sanjiv S Agarwala, Ahmad A Tarhini, James N Lowder and Michael B Atkins. High Dose Interleukin-2 (Aldesleukin) - Expert Consensus on Best Management Practices—2014. Journal for Immunotherapy of Cancer 2014, 2:26 (16 September 2014).

5.3. General Concomitant Medication and Supportive Care Guidelines

Concomitant medications should be kept to a minimum during the study. However, if these are considered necessary for the patient's welfare and are unlikely to interfere with the investigational products, they may be given at the discretion of the investigator and recorded in the CRF.

5.4. Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for per study protocol until one of the following criteria applies:

X Disease progression,

X Intercurrent illness that prevents further administration of treatment,

X Unacceptable adverse events(s),

X Patient decides to withdraw from the study, or

X General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

X Subject non-compliance if deemed severe enough to impact the quality of the data collected. Such cases must be discussed between the local physician investigator and study chair.

5.5. Duration of Follow Up

Patients will be followed for 5 years after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. The frequency and the type of evaluations during this follow up period will follow the Study Calendar. For patients who complete the study procedures wish not to have long term follow up with a study investigator, they can be followed by their treating physician of choice and also following local standard of care practices. Data on disease progression and survival for these patients during long term follow up will be collected on all patients every 3-6 months.

6. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 6.1) and the characteristics of an observed AE (Section 6.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

6.1. Interleukin-2 Adverse Event Summary List

The following AE list was adapted from the Comprehensive Adverse Event and Potential Risks list (CAEPR) for IL2 and provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system.

Adverse Events with Possible Relationship to Interleukin-2 (CTCAE 4.0 Term)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS	
	Anemia
CARDIAC DISORDERS	
	Conduction disorder
	Left ventricular systolic dysfunction
	Myocardial infarction
	Myocarditis
	Palpitations
	Sinus tachycardia
	Supraventricular tachycardia
	Ventricular arrhythmia
EAR AND LABYRINTH DISORDERS	
	Hearing impaired

EYE DISORDERS	
	Blurred vision
GASTROINTESTINAL DISORDERS	
	Abdominal pain
	Diarrhea
	Dry mouth
	Gastrointestinal disorders - Other (Perforation, GI – Select)
	Gastrointestinal disorders - Other (small bowel fistula)
	Mucositis oral
	Nausea
	Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
	Chills
	Edema limbs
	Fatigue
	Fever
IMMUNE SYSTEM DISORDERS	
	Allergic reaction
	Autoimmune disorder
INFECTIONS AND INFESTATIONS	
	Infections and Infestations – Other (Infection – Select)
INVESTIGATIONS	
	Activated partial thromboplastin time prolonged
	Alanine aminotransferase increased
	Alkaline phosphatase increased
	Aspartate aminotransferase increased
	Blood bilirubin increased
	Creatinine increased
	GGT increased
	INR increased
	Lymphocyte count decreased
	Platelet count decreased
	Weight gain
	White blood cell decreased
METABOLISM AND NUTRITION DISORDERS	
	Acidosis

	Anorexia
	Hyperuricemia
	Hypocalcemia
	Hypoglycemia
	Hypomagnesemia
	Hyponatremia
	Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	
	Arthralgia
	Myalgia
	Myositis
NERVOUS SYSTEM DISORDERS	
	Depressed level of consciousness
	Dizziness
	Headache
	Memory impairment
	Nervous system disorders - Other (sleep disturbances)
	Peripheral sensory neuropathy
	Seizure
PSYCHIATRIC DISORDERS	
	Anxiety
	Confusion
	Personality change
	Psychosis
RENAL AND URINARY DISORDERS	
	Acute kidney injury
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
	Adult respiratory distress syndrome
	Allergic rhinitis
	Apnea
	Cough
	Dyspnea
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	
	Alopecia
	Pruritus
	Rash maculo-papular
VASCULAR DISORDERS	
	Capillary leak syndrome

	Hypotension
	Peripheral ischemia
	Thromboembolic event
	Vascular disorders - Other (vasodilation)

Also reported on interleukin-2 trials but with the relationship to interleukin-2 still undetermined:

CARDIAC DISORDERS - Mobitz type I; Pericardial effusion
EYE DISORDERS - Eye disorders - Other (mydriasis)
GASTROINTESTINAL DISORDERS - Gastrointestinal disorders – Other (Hemorrhage, GI – Select); Pancreatitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - General disorders and administration site conditions - Other (phospholipid syndrome); Hypothermia; Multi-organ failure
INFECTIONS AND INFESTATIONS – Infections and infestations – Other (Infection (documented clinically or microbiologically with Grade 3 or 4 neutrophils [ANC <1.0 x 10e9/L]) – Select)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Soft tissue necrosis lower limb
NERVOUS SYSTEM DISORDERS - Encephalopathy; Syncope
PSYCHIATRIC DISORDERS - Agitation
RENAL AND URINARY DISORDERS - Renal and urinary disorders - Other (acute tubular necrosis)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Bronchospasm; Hypoxia; Pneumothorax; Pulmonary edema
VASCULAR DISORDERS – Phlebitis, splenic infarction (in a patient with a history of thrombocytosis treated with the combination of IL2 and aflibercept).

Note: Interleukin-2 in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

6.2. Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

- **'Expectedness'**: AEs can be 'Unexpected' or 'Expected' for expedited reporting purposes only. 'Expected' AEs are those found in Section 6.1 above or in the Aldesleukin package insert as per the standard of care.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

6.3. Expedited Adverse Event Reporting

6.3.1. Expedited Reporting Guidelines – Reporting Requirements for Adverse Events that occur within **30 Days** of the Last Dose of IL-2 on this trial will adopt the following guidelines:

Phase 2 and 3 Trials									
	Grade 1	Grade 2	Grade 2	Grade 3 and 4		Grade 3 and 4		Grades 5	Grades 5
				Unexpected		Expected			
	Unexpected and Expected	Unex-pected	Expected	with Hospitali-zation	without Hospitali-zation	with Hospitali-zation	without Hospitali-zation	Unex-pected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	Not Required	Not Required	10 Calendar Days	10 Calendar Days	Not Required	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE within 24 hours of learning of the event followed by a complete report within 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

6.3.2 Expedited Reporting Procedure

If the criteria for expedited reporting are met, the Coordinating Center and the local institutional review board (per institutional reporting requirements) will be notified using the departmental SAE form.

All events meeting the criteria for expedited reporting should be recorded on the departmental SAE form and submitted to:

1. Study Chair: tarhiniaa@upmc.edu
2. Study Chair Liaison: kennaj@UPMC.EDU
3. Coordinating Center: Melanoma_Team@upmc.edu and CRSSafetySubmissions@upmc.edu
4. Local Institutional Review Board per institutional reporting requirements

In addition to completing appropriate patient demographic and suspect medication information, the report should include as applicable the following information that is available at the time of report within the Narrative (Section C) on the departmental SAE form:

- CTCAE term(s) and grade(s)
- current status of study drug
- all interventions to address the AE (testing and result, treatment and response)
- hospitalization and/or discharge dates
- event relationship to study drug

Follow-up reports:
Additional information may be added to a previously submitted report by adding to the original departmental SAE form and submitting it as follow-up.

6.4 Data and Safety Monitoring Plan

Investigator/Sub-investigators, regulatory, CRS management, clinical research coordinators, clinical research associates, data managers, and clinic staff meet monthly in disease center Data Safety Monitoring Boards (DSMB) to review and discuss study data to include, but not limited to, the following:

serious adverse events
subject safety issues
recruitment issues
accrual
protocol deviations
unanticipated problems
breaches of confidentiality

All toxicities encountered during the study will be evaluated on an ongoing basis according to the NCI Common Toxicity Criteria version 4.0. All study treatment associated adverse events that are serious, at least possibly related and unexpected will be reported to the IRB. Any modifications necessary to ensure subject safety and decisions to continue, or close the trial to accrual are also discussed during these meetings. If any literature becomes available which changes the risk/benefit ratio or suggests that conducting the trial is no longer ethical, the IRB will be notified in the form of an Unanticipated Problem submission and the study may be terminated.

All study data reviewed and discussed during these meetings will be kept confidential. Any breach in subject confidentiality will be reported to the IRB in the form of an Unanticipated Problem submission. The summaries of these meetings are forwarded to the UPCI DSMC which also meets

monthly following a designated format.

For all research protocols, there will be a commitment to comply with the IRB's policies for reporting unanticipated problems involving risk to subjects or others (including adverse events). DSMC progress reports, to include a summary of all serious adverse events and modifications, and approval will be submitted to the IRB at the time of renewal.

Protocols with subjects in long-term (survival) follow-up or protocols in data analysis only, will be reviewed twice a year rather than monthly by the disease center DSMB.

Both the UPCI DSMC as well as the individual disease center DSMB have the authority to suspend accrual or further investigate treatment on any trial based on information discussed at these meetings.

All records related to this research study will be stored in a locked environment. Only the researchers affiliated with the research study and their staff will have access to the research records.

7. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the commercial agent administered in this study can be found in Section 6.1.

7.1. Commercial Agents

7.1.1. Interleukin-2

Other Names: Aldesleukin, IL-2, rlL-2, T-cell growth factor

Classification: Biological response modifier

Mode of Action: Endogenous substance secreted by OK-T4 cells and lymphocytes. Enhances primary and secondary cytotoxic T-cell responses, causes T-cell mitogenesis and proliferation, and enhances non-killer cell activity.

Storage and Stability: Intact vials are stored in the refrigerator (2-8°C) with protection from light. Each vial bears an expiration date.

Reconstituted IL-2 should be further diluted with 5% Dextrose, USP. It is not to be mixed with saline-containing solutions. Reconstituted IL-2 may be diluted as necessary in volumes of 50 ml to 500 ml with 5% Dextrose, USP plus 0.1% Albumin Human, USP. When diluting, the Albumin Human, USP should be added to the 5% Dextrose Injection, USP prior to the addition of the IL-2. When diluted for IV administration in 5% Dextrose Injection, USP, a plastic bag (e.g., Viaflex, manufactured by Travenol Laboratories, Inc.) containing 0.1% Albumin Human. IL-2 is chemically stable for 48 hours at refrigerated and room temperatures, 2-30°C.

Dose Specifics: Interleukin-2 600,000 MIU/kg/dose or 720,000 MIU/kg/dose over 15 minute IV infusion every 8 hours on Days 1-5 of each cycle for a maximum of 14 doses. For the purpose of this study, interleukin-2 will be given at 600,000 MIU/kg.

Preparation: Aseptically inject 1.2 ml of sterile water for injection into the vial to dissolve the lyophilized cake. Since contents of the vial are under vacuum, the diluent should be directed against the sides of the vial to avoid excess foaming. Remove flip-off plastic cap and swab the target area of the stopper with antiseptic.

Administration: For sterility considerations, the reconstituted IL-2 should be administered immediately or held at 2-8°C for up to 12 hours in 1.2 ml of sterile water for injection, and is stable for at least 24 hours at room temperature.

Incompatibilities: Incompatible with normal saline (results in a precipitate). It should not be mixed with anything except D5W and sterile water.

Availability: IL-2 is a FDA approved therapy for melanoma and is commercially available.

Toxicity: See section 6.1.

For more information please refer to the drug's package insert.

8. CORRELATIVE/SPECIAL STUDIES

8.1. Laboratory Correlative Studies

Correlatives studies will be done, utilizing research samples collected on this study that will primarily focus on biomarkers of prognosis or prediction of therapeutic benefit based on current or future scientific evidence.

8.1.1. Collection of Specimens

Blood specimens will be collected for the purpose of laboratory corollary studies as follows:

Table. Blood sample Collection

Course 1	Red Top Tubes[2]	Green Top Tubes[3]	PAX tubes[4]	Yellow Top Tube[5]
Baseline[1]	3	10	1	1
Cycle 2 of IL-2, within 1-3 weeks after the last dose of IL-2	3	10	1	none

Course 2/3				
Cycle 2 of IL-2, within 1-3 weeks after the last dose of IL-2	3	10	1	none
Month 12	3	10	1	none
Progression	3	10	1	none
1. Baseline: within 2 weeks of the first dose of IL-2. 2. 10 cc RED top tubes (BDcat #367820 or SST 367988 gel separator/gold top/ tiger tubes if the center can centrifuge them) 3. 10 cc GREEN top tubes (BD cat # 366480) 4. PAX tube (Fisher #23 021 01) 5. 10 cc YELLOW top tube. (BD cat # 364606)				

Transfer or, if applicable, ship blood samples by overnight courier Monday-Thursday only to:

Immunologic Monitoring and Cellular Products Laboratory
University of Pittsburgh Cancer Institute
UPCI-IMCPL, Suite 1.26
Study Coordinator
Hillman Cancer Center
5117 Centre Avenue
Pittsburgh, PA 15213
Tel: (412) 624-0078
FAX: (412) 623-6625

Please submit the Specimen Submission Form (template to be provided separately) for each sample sent.

Notify the IMCPL study coordinator by fax (412-623-6625) when the samples are shipped. If you are unable to get through to the laboratory by fax, telephone the study coordinator and provide the tracking number.

The IMCPL has a great deal of experience in shipment and handling of blood, tumor and lymph node samples. The IMCPL provides contact information and a fax request form to the sites, and when a patient is scheduled, a tissue sample kit is shipped (generally via ground) to the site, containing all necessary blood tubes, tumor containers (containing sterile medium) sample instructions as well as return overnight shipping instructions. Upon receipt in the laboratory, the blood and tissue samples are logged in a processed according to the protocol-specific SOPs. Samples which are compromised (hemolyzed or which arrived more than 48 hours after draw/isolation) are discarded (currently less than 2% of >750 samples which arrive at the laboratory annually from ECOG-ACRIN sites).

Pathology Specimen Submissions for Banking for Research Studies (at baseline, then at disease progression):

- Primary Melanoma (for patients with known primary cutaneous melanoma)

  Fifteen (15) unstained slides preferably from the thickest portion of the tumor for immunostains (please do not deparaffinise slides) OR, if the primary pathologist is willing, please request the corresponding block, which will be promptly returned upon request. If the patient has more than one primary lesion, please include above slides and/or block for each primary.

- Resected in-transit or satellite metastases, or cutaneous metastases, or lymph node metastases, or lung metastases

  Fifteen to twenty (15-20) unstained slides from the thickest part of the tumor or, if the primary pathologist is willing, please request the corresponding block, which will be promptly returned upon request.

NOTE: Please provide a surgical pathology report to accompany the slides.

- Progression/Relapse Biopsy (if performed, for banking for future research)

  Fifteen to twenty (15-20) unstained slides from the thickest part of the tumor or, if the primary pathologist is willing, please request the corresponding block, which will be promptly returned upon request.

Please transfer or, if applicable, ship to the IMCPL, as noted above. For shipping, regular mail may be used for these tissue samples OR these may be included in the same package with the blood samples shipped by overnight courier. Also please notify the IMCPL study coordinator as noted above.

NOTE: Patients who do not have archival tumor (as part of a standard of care procedure) available for research at baseline or at progression will be asked whether they are willing to provide a biopsy for research in case they have an accessible tumor for a punch biopsy in clinic.

8.1.2. Banking of Specimens for Future Laboratory Corollary Studies

Specimens will be banked and laboratory corollary studies will be conducted based on the availability of specimens and funding.

9. STUDY CALENDAR

Study investigators should follow the local institutional standard of care guidelines for safety monitoring and safety laboratory testing. Baseline evaluations are to be conducted within 2 weeks prior to administration of HD IL2, unless indicated otherwise, elsewhere in the protocol. Scans and X-rays must be done not more than 28 days prior to the start of HD IL2. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of IL2.

Course 1	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Off Study[f]
Interleukin-2[a]		X		X						
Informed consent	X									
Demographics	X									
Medical history	X									
Concurrent meds	X	X----------X								
Physical exam	X	X		X						X
Vital signs	X	X		X						
Height	X									
Weight	X	X		X						
Performance status	X	X		X						X
CBC w/diff, plts Urinalysis	X	X		X						X
Serum chemistry	X	X		X						X
PT/INR	X									
Cardiac stress test[b]	X									
PFTs[c]	X									
Adverse event evaluation		X ----------X								
Tumor measurements	X								X	X
Radiologic evaluation[d]	X								X	X
B-HCG[e]	X									
Research Biospecimen	See Section 8.1.1									

a: IL-2: 600,000 U/kg/dose IV Q8h x 5 days (max 14 doses) starting on day 1 of weeks 1 and 3. An IL-2 cycle may be delayed until the resolution of limiting toxicities.

b: Patients who are over 40 years old or have had previous myocardial infarction greater than 6 months prior to study entry or have significant cardiac family history (CAD or serious arrhythmias) will be required to have a negative or low probability cardiac stress test (thallium stress test, stress MUGA or exercise stress test) for cardiac ischemia within 8 weeks prior to registration. Patients who are not required to have a cardiac stress test should have an electrocardiogram at baseline to be reviewed by the treating physician investigator. Patients who undergo echocardiography as part of their cardiac stress test are not required to have a separate baseline echocardiogram.

c: Pulmonary function tests (PFTs) are required for patients over 50 years old or with significant pulmonary or smoking history. PFTs may be done up to 4 weeks prior to registration.

d: Radiologic evaluation should include MRI or contrast CT of the brain at baseline and may be repeated at later time points as clinically indicated.

e: Serum pregnancy test (women of childbearing potential).

f. Off study evaluation. Patients will be followed for 5 years after removal from study or until death, whichever occurs first. The frequency and the type of evaluations during this follow up period will follow institutional standard of care practices. For patients who wish not to follow with a study investigator, they can be followed by their treating physician of choice and also following local standard of care practices. Data on disease progression and survival will be collected on all patients every 3-6 months.

For the purposes of this study, patients should be reevaluated for response at the end of each course 1 (8 weeks -/+ 1 week). Following completion of treatment, and in the absence of disease progression will be done every 12 weeks -/+ 2week during the observation phase for the first 2 years, then every 6 months (-/+ 2 weeks) for years 3-5, then yearly (-/+ 4 weeks) afterwards.

MRI or contrast CT of the brain is not required but should be done as clinically indicated. For those subjects who have progressed, Data on survival will be collected on all patients every 6months for 5 years.

10. MEASUREMENT OF EFFECT

10.1. Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be reevaluated for response as noted in Section 9.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST v1.1) Committee, version 1.1[Eur J Cancer, 2009. **45**(2): p. 228-47.]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. See Eisenhauer et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

10.1.1. Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first protocol drug administration.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least course 1 of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of course 1 will also be considered evaluable.)

10.1.2. Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

10.1.3. Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression (or death if there is no progression date). Patients with neither a progression date nor date of death will be censored as of last contact.

11. STATISTICAL CONSIDERATIONS

11.1. Study Design/Endpoints

This is a phase II study of high dose bolus interleukin-2 (HD IL2) in patients with advanced inoperable stage III or stage IV melanoma who have prior anti-PD1 immunotherapy. The safety of HD IL2 is well studied and will be monitored. The focus of the study is to evaluate the efficacy of this HD IL-2 in this specific patient population.

The primary endpoint is (CR+PR) as assessed by RECIST criteria version 1.1. The total accrual goal is 45 patients. We will follow a Bayesian design to establish sequential stopping rules for futility (Thall, Simon and Estey 1995). The expected response rate for this patient population is between 5 and 10%. We would consider the HD IL-2 worth further investigation if a response rate of 20% is achieved. Thus, if there is sufficient evidence that the response rate of the regiment is 7% or less, we will stop the accrual. Let p_0 and p_1 denote the response rate of the standard treatment and the HD IL-2 respectively, by sufficient evidence, we mean that the posterior probability, $\Pr(p_0 + 0.05 > p_1)$, exceeds 85%. Based on the existing data, it is safe to say that the response rate of the studied population under standard care is between 5 and 10%, therefore, we use a Beta(70,930) prior for the standard treatment, which corresponds to a distribution of the response rate centered at 7%. We set a flat prior, Beta(0.4,1.6), for the response rate of HD IL-2.

We will allow the accrual to continue without interruption for the first 10 patients. The stopping boundaries for futility after the "burning period" can be presented as tables of possible outcomes for efficacy as shown in the following table:

Table 1 Bayesian Stopping Rules

Stop the Accrual to if	
Responses<=	in No. Pts
1	10-19
2	20-31
3	32-44
4	45

The operating characteristics of this design can expressed in terms of the probability of

stopping the study early when the regimen is effective (i.e. response rate>0.2) and ineffective (i.e. response rate<0.07) and the median sample size under each situation. The following table summarizes this probability and the median sample size under this design based on 10,000 simulations of hypothetical trials
under different assumptions of true response rates.

Table 2 Frequentist Properties of the Stopping Rules

True Response Rate	Pr (Stop Early)	Median Sample Size
0.05	0.92	17.7
0.1	0.35	27.9
0.15	0.32	35.6
0.2	0.16	40.2
0.25	0.07	42.6
0.3	0.03	43.9

We used MultcLean software for the design of this trial.
(http://biostatitics.mdanderson.org/SoftwareDownload/)

11.2. Sample Size/Accrual Rate

We plan 12-15 months of accrual for 45 patients (approximately 3-4 patients per month) and a minimum of 6 months follow-up.

Evaluable patients include study subjects who received at least one cycle of HD IL-2 and had later formal imaging and clinical assessment of tumor response to treatment and those who failed to return for imaging because of cancer specific death or clinical determination of progression. Non-evaluable subjects will be replaced.

With 45 evaluable subjects, we will have >90% power to declare a significant difference between an response rate of 20% or higher and 7% (the expected response rate of this population under standard care) by a 1-sided exact binomial test (α=0.1).

11.3. Statistical Analyses

The study will be analyzed 6 months after the accrual is finished.

11.3.1. Analysis Sets

Safety population-the data from all patients who received initial treatment of HD IL-2 will be used in the analyses of regimen safety.

Efficacy population- data from patients received at least one cycle of HD IL-2 will be used in the analysis of PFS and OS. For response rate, patients failed to return for

imaging due to reasons **other than** cancer-specific death or clinical determination of progression will not be included.

11.3.2. **Baseline Characteristics**

Baseline descriptive statistics will be provided for all evaluable patients. Statistical summaries will be reported for demographic variables (age, sex, race/ethnicity), performance status, laboratory parameters, and disease characteristics.

11.3.3. **Analysis of Clinical Response**

All patients included in the study will be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

All of the patients who met the eligibility criteria and completed at least one cycle of IL2 should be included in the main analysis of the response rate. Response rate will e estimated by the proportion of patients with a best response of complete response (CR), partial response (PR) by RECIST criteria, with corresponding exact 90% confidence limits being reported. The distribution of response duration (time to progression among patients achieving CR or PR) will be characterized by median and quartiles, with the corresponding Kaplan-Meier estimate being made of PFS among patients responding to treatment.

11.3.4. **Survival**

PFS will be measured from the initial date of treatment to the date of documented progression, or the date of death (in the absence of progression).
OS will be measured from the initial date of treatment to the recorded date of death.
PFS and OS will be estimated by the Kaplan-Meier method. The corresponding median survival times (with 90% confidence limits) will be determined, as will the cumulative percentage of patients remaining progression-free (and the cumulative percentage- alive) at selected time points after initial treatment (e.g., 3, 6,12, 18 months).

11.3.5. **Safety**

Toxicity will be primarily evaluated by examining the number of doses of HD IL-2 administered during a cycle of therapy. Based on previous experience with high dose IL2 at the University of Pittsburgh, the median number of doses per course 1 (first 2 cycles) as monotherapy [16], is 16 (range 8-26) and in sequential combination with temozolomide [21], is 15 (range 7-23). As a result, the median number of doses per course 1 will be considered in addition to toxicity reported via CTCAE criteria.

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APPENDIX A – Performance Status Criteria

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