# High Dose IL-2 in Combination with anti-PD-1 to Overcome anti-PD-1 Resistance inMetastatic Melanoma and Renal Cell Carcinoma

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# High Dose IL-2 in Combination with anti-PD-1 to Overcome anti-PD-1 Resistance in Metastatic Melanoma and Renal Cell Carcinoma


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**IND Holder Name:** Gregory Daniels, MD, PhD

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## Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

**UCSD Principal Investigator**

Gregory Daniels, MD, PhD

Printed Name

Signature Date

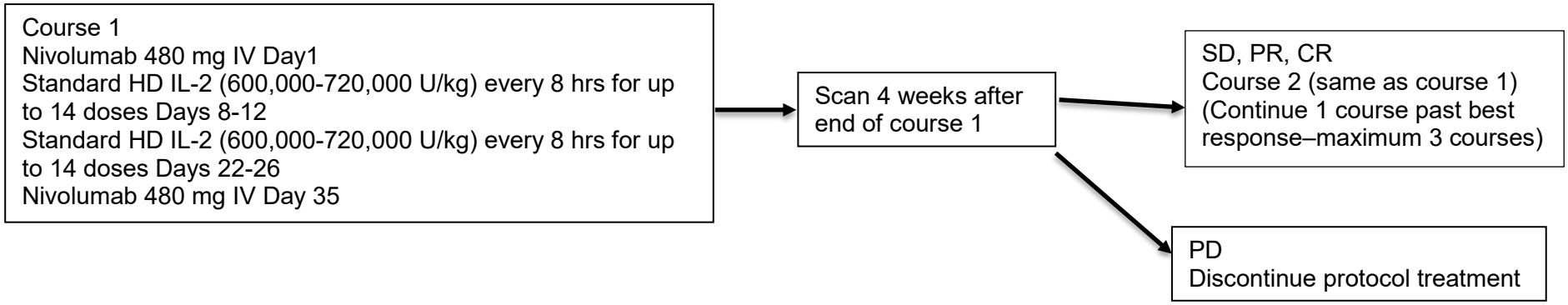
## TABLE OF CONTENTS

**LIST OF ABBREVIATIONS**

| | |
|---|---|
| AE | Adverse Event |
| ALT | Alanine Aminotransferase |
| aPTT | Activated Partial Thromboplastin Time |
| AST | Aspartate Aminotransferase |
| BUN | Blood Urea Nitrogen |
| CBC | Complete Blood Count |
| CMP | Comprehensive Metabolic Panel |
| CNS | Central Nervous System |
| CR | Complete Response |
| CT | Computed Tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DC | Dendritic Cell |
| DSMB | Data and Safety Monitoring Board |
| ECOG | Eastern Cooperative Oncology Group |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| HIPAA | Health Insurance Portability and Accountability Act |
| HRPP | Human Research Protections Program |
| ICH | International Conference on Harmonization |
| IHC | Immunohistochemistry |
| IRB | Institutional Review Board |
| I.V. | Intravenous |
| IVF | I.V. Fluids |
| LDH | Lactate Dehydrogenase |
| MRI | Magnetic Resonance Imaging |
| NCI | National Cancer Institute |
| ORR | Overall Response Rate |
| OS | Overall Survival |
| PD | Progressive Disease |
| PET | Positron Emission Tomography |
| PBMCs | Peripheral Blood Mononuclear Cells |
| PR | Partial Response |
| PT | Prothrombin Time |
| RCC | Renal Cell Carcinoma |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| SAE | Serious Adverse Event |
| SD | Stable Disease |
| SGOT | Serum Glutamic Oxaloacetic Transaminase |
| SPGT | Serum Glutamic Pyruvic Transaminase |
| TSH | Thyroid Stimulating Hormone |
| UA | Urinalysis |

| | |
|---|---|
| ULN | Upper Limit of Normal |
| UPR | Unanticipated Problems involving Risk to subjects or others |

**STUDY SCHEMA**




**These are recommended dosing dates. Nivolumab must be between 1-14 days before initiation of HD IL2 and 1-14 days after discharge from hospital. Scans should be 4-6 weeks after second nivolumab dose in the course. Nivolumab for next course should be administered within 2 weeks of completing scans.

**STUDY SUMMARY**

| | |
|---|---|
| Title | High Dose IL-2 in Combination with anti-PD-1 to Overcome anti-PD-1 Resistance in Metastatic Melanoma and Renal Cell Carcinoma |
| Short Title | HD IL-2 with anti-PD-1 for melanoma and renal cell carcinoma |
| Phase | Phase II |
| Methodology | Single arm 2-stage Phase II Simon design |
| Study Duration | 48 months |
| Study Center(s) | Single Center |
| Objectives | **Primary Objective**<br>Determine the overall response rate (complete response and partial response) for patients receiving anti-PD-1 (nivolumab) and high dose IL-2 (HD IL-2) in subjects with metastatic melanoma or renal cell carcinoma who have previously progressed on anti-PD-1 therapy. Response assessment will be performed using revised RECIST guideline (v 1.1).<br><br>**Secondary Objectives**<br>• Characterize safety, tolerability and adverse effects (AE) profile of nivolumab with HD IL-2 in subjects with metastatic malignant melanoma or renal cell carcinoma<br>• Measure Progression-Free Survival (PFS) using RECIST 1.1 after completion of at least one course of therapy (2 doses of nivolumab, 2 cycles of HD IL-2) for subjects enrolled in the study.<br><br>**Exploratory Objectives**<br>• Correlate PD-L1 expression and tumor mutational burden (TMB) in archived diagnostic tumor tissue with best clinical response for subjects with metastatic melanoma and renal cell carcinoma<br>• Correlate myeloid-derived suppressor cells and T-cell subsets in peripheral blood during therapy with best clinical response (RECIST criteria) and treatment outcome in subjects with metastatic melanoma or renal cell carcinoma. Data will be collected prior to each treatment and after each course of treatment. |
| Number of Subjects | N = Up to 25 subjects |
| Diagnosis and Main Inclusion Criteria | 1. Age ≥ 18 years at the time of consent.<br>2. At least 6 weeks of prior anti-PD-1/anti-PD-L1 therapy with documented clinical or radiographic progression. Last anti-PD-1/anti-PD-L1 therapy must be within 6 months of enrollment. |

| | |
|---|---|
| | 3. Histologically-confirmed diagnosis of unresectable stage III or metastatic (stage IV) melanoma or renal cell carcinoma<br>4. Measurable disease, defined as at least 1 tumor that fulfills the criteria for a target lesion according to RECIST 1.1 (Section 9), and obtained by imaging within 28 days prior to registration for protocol therapy.<br>5. Has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 within 28 days prior to registration for protocol therapy.<br>6. Adequate hepatic function within 28 days prior to registration for protocol therapy defined as meeting all of the following criteria:<br>i. total bilirubin ≤ 1.5 × upper limit of normal (ULN) **OR** direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 x ULN (except in patients with Gilbert's syndrome who must have a total bilirubin less than 3.0 mg/dl.)<br>ii. and aspartate aminotransferase (AST) ≤ 2.5 × ULN or ≤ 5 × ULN for subjects with known hepatic metastases<br>iii. and alanine aminotransferase (ALT) ≤ 2.5 × ULN or ≤ 5 × ULN for subjects with known hepatic metastases<br>7. Adequate renal function within 28 days prior to registration for protocol therapy defined by either of the following criteria:<br>i. Serum creatinine ≤ 1.5 mg/dL<br>ii. **OR** if serum creatinine > 1.5 mg/dL, estimated glomerular filtration rate (GFR) ≥ 50 mL/min<br>8. Adequate hematologic function within 28 days prior to registration for protocol therapy defined as meeting all of the following criteria:<br>i. hemoglobin ≥ 9.0 g/dL<br>ii. and absolute neutrophil count (ANC) ≥ 1000/L without the support of filgrastim<br>iii. white blood cells (WBC) ≥ 3000/L<br>iv. and platelet count ≥ 100 × $10^9$/L<br>9. Adequate coagulation functioning within 28 days prior to registration for protocol therapy defined by either of the following criteria:<br>i. INR < 1.5 × ULN<br>ii. **OR** for subjects receiving warfarin or LMWH, the subjects must, in the investigator's opinion, be clinically stable with no evidence of active bleeding while receiving anticoagulant therapy. The INR for these subjects may exceed 1.5 × ULN if that is the goal of anticoagulant therapy. |

| | |
|---|---|
| | 10. Adequate pulmonary and cardiac function for HD IL-2 (will be assessed clinically)<br>11. Female subjects of childbearing potential must have confirmed negative urine or serum pregnancy test prior to drug administration and be willing to use two methods of birth control.<br>12. Male subjects who are not surgically sterile (vasectomy) must agree to use an adequate method of contraception (condoms).<br>13. Subject's toxicities from prior treatments must have recovered to a grade 1 or less (except for toxicities such as alopecia or vitiligo)<br>14. No second active malignancy. |
| Study Product(s), Dose, Route, Regimen | Each course will consist of: nivolumab 480 mg IV day 1; standard high dose interleukin-2 (600,000 to 720,000 units/kg) IV every 8 hours for up to 14 doses on days 8 to 12, then 9 day rest, then HD IL-2 (600,000 to 720,000 units/kg) IV every 8 hours for up to 14 doses on days 22 to 26; nivolumab 480 mg IV day 35; scan 4 weeks after day 35 nivolumab dose.<br>(These are recommended dosing dates. Nivolumab must be between 1-14 days before initiation of HD IL2 and 1-14 days after discharge from hospital. Scans should be 4-6 weeks after second nivolumab dose in the course. Nivolumab for next course should be administered within 2 weeks of completing scans). |
| Duration of administration | One course past best response for up to three courses |
| Reference therapy | None |
| Statistical Methodology | The Simon two-stage design to test the null hypothesis that P ≤ 0.1 versus the alternative that P ≥ 0.3 with 90% power and 0.1 level of significance proceeds as follows. After testing the drug on 16 patients in the first stage, the trial will be terminated if 1 or fewer respond. If the trial goes on to the second stage, a total of 25 patients will be studied. If the total number responding is less than or equal to 4, the drug is rejected. The probability of early termination at stage 1 with a total sample size of 16 is 0.515; the probability of going on to stage 2 with a total sample size of 25 is 0.485. The sample size calculation is conducted using http://cancer.unc.edu/biostatistics/program/ivanova/SimonsTwoStageDesign.aspx (accessed 7/23/18). |

**SCHEDULE OF EVENTS**

| **Procedures** | **Screening Period -28 days** | **Treatment Period** | | | | **Disease assessment** | **End of Treatment** | **Long Term Follow-up** |
|---|---|---|---|---|---|---|---|---|
| | | Nivolumab Course X Day 1 (e) | HD IL-2 Course X Day 8(e) and Day 22 (e) | HD IL-2 Course X Days 8-12, Days 22-26 (daily) (e) | Nivolumab Course X Day 35 (e) | 4 weeks after Nivolumab day 35 (e) | 4-6 weeks post Nivolumab Course Day 35 | Every 3-6 months (d) |
| Clinic Visit (a) | | | | | | | | |
| Informed Consent | X | | | | | | | |
| History (Medical/Oncology) | X | | X | | | | X | X |
| Demographics | X | | | | | | | |
| Eligibility criteria | X | | | | | | | |
| Physical exam | X | X | X | X | X | X | X | X |
| Vital Signs | X | X | X | X | X | X | X | X |
| Height (only collected at screening), weight | X | X | X | X | X | X | X | X |
| Performance status | X | | X | X | | X | X | X |
| Neurological exam | X | | X | X | | X | | |
| Concomitant Medications | X | | X | | | X | | |
| Adverse Events | X | | X | X | | X | | |
| Laboratory Collection (b) | | | | | | | | |
| Pregnancy test (f) | X | | | | | | | |
| Hematology | X | X | X | X | X | | X | |
| Serum Chemistries | X | X | X | X | X | | X | |
| Magnesium, | X | X | X | X | X | | X | |

| **Procedures** | **Screening Period -28 days** | **Treatment Period** | | | | **Disease assessment** | **End of Treatment** | **Long Term Follow-up** |
|---|---|---|---|---|---|---|---|---|
| | | Nivolumab Course X Day 1 (e) | HD IL-2 Course X Day 8(e) and Day 22 (e) | HD IL-2 Course X Days 8-12, Days 22-26 (daily) (e) | Nivolumab Course X Day 35 (e) | 4 weeks after Nivolumab day 35 (e) | 4-6 weeks post Nivolumab Course Day 35 | Every 3-6 months (d) |
| phosphorus | | | | | | | | |
| Liver Enzymes (AST, ALT, Alk. Phosphatase, total and direct bilirubin) | X | X | X | X | X | | X | |
| LDH | X | X | | | X | | | |
| Lipase | X | X | X | | X | | | |
| Amylase | | | | | | | | |
| INR | X | | X | | | | | |
| PT, aPTT | X | | X | | | | | |
| TSH, T4 | X | X | X | | X | | | |
| Urinalysis | X | X | X | | X | | | |
| Biomarker Sampling | X | X | X | | X | X | | |
| Imaging/Scans (c) | | | | | | | | |
| CT or PET-CT scan | X | | | | | X | | X |
| MRI brain | X | | | | | | | |
| Measurement and Photography of visible skin lesions | X | | | | | X | | X |
| ECG | X | | | | | X | | |
| Study Treatment (d) | | | | | | | | |
| Study drug | | X | X | X | X | | | |
| Research Specimens | | | | | | | | |

| **Procedures** | **Screening Period -28 days** | **Treatment Period** | | | | **Disease assessment** | **End of Treatment** | **Long Term Follow-up** |
|---|---|---|---|---|---|---|---|---|
| | | Nivolumab Course X Day 1 (e) | HD IL-2 Course X Day 8(e) and Day 22 (e) | HD IL-2 Course X Days 8-12, Days 22-26 (daily) (e) | Nivolumab Course X Day 35 (e) | 4 weeks after Nivolumab day 35 (e) | 4-6 weeks post Nivolumab Course Day 35 | Every 3-6 months (d) |
| Serum | X | X | X | | X | X | | |
| Tumor Biopsy | X | | | | | | | |
| Patient Reported Outcomes | | | | | | | | |
| Quality of Life Assessment | X | | | | | X | | |

(a) Clinic visit within 24 hours of treatment visits.
(b) Treatment labs may be done up to 72 hours prior to treatment for days 1, 8, and 22.
(c) Procedures need not be repeated if performed during screening within 28 days prior to study Day 1.
(d) Until confirmed progression.
(e) These are recommended dosing dates. Nivolumab must be between 1-14 days before initiation of HD IL2 and 1-14 days after cycle 2. Scans should be 4-6 weeks **after** second nivolumab dose day 35. Nivolumab for next course should be administered within 2 weeks of completing scans.
(f) Pregnancy test for women of childbearing potential only. Definition of non-child bearing potential would be documented as 12 months without menses or surgically sterile.

## 1.0 BACKGROUND AND RATIONALE

### 1.1 Disease Background

The advent of checkpoint inhibitors has led to improved responses in metastatic melanoma and renal cell carcinoma with the potential for cure, however not all patients will respond to checkpoint inhibitors and patients that relapse have limited treatment options. For melanoma, there were still an estimated 9,940 expected deaths in the United States in 2015 [1] and some studies suggest a mean survival of 8–10 months in large cohort analysis [2]. First line treatment with immunotherapy (pembrolizumab, nivolumab, or ipilimumab/nivolumab) is standard of care for metastatic melanoma per National Comprehensive Cancer Network (NCCN) guidelines [3]. For renal cell carcinoma, there were 14,970 deaths in the United States in 2018 and 5 year survival was 11.7% in 2007-2013 [4]. First line systemic treatments include ipilimumab/nivolumab or single agent nivolumab with the option of targeted therapies. However less than 20% of metastatic melanoma and renal cell carcinoma patients will have long-term, durable remissions with these treatments [5-7]. High dose interleukin-2 (HD IL-2) is also recommended as treatment for metastatic renal cell carcinoma and melanoma in selected patients. In renal cell carcinoma, a 31% overall response rate with a 9% complete response rate was observed, while in metastatic melanoma, a 20% response rate was observed with 5% complete response rate [8]. We propose administering anti-PD-1 therapy in combination with HD IL-2 to see if the drugs can provide synergy and improve response rates over single agent therapy.

### 1.2 Study Agents

HD IL-2 was approved in 1992 for metastatic renal cell carcinoma and 1998 for metastatic melanoma. Interleukin-2 is primarily produced by antigen-stimulated CD4 + T helper cells with contributions from CD8 + T cells, natural killer cells, natural killer T cells, and activated dendritic cells [9]. IL-2 induces proliferation of natural killer cells and augments their killing capacity. It also drives proliferation and activation of CD8+ T cells, promotes proliferation of B cells, and upregulates expression of heavy and light chain genes [10]. It can also expand immunosuppressive CD4+ T-regulatory cells and promote activation-induced cell death of overactivated T cells, thus acting as an immunomodulator. A standard high-dose IL-2 protocol involves administration of the high dose IL-2 every 8 hrs for up to 14 doses over a course of 5 days, followed by a 6-9 day rest, and re-administration every 8 hrs for up to 14 days over a course of 5 days. Each course involves two cycles (up to 14 doses per cycle). The doses used are either 600,000 to 720,000 units/kg. At UCSD, we have experience treating more than 100 patients with melanoma or renal cell cancers with a standard protocol utilizing dosing between 600,000 to 720,000 IU/kg. Patient specific dosing is calculated utilizing admission weight x 720,000 IU/kg and then rounding down to the nearest ½ vial size (22mIU/vial). This strategy keeps the dosing within the published literature while also ensuring minimal drug waste per patient. UCSD maintains a database of toxicity, dosing amount and response that has been used as a reference for this protocol development. HD IL-2 has significant toxicities including hypotension, renal insufficiency, and hypoxia, thus is limited to specialized centers and patients with good performance status and organ function [11, 12].

Nivolumab is a monoclonal antibody which is a checkpoint inhibitor against programmed death-1 (PD-1) It is FDA approved for the treatment of metastatic melanoma and renal cell carcinoma as a single agent or in combination with the CTLA-4 inhibitor ipilimumab. It can be administered at a flat dose of 240 mg every 2 weeks or 480 mg every 4 weeks. CheckMate 214, a phase III study of ipilimumab/nivolumab vs. sunitinib in advanced renal-cell carcinoma, demonstrated a 42% response rate and a complete response rate of 9% [5]. Checkmate 025, a phase 3 study of nivolumab vs. everolimus in advanced renal cell carcinoma, showed a 25% response rate with 1% complete response rate [7]. CheckMate 067 was a

phase III study of nivolumab with ipilimumab vs. monotherapy with a 44% response rate with 9% complete responses for nivolumab alone compared to a 58% response rate for ipilimumab/nivolumab and 12% complete response rate [6]. However, patients who progress immediately upon exposure to anti-PD1 therapy (primary resistance) or who initially respond and then progress (acquired resistance) remain a clinical challenge.

### 1.3 Rationale

Patients resistant to PD-1 blockade appear to maintain the same historic response rate seen with HD IL-2 compared to therapy naïve patients (roughly 20%). Several mechanisms likely govern resistance to PD-1 inhibitors including lack of an inflammatory response, other checkpoints, loss of antigen expression and T cell exhaustion. Interleukin 2 can address several of these barriers. During T cell exhaustion, affected cells fail to proliferate and no longer exert necessary functions such as cytokine secretion or cell killing. IL-2 may augment memory T-cells [13] and increase natural killer cells [14]. Targeting the PD-1 pathway has the potential to reverse T cell exhaustion, but is not always effective [15]. In mouse models, administering IL-2 in combination with anti-PD-L1 blockade showed synergistic increasing in antigen-specific CD8 T cell numbers and function [16]. Recent clinical trial data utilizing a pegylated IL-2 formulation suggested improved clinical response when combined with PD-1 inhibition compared to either agent alone. Thus, we hypothesize that combining anti-PD-1 blockade with nivolumab in patients who are resistant to PD-1 therapy with standard HD IL-2 will improve response rates over HD IL-2 alone. We will determine this approach a success if we can double the historical response rate of HD IL-2 in this treatment refractory population.

## 2.0 STUDY OBJECTIVES

### 2.1 Primary Objectives

To determine the overall response rate (complete response and partial response) for patients receiving anti-PD-1 (nivolumab) and high dose IL-2 (HD IL-2) in subjects with metastatic melanoma or renal cell carcinoma who have previously progressed on anti-PD-1 therapy. Response assessment will be performed using RECIST guideline (v 1.1).

### 2.2 Secondary Objectives

- Characterize safety, tolerability and adverse effects (AE) profile of nivolumab with HD IL-2 in subjects with metastatic malignant melanoma or renal cell carcinoma
- Measure Progression-Free Survival (PFS) using RECIST 1.1 after completion of at least one course of therapy (2 doses of nivolumab, 2 cycles of HD IL-2) for subjects enrolled in the study.

### 2.3 Exploratory Objectives

- Correlate PD-L1 expression and tumor mutational burden (TMB) in archived diagnostic tumor tissue with best clinical response for subjects with metastatic melanoma and renal cell carcinoma
- Correlate myeloid-derived suppressor cells and T-cell subsets in peripheral blood during therapy with best clinical response (revised RECIST criteria) and treatment outcome in subjects with stage IV malignant melanoma. Data will be collected prior to each treatment and after each course of therapy.

### 2.4 Endpoints

#### 2.4.1 Primary Endpoint

The primary endpoint will be the response rate [complete response (CR) and partial response (PR)] of combined therapy with nivolumab and HD IL-2 in metastatic melanoma and renal cell carcinoma and will be evaluated using revised RECIST 1.1. Response rate will be computed with associated 95% confidence intervals.

#### 2.4.2 Secondary Endpoints

- Proportion of subjects with each grade of adverse events as defined by CTCAE v 5.0 will be computed. Toxicity will be reported in a tabular and descriptive manner.
- Median PFS times will be calculate and PFS rate at 1 year +/- 3 months will be calculated with associated 95% confidence intervals based on the Kaplan-Meier method.

## 3.0 PATIENT ELIGIBILITY

### 3.1 Inclusion Criteria

Subjects must meet all of the inclusion criteria to participate in this study.

1. Patient has the ability to understand and the willingness to sign a written informed consent.
2. Age ≥ 18 years at the time of consent.
3. At least 6 weeks of prior anti-PD-1/anti-PD-L1 therapy with documented clinical or radiographic progression. Last anti-PD-1/anti-PD-L1 therapy must be within 6 months of enrollment.
4. Histologically-confirmed diagnosis of unresectable stage III or metastatic (stage IV) melanoma or renal cell carcinoma
5. Measurable disease, defined as at least 1 tumor that fulfills the criteria for a target lesion according to RECIST 1.1 (Section 9), and obtained by imaging within 28 days prior to registration for protocol therapy.
6. Has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 within 28 days prior to registration for protocol therapy.
7. Adequate hepatic function within 28 days prior to registration for protocol therapy defined as meeting all of the following criteria:
   i. total bilirubin ≤ 1.5 × upper limit of normal (ULN) **OR**
   direct bilirubin ≤ ULN for subjects with total bilirubin levels
   > 1.5 x ULN (except in patients with Gilbert's syndrome who must have a total bilirubin less than 3.0 mg/dl.)
   ii. and aspartate aminotransferase (AST) ≤ 2.5 × ULN or ≤ 5 × ULN for subjects with known hepatic metastases
   iii. and alanine aminotransferase (ALT) ≤ 2.5 × ULN or ≤ 5 × ULN for subjects with known hepatic metastases
8. Adequate renal function within 28 days prior to registration for protocol therapy defined by either of the following criteria:
   i. Serum creatinine ≤ 1.5 mg/dL
   ii. **OR** if serum creatinine > 1.5 mg/dL, estimated glomerular filtration rate (GFR) ≥ 50 mL/min
9. Adequate hematologic function within 28 days prior to registration for protocol therapy defined as meeting all of the following criteria:
   i. hemoglobin ≥ 9.0 g/dL
   ii. and absolute neutrophil count (ANC) ≥ 1000/L without the support of filgrastim
   iii. white blood cells (WBC) ≥ 3000/L
   iv. and platelet count ≥ $100 \times 10^9$/L
10. Adequate coagulation functioning within 28 days prior to registration for protocol therapy defined by either of the following criteria:
    i. INR < 1.5 × ULN
    ii. **OR** for subjects receiving warfarin or LMWH, the subjects must, in the investigator's opinion, be clinically stable with no evidence of active bleeding while receiving anticoagulant

iii. t therapy. The INR for these subjects may exceed 1.5 × ULN if that is the goal of anticoagulant therapy.

11. Adequate pulmonary and cardiac function for HD IL-2 (will be assessed clinically)
12. Female subjects of childbearing potential must have confirmed negative urine or serum pregnancy test prior to drug administration and be willing to use two methods of birth control.
13. Male subjects who are not surgically sterile (vasectomy) must agree to use an adequate method of contraception (condoms).
14. Subject's toxicities from prior treatments must have recovered to a grade 1 or less (except for toxicities such as alopecia or vitiligo)

### 3.2 Exclusion Criteria

Subjects meeting any of the exclusion criteria at baseline will be excluded from study participation.

1. Active infection requiring systemic therapy
2. Women who are pregnant or breastfeeding.
3. Second active malignancy within the past 5 years with the exception of localized basal or squamous cell skin cancer, in situ cervical or bladder cancer, or localized prostate cancer under active surveillance, or chronic lymphocytic leukemia which has been stable off of therapy for 6 months or more.
4. Active symptomatic central nervous system (CNS) metastases. Prior treated metastases or asymptomatic metastases are allowed. Patient can receive radiation between treatments if deemed medically necessary.
5. Surgery within 4 weeks prior to study treatment except for minor procedures.
6. Uncontrolled or poorly-controlled hypertension (> 160 mmHg systolic or > 100 mmHg diastolic for > 4 weeks) despite standard medical management.
7. Serious or non-healing wounds, ulcers, or bone fractures within 28 days prior to initiation of study treatment.
8. Any arterial thromboembolic events, including but not limited to myocardial infarction, transient ischemic attack, cerebrovascular accident, or unstable angina, within 6 months prior to initiation of study treatment.
9. Has any condition that, in the opinion of the investigator, might jeopardize the safety of the patient or interfere with protocol compliance.
10. Has any mental or medical condition that prevents the patient from giving informed consent or participating in the trial.
11. Known hypersensitivity to nivolumab or IL-2 or any of their components.
12. Known history of active tuberculosis.
13. Concurrent systemic steroid therapy with doses above physiologic level (more than 10 mg of prednisone daily).
14. Active autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with anti-phospholipid syndrome, granulomatosis with polyangiitis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis requiring treatment. Patients cannot be on immunosuppressive medications other than physiologic replacement doses of prednisone (less than 10 mg per day at enrollment) or equivalent steroid. Asymptomatic patients or those stable on non-immunosuppressive

medications are eligible.

15. Treatment with any investigational agent within 21 days prior to initiation of study treatment and the subject must have recovered from the acute toxic effects of the regimen with the exception of prior anti-PD-1.

## 4.0 TREATMENT PLAN

### 4.1 Study Design

The primary objective of this single arm phase 2 trial is to assess the response rate [complete response (CR) + partial response (PR)] of combined nivolumab and HD IL-2 in subjects with metastatic melanoma and renal cell carcinoma. Response will be performed after each course of nivolumab and IL-2 using RECIST 1.1. Patients will be treated for one course past best response for a maximum of 3 courses. The study will include up to 25 patients with metastatic melanoma or renal cell carcinoma.

### 4.2 Treatment Dosage and Administration

Course length will be 35 days. Subjects will receive 480 mg IV of nivolumab on day 1 of the cycle. The patient will be admitted to UCSD Jacobs Medical center for standard HD IL-2 which will be administered every 8 hrs for up to 14 doses days 8-12 per institutional practice. The patient will be readmitted days 22-28 for HD IL-2 every 8 hrs for up to 14 doses. Nivolumab 480 mg IV will be administered day 35. Scans for response will occur 4 weeks after day 35 nivolumab dose and response will be determined by RECIST 1.1 to determine if the patient will receive the next course.

Correlative research analyses include examining the relationship between clinical response after each course of therapy with PD-L1 expression and TMB of the archived diagnostic tumor tissue. Research analyses also include examining the relationship between changes in soluble PD-L1 level, TMB, and T-cell subsets during therapy relative to baseline to the best clinical response (RECIST 1.1 criteria) and to treatment outcome.

| **REGIMEN DESCRIPTION** | | | | | |
|---|---|---|---|---|---|
| **Agent** | **Precautions** | **Dose** | **Route** | **Schedule** | **Course Length** |
| Nivolumab | None | 480 mg | IV over 30 minutes | Day 1**<br>Day 35** | 5 weeks (35 days)** |
| HD IL-2 | See below* | Standard IL-2 dosing (600,000-720,000 U/kg) every 8 hrs for up to 14 doses | IV over 15 minutes; flush IV before and after administration | Days 8-14;**<br>Days 22-26** | |

*Monitoring during therapy includes vital signs every 1 to 2 hours (blood pressure, temperature, heart rate and pulse oximetry), weight and fluid intake and output along with continuous cardiac monitoring. If an abnormal complex or rhythm is seen, an ECG should be performed. Clinical status and laboratory (CBC, CMP, Mg, Phos) will be checked daily to assess for relative and absolute dose stopping criteria per published guidelines. The treating physician should be called prior to each dose to review vital signs, labs, and patient symptoms.
**These are recommended dosing dates. Nivolumab must be between 1-14 days before initiation of HD IL2 and 1-14 days after discharge from hospital. Scans should be 4-6 weeks after second nivolumab dose in the course. Nivolumab for next course should be administered within 2 weeks of completing scans.

### 4.3 Pre-Medications/Supportive Care

Nivolumab:
For patients who experience a Grade 1 or Grade 2 infusion reaction, acetaminophen 650 mg PO and/or 50 mg IV ranitidine (or equivalent H2 antagonist) may be considered prior to subsequent infusions.

HD IL-2:
Subjects should receive appropriate supportive care measures as deemed necessary by the site investigator. Several treatment-related toxicities have been uniquely associated with the administration of HD IL-2. Established guidelines will be followed for safely administering HD-IL-2 and managing toxicities from this treatment [17, 18].

Subjects should receive full supportive care during the study, including transfusion of blood and blood products, treatment with antibiotics, analgesics as appropriate. Acetaminophen at doses of ≤ 4 grams/day is permitted, however it should be used with caution in subjects with impaired liver function. In addition, ibuprofen and ondansetron are administered prior to each dose of interleukin 2. See appendix A for a complete order set listing care directions.

Nivolumab:
Supportive care for nivolumab (prior to HD IL-2 administration) are listed below per package insert:

**Pneumonitis**

- For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
- For guidelines on treatment holds, timing for restarting treatment or discontinuing treatment permanently, see Section 6.1.3, Table 2.

**Diarrhea/Colitis**

- Subjects should be carefully monitored for signs and symptoms of enterocolitis and bowel perforation
- All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
- For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.
- For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- For guidelines on treatment holds, timing for restarting treatment or discontinuing treatment permanently, see Section 6.1.3, Table 2.

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

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

**Hypophysitis**

- For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- For guidelines on treatment holds, timing for restarting treatment or discontinuing treatment permanently, see Section 6.1.3, Table 2.

**Hyperthyroidism or Hypothyroidism**

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

- **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
  - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
  - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.
- **Grade 3-4** hyperthyroidism
  - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For guidelines on treatment holds, timing for restarting treatment or discontinuing treatment permanently, see Section 4.7, Table 2.

**Hepatic**

- For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
  - Treat with IV or oral corticosteroids
- For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.
  - For guidelines on treatment holds, timing for restarting treatment or discontinuing treatment permanently, see Section 6.1.3, Table 2.

**Renal Failure or Nephritis**

- For **Grade 2** events, treat with corticosteroids.
- For **Grade 3-4** events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
  - For guidelines on treatment holds, timing for restarting treatment or discontinuing treatment permanently, see Section 6.1.3, Table 2.

**Management of Infusion Reactions**

- Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.
- See Table 1 in Section 6.1.2, Management of Allergic Reaction/Hypersensitivity, for detailed information on how Grades 1-4 reactions are treated.

### 4.4 Permitted concomitant therapy

Medications required to treat adverse events and manage cancer symptoms, concurrent stable disease (e.g., controlled hypertension) and supportive care agents such as blood transfusion and pain medications are allowed. The patient needs to notify the investigational site about any new medications he/she takes after the start of the study medication. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug must be recorded in the patient's medical record. Radiation therapy for pain or brain metastases may be allowed at discretion of the principal investigator.

### 4.5 Prohibited concomitant therapy

Subjects are prohibited from receiving the following therapies during screening and treatment and the necessary use of these treatments will require removal from the trial:

- Anti-cancer systemic chemotherapy or biological therapy not specified in this protocol
- Immunotherapy not specified in this protocol
- Concomitant use of chemotherapy
- Investigational agents
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest suspected to be immunologic etiology. The use of physiologic doses of corticosteroids is allowed.

### 4.6 Toxicities and Dosing Delays/Dose Modifications

The NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be used to grade adverse events. Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Study Calendar & Evaluations. Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation as specified in Study Calendar & Evaluations.

**Dose Delays for Nivolumab Administration:**

**Start of a New Cycle**

The next nivolumab infusion will be initiated when all of the following conditions are met:

- AST/ALT≤3 times upper limit of normal
- SCR <1.5 times upper limits of normal

If treatment is unable to restart within 2 weeks of the planned treatment date, the subject maybe permanently discontinued from study therapy.

**Management of Hypersensitivity Reaction for Nivolumab prior to HD IL2**

**Table 1: Management of allergic reaction/hypersensitivity based on CTCAE Grade**

| Description | Action |
|---|---|
| **Grade I Allergic Reaction/Hypersensitivity:** (Transient flushing or rash, drug fever < 38°C): | Supervise without further treatment for allergic reaction/hypersensitivity. |
| **Grade 2 Hypersensitivity Reaction:** (Rash, flushing, dyspnea, urticaria, drug fever greater than or equal to 38°C) and/or asymptomatic bronchospasm: | Interrupt the infusion. If symptoms abate, attempt re-infusion at a slower rate. If the symptoms recur, discontinue infusion and follow for recurrent allergic reaction/hypersensitivity in the next paragraph. |
| **Recurrent Grade 2 or Grade 3 or 4 Hypersensitivity Reaction:** | Stop the infusion. Administer additional doses of H1 and H2 blockers intravenously. Administer IV steroids and consider epinephrine and bronchodilators as clinically indicated. |
| **Grade 3 or 4 Hypersensitivity Reaction:** | Will be permanently discontinued from study treatment. |

Prior to re-challenge of Grade 2 allergic reaction/HSR and if there is a subsequent cycle, the following prophylactic premedications are recommended prior to the nivolumab infusion: give both an H1 and H2 blocker intravenously within 30 to 60 minutes before nivolumab infusion. If treatment delay necessitates a period longer than 2 weeks, treatment is stopped and the subject is discontinued from the study.

**Dose Modification for Toxicity**

Adverse events (both non-serious and serious) associated with nivolumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Nivolumab must be withheld for drug- related toxicities and severe or life-threatening AEs as per Table 2 below.

**Table 2: Nivolumab dose modification on day of Nivolumab dosing.**

| Toxicity | Hold Treatment for Grade | Timing for Restarting | Discontinue Subject |
|---|---|---|---|
| Diarrhea/Colitis | 2-3 | Toxicity resolves to Grade 0-1. | Toxicity does not resolve within 2 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 2 weeks. |
| | 4 | Permanently discontinue | Permanently discontinue |
| AST, ALT, or Increased Bilirubin | 2 | Toxicity resolves to Grade 0-1 | Toxicity does not resolve within 2 weeks of last dose. |
| | 3-4 | Permanently discontinue (see | Permanently discontinue |
| Type I diabetes mellitus (if new onset) or Hyperglycemia | T1DM or Grade 3 | Hold nivolumab for new onset Type 1 diabetes mellitus or Grade 3 hyperglycemia associated with evidence of beta cell | Resume nivolumab when patients are clinically and metabolically stable. |
| | Grade 4 | Permanently discontinue | Permanently discontinue |
| Hypophysitis | 2-3 | Toxicity resolves to Grade 0-1 | Toxicity does not resolve within 2 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 2 weeks. |

| Toxicity | Hold Treatment for Grade | Timing for Restarting | Discontinue Subject |
|---|---|---|---|
| | 4 | Permanently discontinue | Permanently discontinue |
| Hyperthyroidism | 3 | Toxicity resolves to Grade 0-1 | Toxicity does not resolve within 2 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 2 weeks. |
| | 4 | Permanently discontinue | Permanently discontinue |
| Hypothyroidism | 2-4 | Therapy with nivolumab can be continued while treatment for the thyroid disorder is instituted | Therapy with nivolumab can be continued while treatment for the thyroid disorder is instituted. |
| | 3-4 | Permanently discontinue | Permanently discontinue |
| Infusion Reaction | 3-4 | Permanently discontinue | Permanently discontinue |
| Pneumonitis | 2 | Toxicity resolves to Grade 0-1 | Toxicity does not resolve within 2 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 2 weeks. |
| | 3-4 | Permanently discontinue | Permanently discontinue |
| Renal Failure or Nephritis | 2 | Toxicity resolves to Grade 0-1 | Toxicity does not resolve within 2 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 2 weeks. |
| | 3-4 | Permanently discontinue | Permanently discontinue |

| Toxicity | Hold Treatment for Grade | Timing for Restarting | Discontinue Subject |
|---|---|---|---|
| All Other Drug- Related Toxicity[2] | 3 or severe | Toxicity resolves to Grade 0-1 | Toxicity does not resolve within 2 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 2 weeks. |
| | 4 | Permanently discontinue | Permanently discontinue |
| **Note: Permanently discontinue for any Grade 3 drug-related AE or any life-threatening event.** 1 Patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by ≥ to 50% relative to baseline and lasts for at least 1 week should be discontinued.<br>2 Patients who experience signs of hepatic encephalopathy or other serious signs of liver impairment such as hepatorenal syndrome must be permanently discontinued from therapy<br>3 Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 | | | |

**Dose Delays for HD IL-2**

**Start of New Cycle**
A new treatment cycle will only be initiated when all of the following conditions are met:

- ANC ≥ 1,500× $10^9$/L
- Platelets ≥ 100 × $10^9$/L
- Non-hematologic treatment related toxicities have improved to ≤ Grade 1 or to the subject's baseline values (except alopecia)

If blood counts are below this threshold (first two bullet points), blood work is to be repeated weekly until counts are at an acceptable level. If treatment is unable to restart within 2 weeks of the planned treatment date, the subject may be permanently discontinued from study therapy.

**IL-2 Administration**
Standard bolus interleukin 2 therapy is administered at a dose between 600,000 IU/kg to 720,000/kg. IL-2 is supplied at 22 million units per vial, therefore, patients will receive the dose within the target range rounded to the nearest half vial.

| Weight (kg) | Interleukin 2 (IU) |
|---|---|
| 61-73 | 44 million |
| 74-91 | 55 million |
| 92-106 | 66 million |
| 107-121 | 77 million |
| 122-above | 88 million |

Interleukin 2 is administered every 8 hours for a maximum of 14 infusions for each course by incorporating relative and absolute stopping guidelines with clinical experience [8]. Doses may be skipped depending on patient tolerance. Doses will be skipped if patients reach grade III or IV toxicity due to IL-2 except for the reversible grade III toxicities common to IL-2 such as diarrhea, nausea, vomiting, medically manageable hypotension, skin changes, anorexia, mucositis, dysphagia, or constitutional symptoms and laboratory changes. If these toxicities can be easily reversed within 8 hours by supportive measures, then additional doses may be given. Additional instances may arise when in the clinical judgment of the attending physician, doses of IL-2 may be skipped or treatment re-started.

No dose reductions of IL-2 are performed. IL-2 doses are delayed according to symptomatic recovery from the previous dose. Delay greater than 8 hours should result in discontinuation of a cycle of IL-2. Up to 2 doses may be held per course.

Guidelines for delay or discontinuation of IL-2 are given below. The presence of relative criteria implies that a patient is nearing the completion of a cycle of therapy but that with appropriate corrective measures or with a time delay to allow for recovery, it may be safe to proceed. Several relative criteria are usually an indication to discontinue dosing. The presence of absolute criteria is generally considered an indication to stop dosing IL-2.

### 4.7 General Concomitant Medication and Supportive Care Guidelines

Patients cannot be on immunosuppressive medications other than physiologic replacement doses of prednisone (less than 10 mg per day at enrollment) or equivalent steroids at the start of the study. For patients with adrenal insufficiency or hypophysitis stress dose steroids will be allowed for HD IL2 administration of up to an equivalent of 25 mg of prednisone daily. If systemic steroids are utilized for acute toxicity, patients will stop dosing for that course. For additional guidelines on treatment holds, timing for restarting treatment or discontinuing treatment permanently, see Section 6.1.3, Table 2.

#### 4.7.1 Treatment Concomitant Medications

4.7.1.1 Keflex 250 mg orally twice daily after PICC insertion. If Penicillin allergy, use Ciprofloxacin 500 mg orally twice daily after PICC insertion.

4.7.1.2 Acetaminophen 650 mg orally/rectally 30 minutes prior to IL-2 and every 4 hours until 12 hours post final dose of IL-2.

4.7.1.3 Ondansetron 8 mg IV 30 minutes prior to each dose of IL-2.

4.7.1.4 Ibuprofen 600 mg orally 30 minutes prior to IL2 admission. Hold if serum creatinine >3 mg/dL.

4.7.1.5 Famotidine 20 mg orally or IV twice daily starting morning of admission.

4.7.1.6 Electrolyte replacement daily per lab values.

4.7.1.7 Magnesium sulfate 2 grams IV in 50 mL D5W over 2 hours PRN serum Mg $\leq$ 1.6 mg/dL.

4.7.1.8 Magnesium sulfate 1 grams IV in 50 mL D5W over 1 hour PRN serum Mg $\leq$ 1.7-1.9 mg/dL.

4.7.1.9 Calcium gluconate 1 gram IV in 50mL D5W over 1 hour PRN serum total Ca <8.
4.7.1.10 Fosaprepitant (150 mg IV Day 1) 30 minutes prior to IL-2 infusion.
4.7.1.11 Calcium 250-300 mg with vitamin D 100 or 200 IU (per institutional formulary) orally every 8 hours given prior to IL-2 infusion.

### 4.7.2 Fluid Replacement

The following guidelines are recommendations, but may be altered at the discretion of the treating physician.

Intravenous fluids (such as normal saline with 0.5 gm/liter Magnesium, 10mEq KCL and 5mEq phosphorus @ 150 per hour) are the initial therapy for hypotension and the goal is to maintain systolic blood pressure greater than 80-90 mmHg. It is common to require additional fluid in the first 24 hours of therapy in response to hypotension and oliguria. After initial resuscitation, most patients reach a steady state of relative hypotension and tachycardia that will be maintained until the final doses of IL-2. No intervention is generally needed for these parameters unless they exceed predetermined guidelines or oliguria ensues.

Fluid replacement of 1-1.5 liters/day above maintenance requirements should not be exceeded because of extravasation and compounding of generalized edema and pulmonary congestion. The use of additional fluids late in the cycle of treatment should be restricted (often with decrease in IVF rate to 75cc/hour on day 3) because the transient benefit they achieve may be overshadowed by the unwanted consequences of fluid leak (special caution must be exercised if body weight is >10% above baseline). Late in therapy (Day 2 or 3), albumin may be helpful to maintain renal perfusion and blood pressure.

If hypotension persists despite judicious fluid resuscitation, vasopressor support with an α agonist such as phenylephrine is indicated. However, use of a vasopressor with the exception of dopamine will lead to termination of IL-2 for that course. The hypotensive effects of each IL-2 dose generally peaks 4-6 hours after infusion and vasopressors are titrated accordingly. Blood pressure measurements generally return to baseline within 24-48 hours of discontinuation of IL-2.

### 4.7.3 Ancillary Medications (as needed)

4.7.3.1. Meperidine 25 mg IV every 15 minutes PRN rigors/severe chills, up to 100 mg/24 hours.
4.7.3.2. Lorazepam 1 mg orally or IV every 6 hours PRN anxiety.
4.7.3.3. Lomotil 2.5 mg orally every 4 hours PRN diarrhea.
4.7.3.4. Lubriderm lotion or Eucerin cream every 2 hours PRN to affected skin.
4.7.3.5. Compazine 10 mg IV every 6 hours PRN nausea and vomiting.

### 4.7.4 Additional Supportive Care for Expected Toxicities

The following guidelines are recommendations, but may be altered at the discretion of the treating physician.

*Expected Toxicity:* The toxicities of IL-2 therapy are thought to result primarily from a capillary leak syndrome (CLS) as well as lymphoid infiltration which have been observed histologically in many organs. The earliest clinical manifestations of CLS are hypotension and tachycardia which can be seen two hours after the first dose of high-dose of IL-2. Decreased systemic vascular resistance has been measured at this time point and contributes to the early drop in blood pressure. Because of these changes, if patients are receiving antihypertensive medications, they should be discontinued prior to initiating high-dose IL-2 (preferably 24 hours prior to admission).

Within the first 8 hours of starting IL-2, decreased urine output is frequent and is a consequence of hypotension and decreased intravascular volume. Renal dysfunction during IL-2 has been described as prerenal in nature, transient, and without evidence of intrinsic renal damage. Oliguria is first treated with fluid boluses; if 1-1.5 liters of crystalloid does not restore urine flow, dopamine at renal perfusion doses (2 µg/kg/min) can be initiated. Catheters should be avoided to minimize infection risk and to promote patient mobility. Urine output greater than 10-20 cc/hour is desired before additional IL-2 dosing can be considered. Serum creatinine levels are measured at least daily and are considered when making decisions about IL-2 dosing.

Patients receiving high-dose IL-2 may experience progressive shortness of breath during therapy which very infrequently requires endotracheal intubation or drainage of a pleural effusion (either would lead to discontinuation of further dosing for that course). The mechanism of pulmonary congestion has been attributed to increased vascular permeability. Incidence of severe toxicity can be low with careful pre-therapy screening of patients who are smokers or have large tumor burdens in the lung ($FEV_1$ and forced vital capacity should be greater than 65% of predicted and PaO2 >75 on room air) to advise smokers to quit 2 weeks before therapy and provide judicious fluid replacement during therapy. The selective monitoring of transcutaneous $O_2$ saturation has been very helpful in patients experiencing pulmonary symptoms. $O_2$ saturation should be maintained above 95% and if this level cannot be met by 4L $O_2$ by nasal cannula or 40% $O_2$ by mask, IL-2 dosing should be discontinued. The auscultation of rales in the lung bases is not infrequent during therapy but progression to the mid lung fields, coupled with marginal $O_2$ saturation, are reasons to discontinue IL-2 dosing. Chest radiographs revealing interstitial edema and pleural effusions provide complementary information to the clinical assessment and are performed selectively. After discontinuation of IL-2, symptoms of pulmonary congestion resolve promptly and recovery is aided by rapid diuresis. After stopping IL-2 and when the blood pressure is returning to baseline (and not requiring vasopressors), diuresis can be initiated by pharmacologic means. Fluid balance is rapidly restored and the majority of patients are discharged above admission weight about 1-2 days after stopping Il-2.

Neurovascular compression from edema is rare and is best treated with elevation of the involved extremity and use of compression garments. Cautious use of fluids to correct hypotension and oliguria is important in minimizing edema. Diuresis is not always possible during therapy because patients may be hypotensive and are frequently unresponsive to diuretics.

Doses of IL-2 will not be reduced during therapy but may be held for 8 hours for relative stopping criteria. If the dose-limiting toxicity resolves to grade 1 or grade 0 by supportive measures prior to the subsequent scheduled dose, dosing may resume per protocol. A maximum of 2 dose delays per course will be allowed. Dosing for each hospitalization will be stopped for clinical stopping criteria or a maximum of 15 doses per admission. Patients will be dismissed no sooner than 24 hours after the last dose of interleukin 2 AND when discharge criteria are met.

HD IL-2 dosing guidelines during hospitalization

| System | Relative Criteria | Absolute Criteria |
|---|---|---|
| Cardiac | Sinus tachycardia 130-140 | Sinus tachycardia >140 that persists after correcting for fever and hypotension |
| | Ischemia suspicion | ECG changes consistent with ischemia |
| | Atrial fibrillation | Ventricular arrhythmia |
| | | Elevated Troponin I drawn for suspicion of ischemia |
| | | |
| Dermatologic | | Moist desquamation |
| | | |
| Gastrointestinal | Stool >1000cc/8 hours | Stool >2000cc/16 hours |
| | Symptomatic distention | Severe distention effecting breathing |
| | Bilirubin >7 | Severe abdominal pain |
| | | |
| Hemodynamic | | Pressor support required clinically for systolic BP<70 |
| | | |
| Hemorrhagic | | Frank blood in sputum or stool |
| | Platelets 30,000 to 20,000/mm3 | Platelets <20,000/mm3 |
| | | |
| Infectious | Clinical suspicion | Strong clinical suspicion or documentation |
| | | |
| Musculoskeletal | | Extremity paresthesias requiring analgesia |
| | | |
| Neurologic | | Disorientation to person and place<br>Hallucinations<br>Persistent crying/sadness |
| | | |
| Pulmonary | Resting shortness of breath not reversible with 4L oxygen per NC | >4L NC to keep oxygenation sat >94% |
| | | Rales >1/2 of chest volume |
| | | |
| Renal | | UO<50cc/12 hours |
| | | Creatinine > 4.0 mg/dL |

INTERVENTION

The following intervention and corrective measures are highly recommended but may be adjusted as clinically needed at the discretion of the treating physician.

Relative criteria: Initiate intervention
>3 Relative criteria: Hold IL-2 dose, resume if reversible by next dosing time
Absolute criteria: Hold further dosing for current admission

Possible corrective measures as clinically indicated

| | |
|---|---|
| Arrhythmia | Stop IL-2 (most arrhythmias). Correct electrolytes, minerals |
| | |
| Anemia | Consideration of transfusion to keep Hgb >8 |
| | |
| Chills | Warm blankets. Demerol if severe (rigors). |
| | |
| Dermatitis | Lotions |
| | |
| Diarrhea | Lomotil every 4 hours as needed. Avoid > 10mg/24 hours. |
| | |
| Epigastric pain | Evaluate cause, consider antacids |
| | |
| Fever breakthrough | Increase ibuprofen frequency to every 6 hours, consider evaluation for infection |
| | |
| Hypocalcemia | Maintain serum level above lowest level of institutional normal with oral or IV supplementation |
| | |
| Hypokalemia | Maintain serum level >3.6 mmol/L |
| | |
| Hypomagnesemia | Maintain serum level >1.7 mmol/L |
| | |
| Infection | Stop IL-2 |
| | |
| Mucositis | Frequent oral care, topical analgesics and consideration of nystatin |
| | |
| Oliguria | Consideration of small (250cc) IV saline bolus and/or albumin 100cc 25%. |
| | |
| Nausea | Antiemetics |
| | |
| Nasal congestion | Room humidifier, decongestants |
| | |
| Pruritus | Cool sponge baths, lotions |
| | |
| Shortness of breath | Oxygen supplementation per NC. Use fluids judiciously, inhaled beta agonists if wheezing, consideration of albumin, consideration of lasix. |
| | |
| Tachycardia | Correct fever, hypotension, anemia, decreasing dopamine if used. |

**Hospital Discharge**

Patients will be discharged from the hospital when the following criteria are met:

Absolute neutrophil count (ANC) > 500/μL.
Platelet count > 20,000/μL.
Hemodynamically stable.
Creatinine on downward trend after high dose IL-2.
Liver function tests stable.
Not requiring daily blood product infusion.

**Protocol Therapy Discontinuation**

In addition to discontinuation from therapy related to toxicities as outlined in sections 6.1.3, a subject will also be discontinued from protocol therapy and followed per protocol under the following circumstances outlined below. The reason for discontinuation of protocol therapy will be documented on the electronic case report form (eCRF).

- Documented disease progression
- Subject completes 3 courses of therapy
- Subject completes one course past best response
- Site investigator determines a change of therapy would be in the best interest of the subject
- Subject requests to discontinue protocol therapy, whether due to unacceptable toxicity or for other reasons
  - o If a subject decides to prematurely discontinue protocol therapy ("refuses treatment"), the subject should be asked if he or she may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.
- Female subject becomes pregnant
- HD IL-2 will be discontinued if there is a ≥ 2-week delay between cycles
- Nivolumab will be discontinued if there is a ≥ 2-week delay between cycles

**Protocol Discontinuation**

If a subject decides to discontinue from the protocol (and not just from protocol therapy) all efforts should be made to complete and report study assessments as thoroughly as possible. A complete final evaluation at the time of the subject's protocol withdrawal should be made with an explanation of why the subject is withdrawing from the protocol. If the reason for removal of a subject from the study is an adverse event, it will be recorded on the eCRF.

### 4.8 Contraception/Pregnancy/Breast Feeding

It is not known if nivolumab has adverse effects on a fetus *in utero,* if there are transient adverse effects on the composition of sperm, or if it is excreted in breast milk. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study drug. Male subjects who are not surgically sterile (vasectomy) must agree to

use an adequate method of contraception (condoms). Subjects who are breast-feeding are not eligible for enrollment.

### 4.9 Duration of Study Treatment

Treatment will continue until one course past best response for a maximum of three courses or until progression.

### 4.10 Duration of Follow Up

Patient will be followed up every 3-6 months after removal from treatment until progression, death or 3 years after the last patient has completed therapy whichever occurs first. Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

### 4.11 Discontinuation from Study Participation

If a subject decides to discontinue from the protocol (and not just from protocol therapy) all efforts should be made to complete and report study assessments as thoroughly as possible. A complete final evaluation at the time of the subject's protocol withdrawal should be made with an explanation of why the subject is withdrawing from the protocol. If the reason for removal of a subject from the study is an adverse event, it will be recorded on the eCRF.

## 5.0 STUDY PROCEDURES

Refer to the study Schedule of Events for procedures.

All patients will be closely monitored for safety and tolerability during all cycles of therapy, at study treatment completion/early study treatment discontinuation, and during the follow-up period.

### 5.1 Definitions of Study Assessments

#### 5.1.1 Medical history

A complete medical, surgical and oncology history as well as history of infections are obtained at screening. Any changes from Screening (e.g. worsening severity or abnormal findings) are considered to be adverse events (AEs).

#### 5.1.2 Demographics

Demographic profile will include date of birth, gender, race, and ethnicity.

#### 5.1.3 Review subject eligibility criteria

Review of eligibility criteria as described in Section 3 to ensure subject qualification for study entry.

#### 5.1.4 Concomitant medications

All concomitant therapy, including anesthetic agents, vitamins, homeopathic/herbal remedies, nutritional supplements, received by patients from five days prior to the first day of study treatment until 28 days after the last study dose (or until the start of a new treatment, whichever comes first) will be recorded in the patient's medical record. If a reportable adverse event deemed related to study intervention (see Section 7) occurs within 28 days after last study dose and the patient has not started a new treatment, recording of concomitant medications related to the treatment of that adverse event should continue until resolution of the adverse event.

#### 5.1.5 Physical exam

A complete physical examination should include the evaluation of general appearance; evaluation of head, eyes, ears, nose, and throat (HEENT); and cardiovascular, pulmonary, abdominal, musculoskeletal, skin, lymph nodes, neurological (cranial nerves, strength, sensation and coordination), and genitourinary systems. Subsequent exams may be targeted as appropriate.

Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as adverse events if clinically significant.

#### 5.1.6 Vital signs and height

Vital signs should include temperature, pulse, and blood pressure and weight. Height will only be collected at screening.

#### 5.1.7 Performance status

Performance status is evaluated by the ECOG performance status. Patients with ECOG of 0 or 1 will be eligible for the study.

| ECOG Score | Performance Status |
|---|---|
| 0 | Asymptomatic |
| 1 | Symptomatic, fully ambulatory |
| 2 | Symptomatic, in bed < 50% of the day |
| 3 | Symptomatic, in bed > 50% of the day but not bedridden |
| 4 | Bedridden |
| 5 | Dead |

#### 5.1.8 Adverse event assessment

Baseline assessment of subject status for determining adverse events. See Section 7 for Adverse Event monitoring and reporting.

#### 5.1.9 Hematology

Hematology to include hemoglobin (Hgb), platelets, total white blood cell count (WBC), and differential.

#### 5.1.10 Serum chemistries

Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin. Additional chemistries: lactate dehydrogenase (LDH), phosphate, lipase, and amylase may be performed.

#### 5.1.11 Coagulation

Coagulation profile includes International Normalized Ratio (INR), prothrombin time (PT) and activated partial thromboplastin time (PTT).

#### 5.1.12 Blood draw for correlative studies

See Section 5.5 for details.

#### 5.1.13 Pregnancy test (for females of child bearing potential)

See section 3.1 for definition.

#### 5.1.14 Urine Analysis

Standard urinalysis dipstick assessment (pH, protein, glucose, blood, ketones, and leukocytes) should be performed. This must be supplemented with laboratory quantification of any potentially relevant abnormalities. In addition, levels for protein and creatinine must be obtained, as a protein: creatinine ratio will be measured.

#### 5.1.15 ECG

Resting 12-lead ECG.

### 5.1.16 Quality of Life Questionnaire

Quality of life will be assessed by the HRQL (Health related quality of life RAND-36) questionnaire. (Appendix A).

### 5.1.17 Tumor assessment

Tumor size will be assessed by CT scan or PET-CT scan.

### 5.1.18 Tumor tissue collection

See Section 5.5 for details.

## 5.2 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 28 days prior to registration unless otherwise stated. The screening procedures include:

- Written informed consent (within 28 days).
- Review of inclusion and exclusion criteria.
- Complete medical/oncology history.
- Demographics.
- Documentation of concomitant medications.
- Complete physical examination, including vital signs and height.
- Performance status assessment.
- Laboratory tests (within 7 days; pregnancy test within 72 hours).
- Blood collection for correlative studies.
- Documentation of tumor staging.
- Tumor biopsy tissue collection for correlative studies (can use archival tissue or new biopsy).

## 5.3 Procedures During Treatment

### 5.3.1 Prior to nivolumab and IL-2 each cycle

- Documentation of concomitant medications and adverse events
- Physical exam, vital signs
- Hematology
- Serum chemistries
- TSH, amylase, lipase, UA (prior to nivolumab)

### 5.3.2 Tumor Assessments

- Imaging evaluation at the end of each course of treatment

### 5.3.3 End of Treatment Visit

- Documentation of concomitant medications and adverse events
- Physical exam, vital signs
- Hematology
- Serum chemistries

## 5.4 Follow-up Procedures

Patients discontinuing study treatment for any reason will be followed every 3-6 months after the last dose of study treatment until progression. Follow-up will consist of survival contacts via medical record review, telephone call, or review of the Social Security Index.

## 5.5 CORRELATIVE STUDIES AND PROCEDURES

### 5.5.1 Correlate PD-L1 expression and tumor mutational burden (TMB) in archived diagnostic tumor tissue with best clinical response (revised RECIST criteria) and treatment outcome in subjects with metastatic malignant melanoma and renal cell carcinoma

Expression of PD-L1 in archived diagnostic tumor tissue will be determined by IHC by referring laboratory using anti-PD-L1 antibody clone 22C3. TMB will be assessed by next generation sequencing. PD-L1 expression and TMB will be correlated with clinical response assessed by imaging. Unstained slides are to be submitted; a tumor block is not acceptable.

### 5.5.2 Correlate T-cell subsets and MDSCs in peripheral blood during therapy with best clinical response (revised RECIST criteria) and treatment outcome in subjects with stage IV malignant melanoma

Whole blood for cell and serum submission will be collected pre-dose Cycle 1 Day 1 of nivolumab, prior to HD IL-2 administration (days 8, 22), and day 35 for analysis of T-cell subset ratios levels, cytokine levels and MDSC quantification. Change in Th1/Th2 ratio and MDSCs levels as a result of treatment will be examined in relation to the best clinical response (RECIST, v1.1) and treatment outcome.

### 5.5.3 Correlative samples for future unspecified cancer related studies

Subject consent will be requested (but not required) for participation in UC San Diego Biorepository for additional samples (whole blood, plasma and PBMCs) to be collected and banked for future unspecified cancer related research. Samples will be collected at baseline and prior to each treatment (nivolumab and day 1 of HD IL-2). These samples will be banked in the biorepository.

### 5.5.4 Specimen Banking

Patient samples collected for this study will be retained at the UC San Diego Biorepository for analysis and future cancer research. Specimens will be stored indefinitely or until they are used up. Samples will be labeled with the protocol number, subject's de-identified study number and collection date. The link between study number and medical record number will be viewed over a password secured encrypted server-client.

The study research coordinator will review their subject's medical record for demographic and clinical information pertaining to the subject's general medical history, diagnosis, and outcomes of any treatments received. Samples and data extracted from the subject's medical record will be coded with a de-identified study number so that the subject's name and identifying information is removed. A log that links the subject's name and identifiers to the study number will be maintained in a secure database distinct from the secure database into which the subject's clinical information will be entered by study personnel.

The biorepository with consultations from the PI will be responsible for reviewing and approving requests for clinical specimens from potential research collaborators outside of UCSD. Collaborators will be required to complete an agreement (a Material Transfer Agreement or recharge agreement) that states specimens will only be released for use in disclosed research. Any data obtained from the use of clinical specimens will be the property of UCSD for publication and any licensing agreement will be strictly adhered to. These outside collaborators may include for-profit biotechnology corporations interested in collaborating with UCSD investigators in research diagnostic, prognostic assays and drug development.

The specimens, DNA, and their derivatives may have significant therapeutic or commercial value. The Informed Consent form contains this information and informs the subject that there is the potential for financial gain by UCSD, the investigator or a collaborating researcher or entity.

If patients later decide they do not want their specimens collected to be used for future research, they may tell this to Dr. Daniels, who will inform the biorepository. Best efforts will be made to stop any additional studies and to destroy the specimens. Samples stored in the biorepository will be destroyed; for samples that have been disseminated outside of the biorepository, the biorepository staff will contact the recipient to notify them of the need to halt further research and destroy specimens.

## 6.0 Measurement of Effect

### 6.1 Safety/tolerability

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE version 5.0 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf) for reporting of adverse events.

### 6.2 Antitumor Effect- Solid Tumors

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria.

#### 6.2.1 Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation.

#### 6.2.2 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of study treatment until objective tumor progression or death.

#### 6.2.3 Time to Progression

Time to progression is defined as the duration of time from start of study treatment until objective tumor progression.

#### 6.2.4 Overall Survival

Overall survival is defined as the duration of time from start of study treatment to death.

### 6.3 Quality of Life

Quality of Life will be assessed the by the RAND-36 health related quality of life assessment.

## 7.0 ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

Progression of the cancer under study or events which are unequivocally due to disease progression should not be reported as an AE during the study (unless it is considered to be drug related by the investigator).

### 7.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

- As far as possible, each adverse event should be evaluated to determine:
- duration (start and end dates)
- severity (grade)
- seriousness
- relationship to study agent
- action taken (i.e., none, study agent modification, medical intervention)
- outcome (i.e., resolved without sequelae, resolved with sequelae, ongoing)

Adverse events monitoring begins after initiation of study treatment and ends 90 days following the last administration of study treatment, regardless of initiation of subsequent anticancer therapy.

All patients experiencing an adverse event, regardless of its relationship to study drug [or at least possibly related to the drug], will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any clinically significant abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

### 7.2 Severity

All adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The CTCAE v5.0 is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.

If no CTCAE grading is available, the severity of an AE is graded as follows:

Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
Moderate (grade 2): the event causes discomfort that affects normal daily activities.

Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
Life-threatening (grade 4): the patient was at risk of death at the time of the event.
Fatal (grade 5): the event caused death.

### 7.3 Seriousness

A "serious" adverse event is defined in regulatory terminology as any untoward medical occurrence that:

1. **Results in death.**
   If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
2. **Is life-threatening.**
   The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. **Requires in-patient hospitalization or prolongation of existing hospitalization.**
   Note: Hospitalization (including hospitalization for an elective procedure) for a pre-existing condition which has not worsened does not constitute a serious adverse event.
4. **Results in persistent or significant disability or incapacity.**
5. **Is a congenital anomaly/birth defect**
6. **Is an important medical event**
   Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".
   *For example:* allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

### 7.4 Relationship

Attribution categories for adverse events in relationship to protocol therapy are as follows:
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.

### 7.5 Prior experience

Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in the current known adverse events listed in the agent clinical experience section of this protocol or the current Product Label when applicable.

### 7.6 Reporting Requirements for Adverse Events

#### 7.6.1 Expedited Reporting

**A.** The **Principal Investigator** must be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of the

last administration of the study drug.

**B.** The **UCSD Human Research Protections Program (HRPP)** and **Moores Cancer Center Data and Safety Monitoring Board (DSMB)** must be notified within 10 business days of "any unanticipated problems involving risk to subjects or others" (UPR).

The following events meet the definition of UPR:

1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.
5. Any breach in confidentiality that may involve risk to the subject or others.
6. Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.

**C.** The **FDA** must be notified according to the following timelines:

- within 7 calendar days of any unexpected fatal or life-threatening adverse event with possible relationship to study drug, and
- within 15 calendar days of any event that is considered: 1) serious, 2) unexpected, and 3) at least possibly related to study participation.

### 7.6.2 Routine Reporting Requirements

**A.** The **UCSD HRPP** must be notified of any adverse events that are not unanticipated problems involving risk to subjects or others (non-UPRs) at the time of the annual Continuing Review.

**B.** The **FDA** must be notified of all non-serious adverse events annually at the time of the annual report.

## 8.0 AGENT INFORMATION

### 8.1 Proleukin (Aldesleukin; Interleukin-2)

#### 8.1.1 Chemical name and properties

Desalanyl-1, serine-125 human recombinant interleukin-2
MW: 15.3 KD

This IL-2 differs from native interleukin-2 in the following ways:

- Not glycosylated
- No N-terminal alanine
- C125S mutation
- Aggregation state

Biological potency: 1.1 mg = 18 x $10^6$ IU

#### 8.1.2 Availability

Proleukin is commercially available and will be ordered through outpatient pharmacy where the subject is being treated.

#### 8.1.3 Package

Sterile single-use vials intended for intravenous administration. Each vial contains 22 x $10^6$ units of lyophilized Proleukin.

#### 8.1.4 Storage

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Store vials of lyophilized Proleukin in a refrigerator at 2° to 8°C. Protect from light. 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.

#### 8.1.5 Dosage and Administration

Please refer to the package insert for a comprehensive description of Proleukin preparation. Reconstituted or diluted Proleukin is stable for up to 48 hours at 2° to 8° C. Proleukin will be provided per standard of care. Proleukin is supplied as a sterile, white to off-white, lyophilized cake in single-use vials intended for intravenous administration. When reconstituted with 1.2 mL sterile water for injection, USP, each mL contains 18 x $10^6$ IU (1.1 mg) Proleukin, 50 mg mannitol, and 0.18 mg sodium dodecyl sulfate, buffered with approximately 0.17 mg monobasic and 0.89 mg dibasic sodium phosphate to a pH of 7.5 (range 7.2 to 7.8). The manufacturing process for Proleukin involves fermentation in a defined medium containing tetracycline hydrochloride. The presence of the antibiotic is not detectable in the final product. Proleukin contains no preservatives in the final product.

The recommended Proleukin treatment regimen is administered in the inpatient setting on a monitored unit. Each course of treatment consists of two 5-day treatment cycles, the cycles separated by rest period for 9 days. In each cycle, 600,000 - 720,000 units/kg (0.037 mg/kg) will be administered as a 15-minute intravenous infusion every 8 hours for up to 14 consecutive doses over 5 days.

### 8.1.6 Side Effects

Please refer to the current version of the package insert for a complete list of adverse events.

The following adverse events (Grades 1-4) were seen in ≥30% of 525 patients (255 with metastatic renal cell cancer and 270 with metastatic melanoma) treated with Proleukin®: hypotension (71%), diarrhea (67%), oliguria (63%), chills (52%), vomiting (50%), dyspnea (43%), rash (42%), bilirubinemia (40%), thrombocytopenia (37%), nausea (35%), confusion (34%), and creatinine increase (33%). Due to the potential severe adverse events that might accompany Proleukin therapy at the recommended dosages, thorough clinical evaluation will be performed to exclude subjects that are contraindicated to Proleukin therapy and patients that have significant cardiac, pulmonary, renal, hepatic, or CNS impairment. Adverse events are frequent, often serious, and sometimes fatal. Further details around frequency, reporting, and management of immune-related adverse events (irAEs) can be found in the current version of the Investigator's Brochure. In addition to the previously noted identified risks, infusion-related reactions are a risk but are not considered immune mediated; these are also further described in the current package insert.

## 8.2 Opdivo® (Nivolumab)

Please refer to the current version of the package insert for additional information regarding this drug.

### 8.2.1 Chemical name and properties

Humanized anti-PD-1_mAb IgG4

### 8.2.2 Availability

Nivolumab is commercially available and will be ordered through outpatient pharmacy where the subject is being treated.

### 8.2.3 Storage

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.

### 8.2.4 Dosage and Administration

Nivolumab is a sterile, preservative-free, non-pyrogenic, clear to opalescent, colorless to pale-yellow liquid. One vial of 24 mL contains 240 mg of nivolumab. Each mL of concentrate contains 0.1 mmol (or 2.5 mg) sodium.

### 8.2.5 Side Effects

Please refer to the current version of the package insert for a complete list of adverse events.

Nivolumab is generally well tolerated and demonstrates a favorable safety profile in comparison to chemotherapy. Nivolumab is an immunomodulatory agent, and based on this mechanism of action, immune mediated adverse events are of primary concern. Important identified risks for nivolumab are of an immune mediate nature, including: pneumonitis, colitis, thyroid disorders (hypothyroidism/hyperthyroidism), hepatitis, hypophysitis, Type I diabetes mellitus, uveitis, nephritis, pancreatitis, myositis, and severe skin reaction. After a recent review of data, events newly characterized as identified risks also include vitiligo, Guillain-Barre Syndrome, and adrenal insufficiency. The majority of immune-mediated adverse events were mild to moderate in severity, were manageable with appropriate care, and rarely required discontinuation of therapy.

Further details around frequency, reporting, and management of immune-related adverse events (irAEs) can be found in the current version of the package insert. In addition to the previously noted identified risks, infusion-related reactions are a risk but are not considered immune mediated; these are also further described in the current package insert.

## 9.0 STATISTICAL CONSIDERATIONS

### 9.1 Study Design/Study Endpoints

This is a prospective, unblinded, non-randomized single arm phase II study. The primary end point is objective response rate per RECIST 1.1. Secondary objectives include safety, tolerability, and progression free survival.

### 9.2 Sample Size and Accrual

The Simon two-stage design to test the null hypothesis that P≤ 0.1 versus the alternative that P ≥ 0.3 with 90% power and 0.1 level of significance proceeds as follows. After testing the drug on 16 patients in the first stage, the trial will be terminated if 1 or fewer respond. If the trial goes on to the second stage, a total of 25 patients will be studied. If the total number responding is less than or equal to 4, the drug combination is rejected. The probability of early termination at stage 1 with a total sample size of 16 is 0.515; the probability of going on to stage 2 with a total sample size of 25 is 0.485. The sample size calculation is conducted using http://cancer.unc.edu/biostatistics/program/ivanova/SimonsTwoStageDesign.aspx (accessed 7/23/18).

| **Accrual Targets** | | | |
|---|---|---|---|
| **Ethnic Category** | **Sex/Gender** | | |
| | **Females** | **Males** | **Total** |
| Hispanic or Latino | 6 | 7 | 13 |
| Not Hispanic or Latino | 6 | 6 | 12 |
| **Ethnic Category: Total of all subjects** | 12 | 13 | 25 |
| **Racial Category** | | | |
| American Indian or Alaskan Native | 1 | 1 | 2 |
| Asian | 2 | 2 | 4 |
| Black or African American | 1 | 1 | 2 |
| Native Hawaiian or other Pacific Islander | 1 | 1 | 2 |
| White | 7 | 8 | 15 |
| **Racial Category: Total of all subjects** | 12 | 13 | 25 |

#### 9.2.1 Evaluable Subjects and Subject Replacement

All patients who receive at least one dose of study drug will be evaluable for response unless a patient has a complete or partial response and receives non-protocol therapy prior to confirmation of that response. Subjects who are not evaluable for response will be replaced.

Patients will be evaluable for toxicity if they receive at least on dose of the study drug and one of the following happens:

a. Experience a reportable toxicity or adverse event
b. Die on protocol therapy for reason at least possibly related to study drug
c. Complete at least one cycle of protocol therapy with no toxicity

Patients who are not evaluable for toxicity will not be replaced.

### 9.3 Data Analyses Plans

#### 9.3.1 Primary AnalysisOverall response rate will be described using a point estimate and 95% confidence interval adjusted for the two-stage design by the method of Jung and Kim [19].

#### 9.3.2 Secondary Analyses

Toxicities will be analyzed descriptively by grade and cycle using CTCAE version 5.0. Progression free survival will be estimated using Kaplan-Meier methodology with the Greenwood estimate for the variance.

#### 9.3.3 Exploratory Analyses

Correlative markers will be described graphically and ANOVA will be used to compare PD-L1 expression and TMB to best clinical response. Linear mixed effects models will be used to compare changes to T-cell subsets and myeloid-derived suppressor cells to best clinical response.

## 10.0 STUDY MANAGEMENT

### 10.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed according to UCSD conflict of interest policy.

### 10.2 Institutional Review Board (IRB) Approval and Consent

The IRB should approve the consent form and protocol prior to any study-related activities. It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

### 10.3 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), subjects who have provided written informed consent must also sign a subject authorization to release medical information to the study Sponsor and allow a regulatory authority, or Institutional Review Board access to subject's medical information relevant to the study.

### 10.4 Data and Safety Monitoring/Auditing

In addition to adverse event monitoring and clinical oversight by the Study Chair, site principal investigator and co-investigators, quality assurance of the study will be performed by the UCSD Moores Cancer Center Clinical Trials Office internal monitor. Monitoring intervals will be dependent upon the number of patients enrolled and the complexity of the study.

This study will also use the UCSD Moores Cancer Center Data Safety and Monitoring Board (DSMB) to provide oversight in the event that this treatment approach leads to unforeseen toxicities. Data from this study will be reported annually and will include:

1) the protocol title, IRB protocol number, and the activation date of the study.
2) the number of patients enrolled to date
3) the dates of patient enrollment
4) a summary of all adverse events regardless of grade and attribution
5) a response evaluation for evaluable patients when available
6) a summary of any recent literature that may affect the ethics of the study.

### 10.5 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, investigators are required to conduct their research according to the plans reviewed and approved by the IRB.

### 10.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Study Chair. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB and FDA for approval prior to implementation.

### 10.7 Record Retention

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

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

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

### 10.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require her final signature to verify the accuracy of the data.

## 11.0 REFERENCES


1. *SEER database. http://seer.cancer.gov/statfacts/html/melan.html. Accessed: July 27, 2018.*
2. Balch, C.M., et al., *Final version of 2009 AJCC melanoma staging and classification.* J Clin Oncol, 2009. **27**(36): p. 6199-206.
3. *NCCN guidelines: Melanoma. https://www.nccn.org/professionals/physician_gls/PDF/melanoma.pdf. Accessed: July 27, 2018.*
4. *NCCN guidelines: Kidney Cancer. https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf. Accessed: July 27, 2018.*
5. Motzer, R.J., et al., *Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma.* N Engl J Med, 2018. **378**(14): p. 1277-1290.
6. Larkin, J., et al., *Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma.* N Engl J Med, 2015. **373**(1): p. 23-34.
7. Motzer, R.J., et al., *Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma.* N Engl J Med, 2015. **373**(19): p. 1803-13.
8. Alva, A., et al., *Contemporary experience with high-dose interleukin-2 therapy and impact on survival in patients with metastatic melanoma and metastatic renal cell carcinoma.* Cancer Immunol Immunother, 2016. **65**(12): p. 1533-1544.
9. Granucci, F., et al., *Inducible IL-2 production by dendritic cells revealed by global gene expression analysis.* Nat Immunol, 2001. **2**(9): p. 882-8.
10. Gaffen, S.L. and K.D. Liu, *Overview of interleukin-2 function, production and clinical applications.* Cytokine, 2004. **28**(3): p. 109-23.
11. McDermott, D.F., et al., *Randomized phase III trial of high-dose interleukin-2 versus subcutaneous interleukin-2 and interferon in patients with metastatic renal cell carcinoma.* J Clin Oncol, 2005. **23**(1): p. 133-41.
12. Atkins, M.B., et al., *High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993.* J Clin Oncol, 1999. **17**(7): p. 2105-16.
13. Boyman, O., J.H. Cho, and J. Sprent, *The role of interleukin-2 in memory CD8 cell differentiation.* Adv Exp Med Biol, 2010. **684**: p. 28-41.
14. Floros, T. and A.A. Tarhini, *Anticancer Cytokines: Biology and Clinical Effects of Interferon-alpha2, Interleukin (IL)-2, IL-15, IL-21, and IL-12.* Semin Oncol, 2015. **42**(4): p. 539-48.
15. Blackburn, S.D., et al., *Selective expansion of a subset of exhausted CD8 T cells by alphaPD-L1 blockade.* Proc Natl Acad Sci U S A, 2008. **105**(39): p. 15016-21.
16. West, E.E., et al., *PD-L1 blockade synergizes with IL-2 therapy in reinvigorating exhausted T cells.* J Clin Invest, 2013. **123**(6): p. 2604-15.
17. Schwartzentruber, D.J., *Guidelines for the safe administration of high-dose interleukin-2.* J Immunother, 2001. **24**(4): p. 287-93.
18. Poust, J.C., J.E. Woolery, and M.R. Green, *Management of toxicities associated with high-dose interleukin-2 and biochemotherapy.* Anticancer Drugs, 2013. **24**(1): p. 1-13.
19. Jung, S.H. and K.M. Kim, *On the estimation of the binomial probability in multistage clinical trials.* Stat Med, 2004. **23**(6): p. 881-96

## 12.0 APPENDICES

### Appendix A. Quality of Life Questionnaire

### Health Related Quality of Life-RAND 36

# RAND 36-Item Health Survey 1.0 Questionnaire Items

Choose one option for each questionnaire item.

1. In general, would you say your health is:

- 1 - Excellent
- 2 - Very good
- 3 - Good
- 4 - Fair
- 5 - Poor

---

2. Compared to one year ago, how would you rate your health in general now?

- 1 - Much better now than one year ago
- 2 - Somewhat better now than one year ago
- 3 - About the same
- 4 - Somewhat worse now than one year ago
- 5 - Much worse now than one year ago

---

The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

| | Yes, limited a lot | Yes, limited a little | No, not limited at all |
|---|---|---|---|
| 3. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports | ○ 1 | ○ 2 | ○ 3 |
| 4. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf | ○ 1 | ○ 2 | ○ 3 |
| 5. Lifting or carrying groceries | ○ 1 | ○ 2 | ○ 3 |
| 6. Climbing **several** flights of stairs | ○ 1 | ○ 2 | ○ 3 |
| 7. Climbing **one** flight of stairs | ○ 1 | ○ 2 | ○ 3 |
| 8. Bending, kneeling, or stooping | ○ 1 | ○ 2 | ○ 3 |
| 9. Walking **more than a mile** | ○ 1 | ○ 2 | ○ 3 |
| 10. Walking **several blocks** | ○ 1 | ○ 2 | ○ 3 |
| 11. Walking **one block** | ○ 1 | ○ 2 | ○ 3 |
| 12. Bathing or dressing yourself | ○ 1 | ○ 2 | ○ 3 |

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health?**

| | Yes | No |
|---|---|---|
| 13. Cut down the **amount of time** you spent on work or other activities | ○ 1 | ○ 2 |
| 14. **Accomplished less** than you would like | ○ 1 | ○ 2 |
| 15. Were limited in the **kind** of work or other activities | ○ 1 | ○ 2 |
| 16. Had **difficulty** performing the work or other activities (for example, it took extra effort) | ○ 1 | ○ 2 |

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

| | Yes | No |
|---|---|---|
| 17. Cut down the **amount of time** you spent on work or other activities | ○ 1 | ○ 2 |
| 18. **Accomplished less** than you would like | ○ 1 | ○ 2 |
| 19. Didn't do work or other activities as **carefully** as usual | ○ 1 | ○ 2 |

20. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

- ○ 1 - Not at all
- ○ 2 - Slightly
- ○ 3 - Moderately
- ○ 4 - Quite a bit
- ○ 5 - Extremely

21. How much **bodily** pain have you had during the **past 4 weeks**?

- ○ 1 - None
- ○ 2 - Very mild
- ○ 3 - Mild
- ○ 4 - Moderate
- ○ 5 - Severe
- ○ 6 - Very severe

---

22. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

- ○ 1 - Not at all
- ○ 2 - A little bit
- ○ 3 - Moderately
- ○ 4 - Quite a bit
- ○ 5 - Extremely

---

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks**...

| | All of the time | Most of the time | A good bit of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|---|
| 23. Did you feel full of pep? | ○ 1 | ○ 2 | ○ 3 | ○ 4 | ○ 5 | ○ 6 |
| 24. Have you been a very nervous person? | ○ 1 | ○ 2 | ○ 3 | ○ 4 | ○ 5 | ○ 6 |
| 25. Have you felt so down in the dumps that nothing could cheer you up? | ○ 1 | ○ 2 | ○ 3 | ○ 4 | ○ 5 | ○ 6 |
| 26. Have you felt calm and peaceful? | ○ 1 | ○ 2 | ○ 3 | ○ 4 | ○ 5 | ○ 6 |
| 27. Did you have a lot of energy? | ○ 1 | ○ 2 | ○ 3 | ○ 4 | ○ 5 | ○ 6 |
| 28. Have you felt downhearted and blue? | ○ 1 | ○ 2 | ○ 3 | ○ 4 | ○ 5 | ○ 6 |
| 29. Did you feel worn out? | ○ 1 | ○ 2 | ○ 3 | ○ 4 | ○ 5 | ○ 6 |
| 30. Have you been a happy person? | ○ 1 | ○ 2 | ○ 3 | ○ 4 | ○ 5 | ○ 6 |
| 31. Did you feel tired? | ○ 1 | ○ 2 | ○ 3 | ○ 4 | ○ 5 | ○ 6 |

32. During the **past 4 weeks**, how much of the time has **your physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

○ 1 - All of the time

○ 2 - Most of the time

○ 3 - Some of the time

○ 4 - A little of the time

○ 5 - None of the time

How TRUE or FALSE is **each** of the following statements for you.

| | Definitely true | Mostly true | Don't know | Mostly false | Definitely false |
|---|---|---|---|---|---|
| 33. I seem to get sick a little easier than other people | ○ 1 | ○ 2 | ○ 3 | ○ 4 | ○ 5 |
| 34. I am as healthy as anybody I know | ○ 1 | ○ 2 | ○ 3 | ○ 4 | ○ 5 |
| 35. I expect my health to get worse | ○ 1 | ○ 2 | ○ 3 | ○ 4 | ○ 5 |
| 36. My health is excellent | ○ 1 | ○ 2 | ○ 3 | ○ 4 | ○ 5 |

**Appendix B. Sample Order Set (IL-2)**

**UCSD THORNTON HOSPITAL**
**HIGH DOSE IL-2 (IMU)**

Course_____ Cycle_____ Day 1 = _____ / _____ / _____

Height_____cm Weight_____kg BSA_____

Allergies_____

Admit to IMU to Dr. Daniels for high dose infusion Interleukin-2.
Diagnosis: Renal Cell Cancer / Melanoma
Metastatic Disease Sites: Lung Liver Spleen
Soft Tissue/SubQ Adrenal
Lymph node Other_____

**Standing Orders**:

1. Activity: OOB as tolerated, bedside commode prn, no showers-sponge bath only, incentive spirometer every hour while awake.
2. Diet: Regular, as tolerated.
3. Vitals on admission, prior to first dose, every hour x 3 at start of infusion then every 2 hours
   x 2. Repeat with every dose.
4. Height and weight on admission done by RN.
5. Daily weights every AM.
6. Strict Intake and Output.
   - With Foley, monitor urine output every hour.
   - Without Foley, monitor urine output every 4 hours.
7. No intramuscular injections.
8. No IV radiographic contrast during this admission.
9. For PICC:
   - When the catheter is not in use, flush with 3 ml of 100 units/ml of heparin every 8 hours and prn

**Notify MD for:**

- Temp 39 C, HR >140bpm, Systolic BP <80mmHg.
- Critical abnormal lab values:
  - CO2 < 20,
  - Mg ≤ 1.4,
  - Phos ≤ 1.5,
  - K < 3 or >5.5,
  - Ca ≤ 7,
  - platelets <20,000,
  - Hgb <8

**On Admission to IMU**

1. ECG upon admission
2. Obtain baseline pulse oximetry reading. Oxygen 2 to 4L nasal cannula PRN for shortness of breath or saturation ≤95%.
3. Double lumen PICC inserted. Page PICC nurse upon arrival to floor (only if patient does not have prior central access).
4. Chest x-ray following insertion of central line.
5. Begin IVF D5W NS with 20mEq KCl/liter @150cc/hour.
6. Labs (only if prior labs not available within last 7 days)
    - Type and screen
    - CBC with diff. and platelets, Na, K, Cl, CO2, glucose, creatinine, BUN, T bili, AST, ALT, Alk Phos, albumin, CPK, LDH, Phos, Mg, total Ca, TSH, PT/PTT, serum bHCG (for all pre-menopausal women).

**Dr. Gregory Daniels (pager: 619-290-7306 or cell phone: 858-228-7160).**
**Call 60 minutes prior to delivery and preparation of each dose to review vitals, I&O, labs and patient status**.

**Pharmacy Note to Nursing: Please call pharmacy, approximately 1 hour before each dose, to let them know if physician has decided if patient will receive next dose or not. Each dose of IL2 will be prepared after confirmation from physician.**

**Medications**

1. Interleukin-2 (Proleukin) 720,000 IU/kg/dose=_____ MU total dose in D5W IV to be infused over 15 minutes every 8 hours x 14 doses (max).
2. Do not piggyback through running IV solution.
3. Flush IV tubing with 50cc D5W before (unless preloaded by pharmacy) and after each dose.
4. Keflex 250 mg orally twice daily after PICC insertion. If Penicillin allergy, use Ciprofoxicin 500 mg orally twice daily after PICC insertion.
5. Acetaminophen 650 mg orally/rectally 30 minutes prior to IL-2 and every 4 hours until 12 hours post final dose of IL-2.
6. Ondansetron 8 mg IV 30 minutes prior to each dose of IL-2.
7. Cacium citrate 250mg and vitD 200IU orally 30 minutes prior to IL2 admission.
8. Ibuprofen 600 mg orally 30 minutes prior to IL2 admission. Hold if serum creatinine >3 mg/dL
9. Famotidine 20 mg orally or iv twice daily starting AM of admission.
10. Electrolyte replacement per daily lab values
    - Magnesium sulfate 2 grams IV in 50 mL D5W over 2 hours PRN serum Mg $\leq$ 1.6 mg/dL
    - Magnesium sulfate 1 grams IV in 50 mL D5W over 1 hour PRN serum Mg $\leq$ 1.7-1.9 mg/dL
    - Calcium gluconate 1 gram IV in 50mL D5W over 1 hour PRN serum total Ca <8
11. Day 1 - Aprepitant 125mg PO given at 1400, 30 minutes prior to IL-2 infusion
12. Day 2 – Aprepitant 80 mg PO given at 1400, 30 minutes prior to IL-2 infusion
13. Day 3 – Aprepitant 80 mg PO given at 1400, 30 minutes prior to IL-2 infusion
14. Please give NS 250 mL bolus 2 hours after each IL-2 dose.

**PRN Medications**

1. Meperidine 25 mg IV every 15 minutes PRN rigors, up to 100 mg/24 hours.
2. Lorazepam 1 mg orally/IV every 6 hours PRN anxiety.
3. Lomotil 2.5 mg orally every 4 hours PRN diarrhea.
4. Lubriderm lotion or Eucerin cream every 2 hours PRN to affected skin.
5. Compazine 10 mg IV every 6 hours PRN nausea and vomitting.

**Labs**

Daily at noon (start on 2nd day of admission): CBC with diff and platelets , Chem 10, magnesium, phosphate, Liver Panel

## Appendix C. Response Evaluation Criteria in Solid Tumors (RECIST)

Tumor assessments will be made according to the schedule of assessments. Response and progression will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guidelines [Eisenhauer et al. 2009].

### 1 Definitions

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle 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 cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

### 1.1 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray or as ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Tumor lesions situated in a previously radiated area will not be considered measurable.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A

sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

### 1.2 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Conventional CT. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

### 1.3 Response Criteria

#### 1.3.1 Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute

increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

1.3.2 Evaluation of non-target lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the Principal Investigator.

### 1.3.3 Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (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.

**For Patients with Measurable Disease (*i.e.*, Target Disease)**

| **Target Lesions** | **Non-Target Lesions** | **New Lesions** | **Overall Response** | **Best Overall Response when Confirmation is Required*** |
|---|---|---|---|---|
| CR | CR | No | CR | ≥4 wks. Confirmation** |
| CR | Non-CR/Non-PD | No | PR | ≥4 wks. Confirmation** |
| CR | Not evaluated | No | PR | |
| PR | Non-CR/Non-PD/not evaluated | No | PR | |
| SD | Non-CR/Non-PD/not evaluated | No | SD | Documented at least once ≥4 wks. from baseline** |
| PD | Any | Yes or No | PD | no prior SD, PR or CR |
| Any | PD*** | Yes or No | PD | |
| Any | Any | Yes | PD | |

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of

treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

### 1.3.4 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.