

**Phase Ib/II Trial of Interleukin-2 and PD-1 Checkpoint Inhibitor, Nivolumab
In Metastatic Clear Cell Renal Cell Cancer: UMCC 2016.103**

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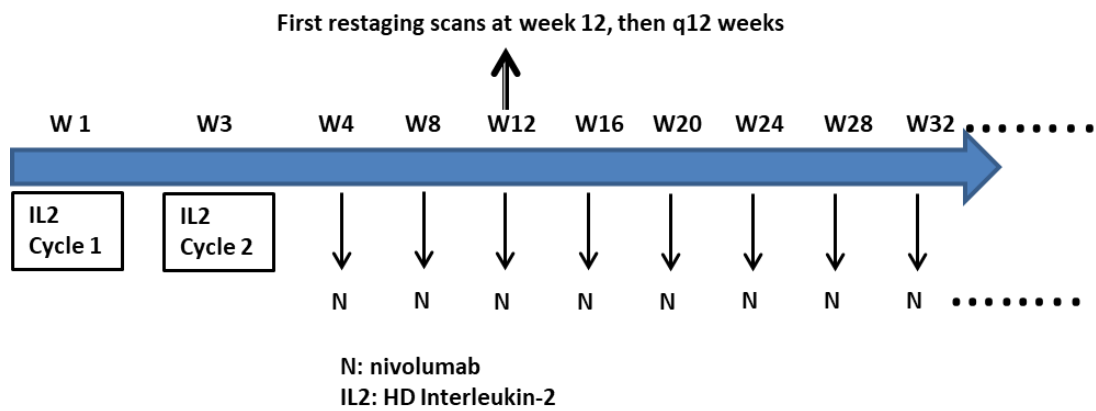
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ABBREVIATIONS

ADA	Anti-Drug Antibody
AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTSUD	Clinical Trials Support Unit
DLT	Dose Limiting Toxicity
DSMC	Data and Safety Monitoring Committee
H&P	History & Physical Exam
HRPP	Human Research Protections Program
IND	Investigational New Drug
IRB	Institutional Review Board
IV (or iv)	Intravenously
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PFS	Progression Free Survival
PI	Principal Investigator
p.o.	per os/by mouth/orally
PR	Partial Response
PRC	Protocol Review Committee
RCC	Renal Cell Carcinoma
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
UaP	Unanticipated Problem
ULN	Upper Limit of Normal
WBC	White Blood Cells
WOCBP	Women of Child Bearing Potential

STUDY SCHEMA



STUDY SYNOPSIS

Title	Phase Ib/II Trial of Interleukin-2 and PD-1 Checkpoint Inhibitor, Nivolumab In Metastatic Clear Cell Renal Cell Cancer
Phase	Phase Ib/II
Methodology	<p>Single arm, multi-site phase Ib/II clinical trial of standard doses of High Dose Interleukin-2 (HD IL2) (600,000 IU/kg/dose intravenously during two 5-day cycles 9 days apart) in IL-2 eligible clear cell metastatic RCC subjects in combination with Nivolumab.</p> <p>Nivolumab will be administered intravenously at 480 mg/dose over 60 minutes every 28 days, starting 1 week to 3 weeks after the start date of the first cycle of IL2 and continued for up to 48 weeks total in the absence of disease progression by RECIST 1.1 criteria, unacceptable toxicity, withdrawal of consent or lack of clinical benefit as determined by the PI.</p> <p>Nivolumab may be continued beyond 48 weeks off-study at the discretion of the investigator at his or her clinical judgment.</p> <p>Initially 10 patients will be enrolled in the phase 1b portion of the study.</p> <p>The first 3 patients will be treated with sequential (rather than interspersed) treatment. They will receive 2 cycles of HD-IL2 given in standard fashion (two 5-day cycles one week apart) followed by nivolumab starting the week after the second IL-2 cycle and continuing every 4 weeks as per standard nivolumab dosing.</p> <p>We will perform a safety analysis after the first 3 patients are treated. If 2 out of 3 of the first patients suffer a grade 3 or 4 immune related toxicity, the study will stop. The 4th patient will not be enrolled until after the analysis of the 3 patient cohort is complete and submitted to the regulatory bodies.</p> <p>If <2 patients suffer a grade 3 or 4 immune related toxicity, the study will enroll up to 7 more patients treated with Nivolumab administered intravenously at 480 mg/dose over 60 minutes every 28 days, starting 1 to 3 weeks after the start date of the first cycle of IL2. We will monitor these patients continuously for immune mediated dose limiting toxicities for 28 days from the first dose of nivolumab. If, at any time during accrual to the phase1 b portion, 6 patients or more have a grade 3 or 4 immune mediated event of interest (as described in section 5.2.1) we will pause the study and modify/discontinue the protocol in consultation with the site principal investigators and applicable regulatory authorities. If ≤ 5 of the 10 patients have a grade 3 or 4 immune mediated event of interest (as described in section 5.2.1), we will proceed to the phase II portion of the study. Please note: immune mediated events of interest do not include those that are known to occur during high dose IL-2 monotherapy and are reversible by holding IL2 dose(s) such as capillary leak syndrome.</p>

Study Duration	<p>24 months of accrual</p> <p>24 months of follow-up (counting from week 1)</p>
Study Center(s)	4 Sites including lead site: University of Michigan.
Objectives	<p>Phase Ib:</p> <p><u>Primary Objective:</u></p> <ol style="list-style-type: none"> 1. To estimate the safety and toxicities of High Dose Interleukin-2 in combination with the immune checkpoint inhibitor Nivolumab in metastatic clear cell renal cell carcinoma. <p>Phase II:</p> <p><u>Primary Objective:</u></p> <ol style="list-style-type: none"> 1. To estimate the efficacy of High Dose Interleukin-2 in combination with the immune checkpoint inhibitor Nivolumab in metastatic clear cell renal cell carcinoma. <p><u>Secondary Objectives:</u></p> <ol style="list-style-type: none"> 1. To determine the safety of High Dose Interleukin-2 in combination with Nivolumab in metastatic clear cell renal cell carcinoma. 2. To profile circulating T cell repertoire by flow cytometry before and during therapy. <p><u>Exploratory Objectives:</u></p> <ol style="list-style-type: none"> 1. To bank tissue and serum specimens for correlative analyses and anti-drug antibody testing in the future.
Number of Subjects	<p>Number of evaluable subjects (those who receive at least 1 dose of HD IL2 and at least 1 dose of nivolumab) = 23. Subjects in the Phase 1b portion will be included in the overall toxicity and efficacy analysis of the study. Subjects who are not evaluable will be replaced. Up to 28 patients may need to be registered (enrolled) in order to obtain the 23 evaluable patients.</p>

Key Inclusion Criteria	<ol style="list-style-type: none"> 1. Subjects must have a histologic diagnosis of clear cell renal cell carcinoma (pure or mixed) with radiologic or histologic or cytologic evidence of metastatic disease. 2. An archived tissue block must be identified to submit unstained slides from prior to registration. 3. Subjects must have measurable disease per RECIST 1.1 criteria. 4. ECOG performance status of 0 or 1. 5. Subjects may have received up to 2 prior lines of systemic therapy (excluding any neoadjuvant/adjuvant therapy) including anti-VEGF or VEGFR inhibitor or mTOR inhibitor for metastatic RCC. 6. White blood count of $\geq 3000/\text{mm}^3$, platelet count $\geq 100,000/\text{mm}^3$, hemoglobin $\geq 10 \text{ g/dl}$; total bilirubin $\leq 1.5 \times$ upper limit of normal (patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia in the absence of evidence of hemolysis or hepatic pathology) will be allowed to enroll after discussion with the principal investigator if total bilirubin is $\leq 3 \times$ the upper limit of normal), ALT/AST $\leq 2.5 \times$ upper limit of normal; serum creatinine $\leq 1.5 \times$ laboratory upper limit of normal or calculated creatinine clearance of $\geq 50 \text{ ml/min/1.73 m}^2$, PT/INR ≤ 1.5, Urine Protein/Creatinine ratio ≤ 1) 7. Subjects must be considered appropriate candidates for HD IL-2 by the treating investigator. HD IL-2 candidacy evaluation is per institutional guidelines at each site and should include a dobutamine stress echocardiogram or equivalent. Subjects with a positive stress test for cardiac ischemia would be excluded from this trial. 8. Subjects must have recovered to grade 1 or less from adverse events of prior therapy and be ≥ 2 weeks from most recent systemic therapy or most recent radiation therapy by the time of first dose of HD IL2. 9. Informed consent from subject must be obtained prior to entrance onto study. 10. Women of childbearing potential must have a negative urine or serum pregnancy test and must take adequate precautions to prevent pregnancy during treatment.
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Key Exclusion Criteria	<ol style="list-style-type: none"> 1. Medical need for systemic corticosteroids >10mg prednisone daily or equivalent alternative steroid (except physiologic dose for adrenal replacement therapy) or other immunosuppressive agents (such as cyclosporine or methotrexate). Topical and inhaled corticosteroids are permitted if medically needed. 2. Patients with autoimmune diseases such as rheumatoid arthritis are NOT allowed. Vitiligo, mild psoriasis (topical therapy only) or hypothyroidism are allowed 3. Prior anti-PD-1/PD-L1 targeted therapy is not permitted. 4. Prior history of psychiatric disorder which could be exacerbated by interleukin-2 in the treating investigator's judgment; 5. Active uncontrolled infection. 6. Evidence of significant cardiovascular disease including history of recent (< 6 months prior) myocardial infarction, congestive heart failure, primary significant cardiac arrhythmias (not due to electrolyte disorder or drug toxicity, for example) beyond occasional PVCs, angina, or cerebrovascular accident; evidence of significant pulmonary disease on pulmonary function testing. 7. Current untreated brain metastasi(e)s. If treated history of CNS metastases, should have completed radiation or surgery at least 4 weeks prior and off systemic corticosteroids.
Study Product(s), Dose, Route, Regimen	<p>High Dose Interleukin-2/IL2 (600,000 IU/kg/dose intravenously every 8 hours for maximum of 28 doses during two 5-day cycles one week apart).</p> <p>Nivolumab will be administered intravenously at 480 mg/dose over 60 minutes every 28 days, starting 1 week (or up to 3 weeks) after the first cycle of IL2 start date and continued for total of up to 48 weeks.</p>
Duration of Administration	<p>High Dose Interleukin-2/IL2 will be administered over two 5-day cycles. Further doses of IL-2 will be allowed per investigator discretion. Nivolumab will be administered for up to 48 weeks.</p>
Reference Therapy	Nivolumab and Interleukin-2 as monotherapies

Statistical Methodology	<p>This is a single arm phase Ib/II trial of Nivolumab and IL-2 in patients with Renal Cell Carcinoma. The phase Ib has an endpoint of safety and the phase II primary endpoint is overall response rate (ORR = CR or PR) at 12 weeks. A recently reported trial of Nivolumab after 1 prior therapy in RCC reported had an ORR of 25%. With the addition of IL-2 treatment to nivolumab, we hypothesize an ORR of approximately 46% in this population.</p> <p>Study Design/Study Endpoints/Sample Size and Accrual</p> <p>For the phase Ib portion of the study: We will accrue an initial cohort of 3 patients who will be treated with sequential (rather than interspersed) treatment. They will receive 2 cycles of HD-IL2 given in standard fashion (two 5-day cycles one week apart) followed by nivolumab starting the week after the second IL-2 cycle and continuing every weeks as per standard nivolumab dosing. If 2 out of 3 of the first patients suffer a grade 3 or 4 immune related toxicity of interest (see 5.2.1) the study will stop. The 4th patient will not be enrolled until after the analysis of the 3 patient cohort is complete and submitted to the regulatory bodies.</p> <p>If <2 patients suffer a grade 3 or 4 immune related toxicity in the cohort of 3 patients, the study will enroll 7 more patients treated with Nivolumab administered intravenously at 480 mg/dose over 60 minutes every 28 days, starting 1 week to 3 weeks after the start date of the first cycle of IL2. We will monitor these patients continuously for immune mediated dose limiting toxicities for 28 days from the first dose of nivolumab with DLTs being reported as they occur. 10 total patients will be treated and observed for toxicity for 28 days from the first dose of Nivolumab. If, at any time during accrual, 6 patients or more have a grade 3 or 4 immune mediated event of interest (as described in section 5.2.1) we will pause the study and modify/discontinue the protocol in consultation with the site principal investigators and applicable regulatory authorities. If 5 or fewer patients experience grade 3 or 4 immune mediated toxicity of interest (see 5.2.1) during the toxicity window, then the study will continue to the phase II portion. We choose to examine toxicity after 10 patients because if 6 patients or more are found to have a DLT then the 95% exact binomial confidence interval will be > 25% and be indicative that there is too high an incidence of serious immune mediated toxicities.</p> <p>The phase II portion of the trial will be a Simon mini-max 2-stage design. The first stage will accrue 12 patients (INCLUDING any evaluable patients accrued in the phase 1b portion). If more than 2 patients have a response (CR or PR) out of the 12 patients, then we will accrue 11 more patients for a total sample size of 23 evaluable patients. If more than 8 responses (CR or PR) are observed, then we will recommend further study of the combination. This design has 80% power and 10% type I error. If the true ORR of the combined treatment is 25% or less, the probability of early termination of the trial is 39%. If the true ORR is 46% or greater, then the probability of stopping early is only 3.6%. Patients accrued in the Phase Ib portion of the trial will also be included in the Phase II if they are evaluable as defined below.</p> <p>Evaluable Patients: All patients who receive at least 1 dose of IL-2 and at least 1 dose of Nivolumab will be evaluable for the primary endpoint of overall response proportion in the phase II portion of the</p>
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	<p>trial. If response at 12 weeks is not recorded for the patient then the patient will be considered a non-responder.</p>
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1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

An estimated 64,770 cases of kidney cancer (RCC) were diagnosed in the U.S. in 2012 with an estimated 13,570 deaths (SEER). There has been a steady 2-4% per year increase in the incidence of RCC since 1975 that is not explained by increased and improved imaging studies. Clear cell cancers are the most common variant of kidney cancers comprising up to 80% of RCC. The five-year survival rate for RCC subjects is 70%, however, this includes the majority of subjects with localized disease whose five-year survival is 91%. At the time of diagnosis approximately 30% of RCC subjects have metastatic disease and another 30% of subjects recur, and five-year survival for metastatic disease is less than 10%. Therefore, there remains an urgent need for improvement in the therapeutic management of metastatic clear cell RCC (mRCC).

RCC was one of the first cancers in which immuno-stimulatory therapy, such as interleukin-2 (IL-2), was shown to induce durable treatment response including durable complete responses (DCR) leading to FDA approval of High Dose (HD) IL-2 treatment for mRCC subjects as early as 1992. Although HD IL-2 remains the only first-line therapy for clear cell mRCC subjects offering a potential durable complete response, only a small minority of subjects exhibits complete response (CR). Strategies for enhancing the percentage of subjects exhibiting a DCR and enhancing the overall response rate associated with HD IL-2 address an urgent unmet clinical need in this subject population.

1.2 Study Agent(s) Background and Associated Known Toxicities

Interleukin-2:

IL-2 is a cytokine that is a potent growth factor for T cells. It exerts its activity by binding to the IL-2 receptor (IL-2R) present on the cell surface of T cells and leads to its auto phosphorylation via JAK/STAT5-dependent pathways, eventually leading to activation and proliferation of the T cells¹. Although the exact mechanism by which HD IL-2 results in durable CR is not known, the discovery that recombinant IL-2 can have potent anti-tumor activity was shown in murine models as early as 1980s². The stimulatory effects of IL-2 have been demonstrated in multiple pathways required for a successful generation of adaptive and CTL (cytotoxic lymphocyte)-mediated anti-tumor response. For example, IL-2 is produced by the antigen-presenting cells (APCs) after they have phagocytosed dying tumor cells (or pathogens), presented their antigen in conjunction with MHC class II and have bound to their corresponding T cell receptor (TCR) on the surface of CD4+ T cells. In this setting, IL-2 is considered the third essential signal that is necessary for clonal expansion and effector function of T cells, the first being TCR recognition of antigen in MHC and the second being binding of co-stimulatory molecule CD 28 to B71. Similarly, CD8+ CTL function is also critically dependent on IL-2 as shown by experiments that effector or cytotoxic function is limited in IL-2 or IL-2R-deficient mice³⁻⁵. IL-2 is postulated to increase trafficking of CTL to the extralymphatic sites of infection or tumor^{1,6}. IL-2 induces Th1 differentiation of CD4 T helper cells which leads to activation of macrophages. Th1 cells also activate antibody production by activating B cells. IL-2 is produced by Th1 cells in response to activation by DC that results in CD8 activation and proliferation. A distinct mechanism of antitumor activity of IL-2 may be mediated by activation of natural killer (NK) cells⁷.

While the exact mechanism of anti-tumor activity of HD IL-2 is unclear, seven phase II and multiple phase III trials have clinically proven the efficacy of IL-2 in inducing durable CR and PR in clear cell RCC subjects⁸⁻¹⁰. In contrast, molecularly targeted therapies do not induce durable CR. The reported RR for treatment with HD IL-2 (600,000-800,000 IU/kg q8h x 14 as tolerated) in multiple phase III trials ranges from 20% to 23.2% and the

CR ranges from 7%-9%. Among the subjects who achieve CR, >80% remained disease free at last follow-up with a median survival over 10 years^{9,11,12} suggesting a durable response or a cure of mRCC. Alternate schedules and decreased doses of IL-2 have been tried without any improvement in outcome^{8,10}.

There are significant but manageable toxicities from HD IL-2 affecting multiple organ systems. These side effects include hypotension, cardiac arrhythmias, metabolic acidosis, fever, nausea and vomiting, dyspnea, edema, oliguria and renal failure, neurotoxicity, and dermatologic complications, and a mortality rate of less than 1% in recent trials.

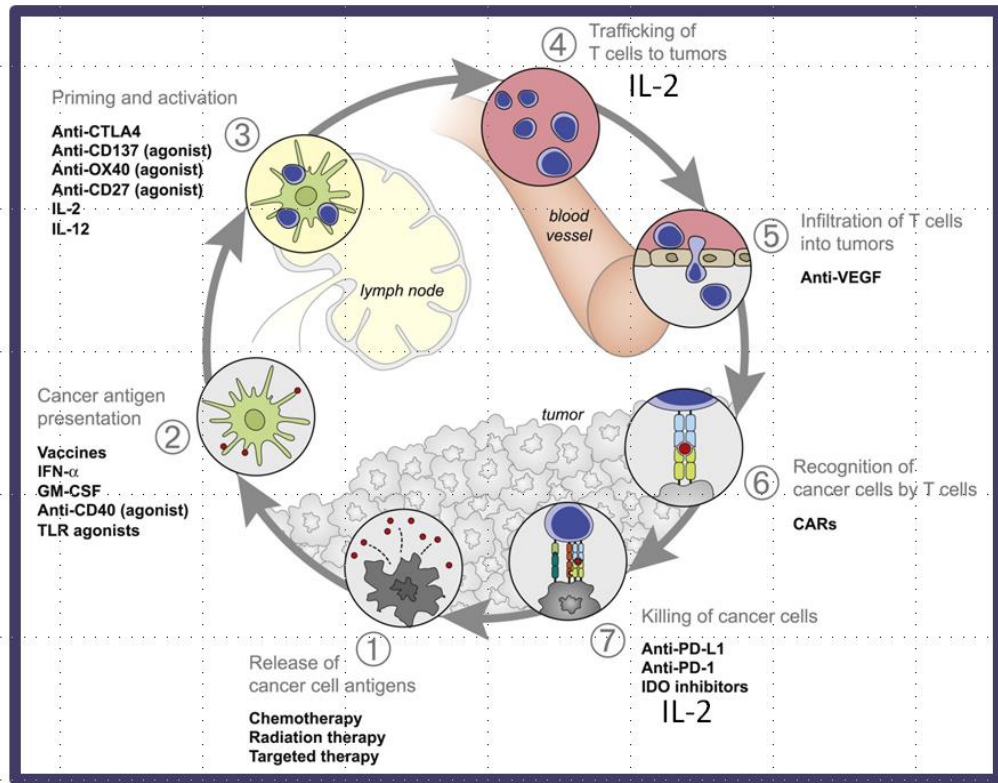
SELECT Trial:

The Cytokine Working Group (CWG) designed and conducted the HD IL2 "Select" Trial¹³. The primary objective of this prospective single-arm study was to evaluate prospectively whether an integrated selection model (ISM) based on clear-cell histology and carbonic anhydrase-9 (CA-9) IHC staining could identify a group of patients with advanced RCC and "good" predictive features who were significantly more likely to respond to HD IL2-based therapy than a historical, unselected patient population. During the course of this trial, retrospective analyses identified potential predictors of increased [e.g., programmed death-ligand 1 (PD-L1) expression, CA-9 gene SNP] and decreased (e.g., elevated pretreatment levels of fibronectin and VEGF) response to immunotherapy in patients with RCC.

One hundred and twenty eligible patients (of any histologic subtype of metastatic renal cell carcinoma type and no prior systemic therapy) were enrolled; 70% were Memorial Sloan Kettering Cancer Center (New York, NY) intermediate risk, 96% had clear cell RCC, and 99% had prior nephrectomy. The independently assessed ORR was 25% (30/120, 95% CI, 17.5%–33.7%, $P = 0.0014$; 3 complete responses (2.5%), 27 partial responses (22.5%)) and was higher than a historical ORR. Thirteen patients (11%) remained progression free at 3 years and the median overall survival was 42.8 months. ORR was not statistically different by ISM classification ("good-risk" 23% vs. "poor-risk" 30%; $P = 0.39$).

Overall response rate was not associated with CA-9 SNP status or plasma VEGF or fibronectin levels (data not shown). Response was positively associated with tumor expression of PD-L1 ($P = 0.01$) and B7H-3 ($P = 0.08$; Table 3) by IHC staining (23). Durable remission (PFS > 3 years) was positively associated with tumor expression of PD-L1 ($P < 0.01$) but not B7-H3 ($P = 0.73$) by IHC staining.

Data from the SELECT trial has led to the hypothesis that IL2 administration may be more effective in "inflamed" tumors that are infiltrated by CD8+ T cells and express immune inhibitory molecules (e.g., PD-L1 or B7-H3) but needs to be confirmed in prospective trials¹⁴.

Figure 1: Anti-cancer lymphocyte activation and proliferation¹⁵**Ref:** Chen DS, et al. *Immunity*. 2013;39:1-10. DOI: (10.1016/j.immuni.2013.07.012)**Nivolumab:**

Tumor immune evasion is the norm in mRCC despite the presence of activated tumor infiltrating lymphocytes (TILs) and indeed is a hallmark of cancer¹⁴. The increasing understanding of immune checkpoints such as CTLA-4 and PD-1 that attenuate the anti-cancer immune response has been clinically validated in multiple tumor types including RCC with the use of checkpoint inhibitors¹⁶⁻¹⁸.

Nivolumab is a PD-1 checkpoint inhibitor, approved by the FDA for treatment of patients with renal cell carcinoma. It is a fully human IgG4 programmed death 1 (PD-1) immune checkpoint inhibitor antibody that selectively blocks the interaction between PD-1, which is expressed on activated T cells, and PD-1 ligand 1 (PD-L1) and 2 (PD-L2), which are expressed on immune cells and tumor cells. Interaction between PD-1 and PD-L1 or PD-L2 lead to the inhibition of cellular immune response. Previous studies have shown that PD-L1 expression is associated with a poor prognosis in renal cell carcinoma^{19,20}. Furthermore, a phase III randomized trial have found significant increase in overall survival in patients treated with nivolumab, as compared to everolimus, with fewer grade 3 or 4 adverse events²¹.

Nivolumab has been investigated in a randomized phase III clinical trial in patients with advanced renal cell carcinoma, previously treated with one or two regimens of antiangiogenic therapy (N=821). Patients were randomized to receive nivolumab at 3 mg/kg of body weight intravenously every 2 weeks or a 10 mg everolimus tablet orally once daily. The primary end point was overall survival, while the secondary end points included the objective response rate and safety²¹. The median overall survival was 25 months with nivolumab as compared to 19.6 months in everolimus treated patients. The

hazard ratio for death with nivolumab versus everolimus was 0.73 (98.5% CI, 0.57 to 0.93; $P = 0.002$), which met the pre-specified criterion for superiority ($P \leq 0.0148$). The objective response rate was greater with nivolumab than with everolimus (25% vs. 5%; odds ratio, 5.98 [95% CI, 3.68 to 9.72]; $P < 0.001$). The median progression-free survival was 4.6 months (95% CI, 3.7 to 5.4) with nivolumab and 4.4 months (95% CI, 3.7 to 5.5) with everolimus (hazard ratio, 0.88; 95% CI, 0.75 to 1.03; $P = 0.11$). Grade 3 or 4 treatment-related adverse events occurred in 19% of the patients receiving nivolumab and in 37% of the patients receiving everolimus; the most common event with nivolumab was fatigue (in 2% of the patients), and the most common event with everolimus was anemia (in 8%). The results of this trial showed that nivolumab was efficacious in improving the overall survival with fewer adverse events, as compared to everolimus in patients with renal cell carcinoma. The following figures and table show the efficacy and safety of nivolumab in metastatic RCC.

Figure 2: Kaplan Meier Curve for Overall Survival in the phase 3 trial of nivolumab versus everolimus²¹. Ref: Motzer RJ et al. N Engl J Med 2015;373:1803-1813

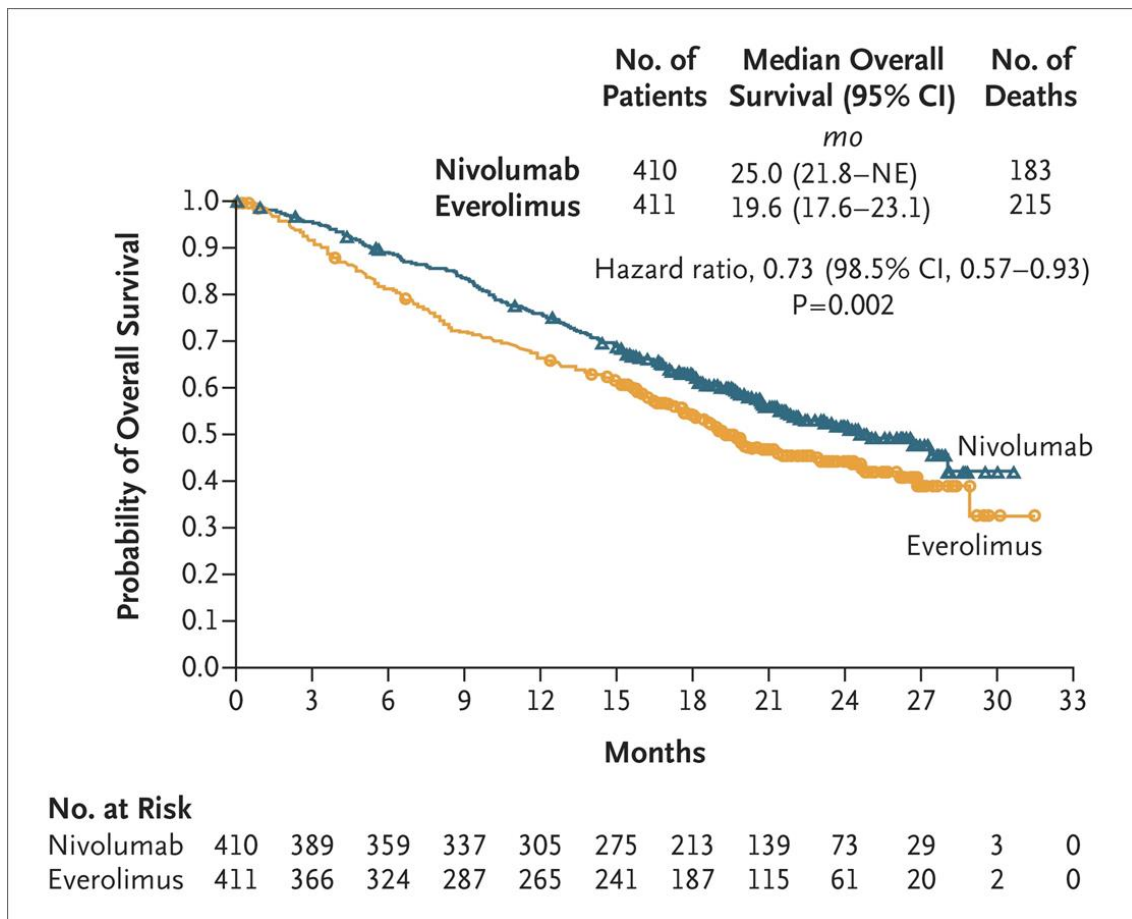


Figure 3: Kaplan Meier Curve for Overall Survival stratified by PD-L1 expression in tumor at baseline in the phase 3 trial of nivolumab versus everolimus²¹
 Ref: Motzer RJ et al. N Engl J Med 2015;373:1803-1813

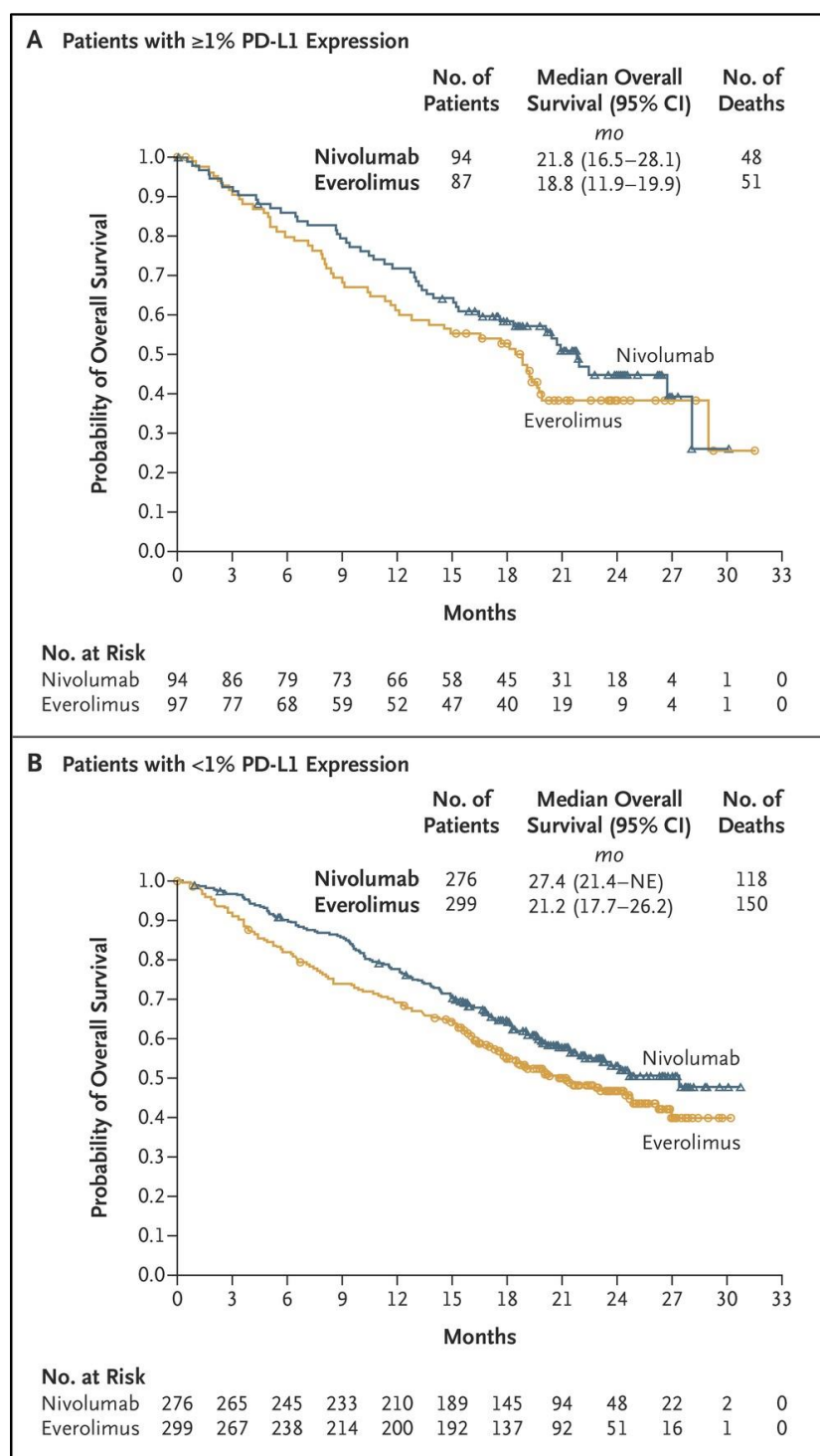
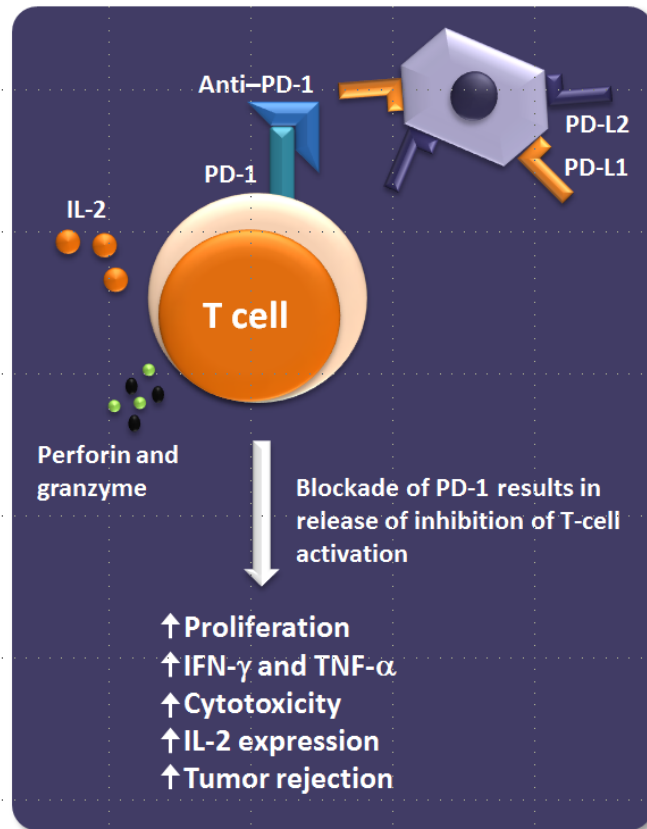


Table 1 Treatment-Related Adverse Events Reported in 10% or more of treated patients in either group in the phase 3 trial of nivolumab versus everolimus
Ref: Motzer RJ et al. N Engl J Med 2015;373:1803-1813

Event	Nivolumab Group (N = 406)		Everolimus Group (N = 397)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	<i>number of patients (percent)</i>			
All events	319 (79)	76 (19)	349 (88)	145 (37)
Fatigue	134 (33)	10 (2)	134 (34)	11 (3)
Nausea	57 (14)	1 (<1)	66 (17)	3 (1)
Pruritus	57 (14)	0	39 (10)	0
Diarrhea	50 (12)	5 (1)	84 (21)	5 (1)
Decreased appetite	48 (12)	2 (<1)	82 (21)	4 (1)
Rash	41 (10)	2 (<1)	79 (20)	3 (1)
Cough	36 (9)	0	77 (19)	0
Anemia	32 (8)	7 (2)	94 (24)	31 (8)
Dyspnea	30 (7)	3 (1)	51 (13)	2 (1)
Peripheral edema	17 (4)	0	56 (14)	2 (1)
Pneumonitis	16 (4)	6 (1)	58 (15)	11 (3)
Mucosal inflammation	11 (3)	0	75 (19)	12 (3)
Dysgeusia	11 (3)	0	51 (13)	0
Hyperglycemia	9 (2)	5 (1)	46 (12)	15 (4)
Stomatitis	8 (2)	0	117 (29)	17 (4)
Hypertriglyceridemia	5 (1)	0	64 (16)	20 (5)
Epistaxis	3 (1)	0	41 (10)	0

Figure 4: Lymphocyte proliferation and activity in the context of IL2 and PD-1 blockade
Ref: Chen DS, et al. Immunity. 2013;39:1-10. DOI: (10.1016/j.immuni.2013.07.012)



1.3 Rationale

High dose Interleukin-2 and nivolumab are both active agents in metastatic clear cell renal cell cancer with complementary and potentially synergistic mechanisms of action at distinct points of the T-lymphocyte activation, trafficking, proliferation and anti-tumor cell cytotoxicity process. PD-L1 expression on tumor cells is thought to be induced by infiltrating CD8+ T cells in the tumor microenvironment²².

We hypothesize that concurrent PD-1 inhibition synergistically enhances the anti-tumor immune response to HD IL-2 in metastatic clear cell RCC. We postulate that the combination of the two therapies would result in an increase in the overall response rate, complete response rate, and improved survival outcomes compared to either of the individual therapies.

We propose a single arm, multi-site, phase Ib/II clinical trial of Nivolumab (480 mg/dose intravenously over 60 minutes every 28 days), a PD-1 inhibitor, in combination with standard doses of High Dose Interleukin-2 (600,000 IU/kg/dose intravenously) every 8 hours for up to a maximum of 28 doses during two 5-day cycles one week apart in interleukin-2 eligible clear cell mRCC subjects.

1.4 Correlative Studies

- 1) We propose to descriptively profile the circulating T-cell repertoire by performing Flow Cytometry and cell sorting in whole blood samples at the time points listed in Section 6.4 Time and Events Table. These studies will be hypothesis generating and could possibly guide timing and combination of immunotherapies in renal cell cancer.
- 2) We will archive patient tumor and serum samples for future testing including but not limited to PD-L1 testing and anti-drug antibody testing.

2.0 STUDY OBJECTIVES

Phase Ib portion:

2.1 Primary Objective

- 2.1.1 To estimate the safety and toxicities of High Dose Interleukin-2 in combination with the immune checkpoint inhibitor Nivolumab in metastatic clear cell renal cell carcinoma

Phase II portion:

2.2 Primary Objective

- 2.3.1 To assess the efficacy of High Dose Interlukin-2 in combination with the immune checkpoint inhibitor Nivolumab in metastatic clear cell renal cell carcinoma.

2.3 Secondary Objectives

- 2.4.1 To determine the safety of High Dose Interlukin-2 in combination with the immune checkpoint inhibitor Nivolumab in metastatic clear cell renal cell carcinoma.
- 2.4.2 To profile circulating T cell repertoire by flow cytometry before and during therapy.

2.4 Exploratory Objectives

- 2.5.1 To bank tissue and serum specimens for future correlative analyses and anti-drug antibody testing.

Study Endpoints

Phase Ib portion:

Primary Endpoint: To establish that the combination of High Dose Interlukin-2 and Nivolumab is safe and tolerable by monitoring 10 patients for immune mediated grade 3/4 events of interest for 28 days from the first dose of Nivolumab.

Phase II portion:

Primary Endpoint: Efficacy of the combination therapy will be determined by the overall response (ORR) rate/proportion with response including complete response rate/proportion as assessed by RECIST 1.1 criteria.

Secondary Endpoints:

Safety will be defined by the frequency of protocol specified therapy-related grade 3-5 adverse events including events of clinical interest for duration of protocol specified therapy and an additional 60 days beyond that, as assessed by NCI's CTCAE version 4.0.

Survival endpoints for efficacy are 24-month Overall Survival (OS) and 24-month Progression-Free Survival (PFS) in subjects treated with the combination by RECIST 1.1 criteria.

To descriptively characterize the circulating immune cell repertoire before and after start of combination therapy with High Dose Interlukin-2 in combination with the immune checkpoint inhibitor Nivolumab

3.0 PATIENT ELIGIBILITY

Subjects must meet all of the inclusion and exclusion criteria to be enrolled to the study. Study treatment may not begin until a subject is enrolled.

3.1 Inclusion Criteria

- 3.1.1 Subjects must have a histologic diagnosis of clear cell renal cell carcinoma (pure or mixed) with radiologic or histologic or cytologic evidence of metastatic disease.
- 3.1.2 Subjects may have received up to 2 prior lines of systemic therapy (excluding any neoadjuvant/adjuvant therapy) including anti-VEGF or VEGFR inhibitor (e.g. sorafenib, pazopanib, sunitinib, bevacizumab, axitinib) or mTOR inhibitor (e.g. everolimus or temsirolimus) for metastatic disease.
- 3.1.3 Age \geq 18 years at the time of consent.
- 3.1.4 ECOG performance status of 0 or 1.
- 3.1.5 Adequate organ and marrow function as defined below:

White blood count	$\geq 3000/\text{mm}^3$
Platelet count	$\geq 100,000/\text{mm}^3$
Hemoglobin	$\geq 10.0 \text{ g/dl}$
ALT, AST	$\leq 2.5 \times$ upper limit of institutional normal reference range
Total Bilirubin	$\leq 1.5 \times$ the upper limit of normal (patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia in the absence of evidence of hemolysis or hepatic pathology) will be allowed to enroll after discussion with the principal investigator if total bilirubin is $\leq 3 \times$ the upper limit of normal),
Serum creatinine	$\leq 1.5 \times$ laboratory upper limit of normal or calculated creatinine clearance of $\geq 50 \text{ ml/min/1.73 m}^2$)
PT/INR	≤ 1.5
Urine	≤ 1

Protein/Creatinine ratio	
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- 3.1.6 Women of childbearing potential must have a negative serum or urine pregnancy test within 28 days prior to registration. Women of non-childbearing potential are defined as those who have no uterus, ligation of the fallopian tubes, or permanent cessation of ovarian function due to ovarian failure or surgical removal of the ovaries. All others are considered women of child bearing potential.
- 3.1.7 Females and males of childbearing potential must be willing to use an effective method of contraception (hormonal or barrier method of birth control; abstinence) from the time consent is signed until 12 weeks (for males) and 5 months (for females) after treatment discontinuation.
- 3.1.8 Subjects must have measurable disease on physical exam or imaging per RECIST 1.1 criteria.
- 3.1.9 An archived tissue block with the subject's renal cell carcinoma must be identified prior to registration. Please see Section 10.0 for additional information
- 3.1.10 Subjects must be considered appropriate candidates for HD IL-2 by one of the treating investigators listed on the protocol. HD IL-2 candidacy evaluation is per institutional guidelines at each site and should include a dobutamine stress echocardiogram or equivalent. Subjects with a positive stress test for cardiac ischemia would be excluded from this trial.
- 3.1.11 No clinically significant infections or any other medical condition(s) that render the subject ineligible for high dose IL-2 therapy as judged by the treating investigator.
- 3.1.12 Ability to understand and the willingness to sign a written informed consent.

3.2 Exclusion Criteria

- 3.2.1 Prior interferon or interleukin-2 therapy is NOT allowed.
- 3.2.2 Prior anti-PD-1/PD-L1 targeted therapy is NOT allowed. Prior CTLA-4 therapy or CD40/CD40L targeted therapy is allowed.
- 3.2.3 Prior systemic treatment must be completed at least 14 calendar days prior to registration and the subject must have recovered from the toxicities of treatment to grade 1 or better.
- 3.2.4 Prior radiation therapy is allowed if completed at least 14 calendar days prior to registration.
- 3.2.5 Treatment with any investigational agent or on an interventional clinical trial within 30 days prior to registration.
- 3.2.6 No prior or concurrent malignancy is allowed except for: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, localized or locally advanced prostate cancer definitively treated without recurrence or with

biochemical recurrence only, or any other cancer fully treated or from which the subject has been disease-free for at least 2 years.

- 3.2.7 Current untreated brain metastasi(e)s. If treated history of CNS metastases, should have completed radiation or surgery at least 12 weeks prior and off systemic corticosteroids.
- 3.2.8 Autoimmune diseases such as rheumatoid arthritis are NOT allowed. Vitiligo, mild psoriasis (topical therapy only) or hypothyroidism are allowed
- 3.2.9 Medical need for systemic corticosteroids >10mg prednisone daily or equivalent alternative steroid (except physiologic dose for adrenal replacement therapy) or other immunosuppressive agents (such as cyclosporine or methotrexate) Topical and inhaled corticosteroids are allowed if medically needed
- 3.2.10 History of allergic reaction to interleukin-2 or nivolumab
- 3.2.11 Prior history of psychiatric disorder or seizure disorders which could be exacerbated by Interleukin-2 as judged by the treating investigator.
- 3.2.12 Evidence of significant cardiovascular disease including history of recent (< 6 months prior) myocardial infarction, congestive heart failure, primary cardiac arrhythmias (not due to electrolyte disorder or drug toxicity, for example) beyond occasional PVC's, angina, positive low-level stress test, or cerebrovascular accident. All patients should have baseline pulmonary function tests. Adequate pulmonary function should be documented (FEV1 >2 liters or ≥75% of predicted for height and age) prior to initiating therapy.
- 3.2.13 Any history of HIV or hepatitis B infection
- 3.2.14 Any other medical or surgical condition or disease that, in the judgment of the treating physician, renders subject ineligible for High Dose Interleukin-2 therapy.
- 3.2.15 Any history of organ allografts
- 3.2.16 Any history of cerebrovascular accident or transient ischemic attack

4.0 SUBJECT SCREENING AND REGISTRATION PROCEDURES

After informed consent is obtained and PRIOR to the initiation of protocol therapy all patients satisfying the inclusion/exclusion criteria must have eligibility confirmed by the Coordinating Center. The patient will not be considered registered and enrolled in the study until all information is confirmed by the Coordinating Center's Multi-Site Coordinator.

Patient registration for this trial will be centrally managed as described below:

A potential study subject who has been screened for the trial and who has signed the Informed Consent document will be initially documented by the participating site on a Screening and Enrollment Log.

It is the responsibility of the local site investigator to determine patient eligibility prior to submitting patient registration request to the Coordinating Center. After patient eligibility has been determined, a copy of the **completed** Eligibility Worksheet together with all the pertinent de-identified source documents will be submitted by the requesting site to the Coordinating Center, by email to CTSU-Oncology-Multisite@med.umich.edu.

A Multi-Site Coordinator of the Coordinating Center, who acts as the registrar, will review the submitted documents and process the registration. Sites should inform the Multi-Site Coordinator of a potential registration by 5 p.m. on the day prior to registration. Same day registrations cannot be guaranteed.

An email will be sent by the registrar to the requesting site registrar to confirm patient registration and to provide the study identification number that has been assigned to the patient. In addition, a copy of the Eligibility Worksheet signed and dated by the registrar, will be sent back to the requesting site registrar.

Patients found to be ineligible for participation after being consented will be considered screen failures, and documented as such in the Screening and Enrollment Log. These patients will not have study identification number assigned to them, and will not receive study treatment.

5.0 TREATMENT PLAN

5.1 Treatment Dosage and Administration

Protocol treatment must start within 14 business days of enrollment to the study. The interleukin-2 (Proleukin) and Nivolumab (Opdivo) will be stored and prepared as described in the approved labels.

- 5.1.1 Therapy will start with high dose interleukin-2 (HD IL2) on week1 (day 1-5) and again on week 3 (day 1-5). Nivolumab will start on week 2 (optimally day 1 but can be given up to 3 weeks after IL-2 start but NOT be on the same week as any HD IL2 cycle) and continue every 4 weeks for up to 48 weeks on study unless one of the dose delay or stopping rules apply.
- 5.1.2 HD IL-2 will be administered in standard fashion at a fixed dose of 600,000 IU/kg/dose every 8 hours for a total of up to 14 doses (considered as one cycle) over 5 consecutive days (D1-D5), followed by a 9-day break and then another cycle at the same dose over another 5 consecutive days (D15-D19). Each HD IL-2 course consists of two cycles of up to 14 doses each separated by 9 days of rest.

Monitoring, supportive care measures for HD IL2 will be per institutional guidelines. The standard current guidelines for HD IL-2 administration based on Schwartzentruber et al. have proven to be safe at the participating institutions in the study over the years and will be used for this protocol²³.

Pre-medications and concurrent medications: Per institutional guidelines at each site usually include anti-emetics, anti-histamines, antipyretics/anti-inflammatory agents, anti-motility/anti-diarrheal agents, proton pump inhibitors, vasopressors as needed, medications for rigors as needed, hydration including boluses and maintenance fluids. It is recommended but not mandated that subjects be given anti-emetics for as needed (prn) use after each IL-2 therapy week to treat residual nausea. Furosemide (a loop diuretic) may also be given per treating investigator's discretion following each IL2 week. Please see IL-2 guidance document for more details.

Subjects will undergo placement of a central venous catheter before each course or cycle of therapy per institutional preferences.

NOTE: If the treating investigator determines another course of HD IL-2 beyond the 2 cycles after week 12 of protocol therapy specified in the protocol are in the

subject's best interests, it is permissible and will be recorded in follow-up. If so, nivolumab should be held during IL2 weeks. No protocol specified assessments are required for the repeat course.

- 5.1.3 Nivolumab will be administered intravenously at a standard dose of 480 mg/dose every 4 weeks starting on week 2 (ideally day 1 of week 2 but can be given up to 3 weeks after IL-2 start but NOT be on the same week as any HD IL2 cycle) and continued as long as clinical benefit continues as determined by the treating investigator for up to 48 weeks on study.
- 5.1.4. The first 3 patients will be treated with sequential (rather than interspersed) treatment. They will receive 2 cycles of HD-IL2 given in standard fashion (two 5-day cycles one week apart) followed by nivolumab starting the week after the second IL-2 cycle and continuing every 4 weeks as per standard nivolumab dosing.

We will perform a safety analysis after the first 3 patients are treated and if 2/3 patients suffer a grade 3 or 4 immune related toxicity, the study will stop. The 4th patient will not be enrolled until after the analysis of the 3 patient cohort is complete and submitted to the regulatory bodies

REGIMEN DESCRIPTION

Agent	Premedications	Dose	Route	Schedule
Interleukin-2	Per institutional guidelines, none mandated.	600,000 IU/kg/dose ^Ω every 8 hours Prepare and store according to approved label.	IV over 15 minutes (± 5 minutes)	Week 1 (Days 1-5) AND Week 3 (Days 1-5)
Nivolumab	Per institutional guidelines, none mandated.	480 mg/dose Prepare and store according to approved label.	IV over 60 (± 10 minutes) minutes	Every 28 days starting Week 2 (Optimally Day 1 but can be given up to 3 weeks after IL-2 start)

^ΩThe IL-2 dose should be calculated separately on D1 and D15.

NOTE: Infusions may be performed ±3 business days for reasons such as observed holidays, inclement weather, scheduling conflicts, etc. It should be clearly documented in subject's chart and case report forms.

5.1.5 Missed doses

Missed doses of HD IL-2 are not made up. Missed doses of Nivolumab can be made up within 72 hours of scheduled time and skipped if outside of 72 hours

5.2 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Time and Events Table (Section 6.4). Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

Dose modifications in strength are not permitted for either IL2 or nivolumab.

Dosing delays:

- **DURING IL-2 weeks**

- Individual doses of IL-2 within each cycle may be skipped by the treating investigator at his or her discretion. Skipped doses will not be made up.

- **AFTER IL-2, BEFORE NIVOLUMAB**

- All toxicities (with the exception of fatigue) attributed to IL-2 administration should have resolved or recovered to grade 1 or resolved or to baseline prior to starting nivolumab
 - Fatigue should have recovered to grade 2 or better
 - If toxicities have not improved to the levels listed above, nivolumab and the 2nd cycle of IL-2 should be held until toxicities improve to the above levels
 - If nivolumab or IL-2 is delayed >6 weeks as a result of a toxicity, the subject must be permanently discontinued from study therapy with the following exception:
 - If a steroid taper (to manage drug-related adverse events) is the reason for treatment delay of >6 weeks, and the subject's adverse events recover to grade 1 or better, continuation on study could be possible if approved by the principal investigator

- **AFTER NIVOLUMAB, PRIOR TO 2nd IL-2 CYCLE**

- All immune mediated toxicities should have recovered to grade 1 or better prior to starting the second dose of IL-2 and subjects should be off systemic steroids or on a dose of ≤ prednisone 10mg (or equivalent alternative steroid).
 - Fatigue should have recovered to grade 2 or better
 - If specific toxicities are of unclear attribution (including for example: diarrhea, increased LFTs, cardiovascular disorders, mental status changes, pulmonary disorders and rash) they should be treated as possibly related to nivolumab and treated as per the tables in section 5.2.2. These toxicities must improve to grade 1 or better prior to proceeding with the second week of IL-2 therapy.
 - If toxicities have not improved to the levels listed above, nivolumab and the 2nd cycle of IL-2 should be held until toxicities improve to the above levels

- If nivolumab or IL-2 is delayed >6 weeks as a result of a toxicity, the subject must be permanently discontinued from study therapy with the following exception
 - If a steroid taper (to manage drug-related adverse events) is the reason for treatment delay >6 weeks, and the subject's adverse events recover to grade 1 or better, continuation on study could be possible if approved by the principal investigator
- **DURING NIVOLUMAB ONLY TIME PERIOD:**
 - With any grade 2 or higher **non-hematologic toxicity**, hold nivolumab and refer to section 5.2.1 Events of Interest for relevant management guidelines. If adverse event is not an event of interest and improves to grade 1 or better with symptomatic management and/or supportive medications, nivolumab may be resumed in ≥ 2 weeks. If non-hematologic toxicity does not improve to grade 1 or better within 6 weeks from prior dose, nivolumab should be discontinued.

5.2.1 IMMUNE MEDIATED EVENTS OF INTEREST (ONCE AT LEAST 1 DOSE OF NIVOLUMAB HAS BEEN ADMINISTERED) - APPLY TO NIVOLUMAB ONLY:

Certain adverse events that are possibly immune mediated warrant special monitoring and management, and are outlined below to guide investigators.

5.2.1.1 Pulmonary:

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue protocol therapy. Evaluate with imaging and pulmonary consultation.

Grade of pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic Changes Only	<ul style="list-style-type: none"> • Consider delay of nivolumab • Monitor for symptoms every 2-3 days • Consider pulmonary and infectious disease consultations 	<ul style="list-style-type: none"> • Re-image at least every 3 weeks • If worsening, treat as grade 2,3 or 4
Grade 2 Mild to moderate new symptoms	<ul style="list-style-type: none"> • Delay nivolumab • Consult pulmonary and infectious disease • Monitor symptoms daily, consider hospitalization • 1.0mg/kg/day methylprednisolone IV or oral equivalent • Consider bronchoscopy and/or lung biopsy 	<ul style="list-style-type: none"> • Re-image every 1-3 days • Consider prophylactic antibiotics while on steroids • If improves: <ul style="list-style-type: none"> • When symptoms return to near baseline, taper steroids over at least one month • Resume nivolumab and IL-2 if the event improves to grade 0 or 1 within 12 weeks and corticosteroids have been reduced to the equivalent of ≤ 10mg oral prednisone per day • If not improving after 2 weeks or worsening, treat as grade 3 or 4

Grade 3 or 4 Severe new symptoms and/or new or worsening hypoxia	<ul style="list-style-type: none"> Discontinue nivolumab. Hospitalize Consult pulmonary and infectious disease 1-2mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections like PCP Consider bronchoscopy and/or lung biopsy 	<ul style="list-style-type: none"> If improves to baseline: <ul style="list-style-type: none"> Taper steroids for at least 6 weeks If not improving after 48 hours or worsening <ul style="list-style-type: none"> Add additional immunosuppressive agent(s) (e.g. infliximab, cyclophosphamide, intravenous immunoglobulin or mycophenolate mofetil)
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5.2.1.2 Gastrointestinal:

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue protocol therapy. Opiates or narcotics may mask symptoms of perforation. Infliximab should not be used in case of perforation or sepsis.

Grade of diarrhea/colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea of less than 4 stools per day over baseline or asymptomatic colitis	<ul style="list-style-type: none"> Continue nivolumab Symptomatic treatment such as loperamide 	<ul style="list-style-type: none"> Close monitoring for worsening symptoms Educate patient to report worsening immediately If worsening, treat as grade 2,3 or 4
Grade 2 <ul style="list-style-type: none"> Diarrhea of 4-6 stools per day over baseline OR IV fluids needed < 24 hours due to diarrhea OR Colitis with abdominal pain or blood in stool 	<ul style="list-style-type: none"> Hold nivolumab Symptomatic treatment such as loperamide. 	<ul style="list-style-type: none"> If improves to grade 1, resume nivolumab and/or IL-2 If symptoms persist for > 7 days <ul style="list-style-type: none"> 1-2 mg/kg per day of oral prednisone or equivalent Consider prophylactic antibiotics for opportunistic infections like PCP Resume nivolumab and IL-2 if the event improves to grade 0 or 1 within 12 weeks and corticosteroids have been reduced to the equivalent of \leq 10mg oral prednisone per day When symptoms improve to grade 1, taper steroids over at least one month If worsening, treat as grade 3 or 4
Grade 3	<ul style="list-style-type: none"> Hold nivolumab 	<ul style="list-style-type: none"> If improves

Grade of diarrhea/colitis (NCI CTCAE v4)	Management	Follow-up
<ul style="list-style-type: none"> Diarrhea ≥ 7 stools per day over baseline OR IV fluids needed for ≥ 24 hours due to diarrhea OR Colitis with severe abdominal pain or medical intervention indicated 	<ul style="list-style-type: none"> methylprednisolone IV or IV equivalent Start prophylactic antibiotics for opportunistic infections such as PCP Consider lower endoscopy 	<ul style="list-style-type: none"> Continue steroids until symptoms are grade 1, then taper over at least one month Resume nivolumab and IL-2 if the event improves to grade 0 or 1 within 12 weeks and corticosteroids have been reduced to the equivalent of ≤ 10mg oral prednisone per day If persists for $>3-5$ days or recurs after improvement, add infliximab 5mg/kg if no contraindication (Note: infliximab should not be used in cases of perforation or sepsis)
Grade 4 Life threatening or perforation	<ul style="list-style-type: none"> Discontinue nivolumab 1-2mg/kg/day methylprednisolone IV or IV equivalent Start prophylactic antibiotics for opportunistic infections such as PCP Consider lower endoscopy 	<ul style="list-style-type: none"> If improves Continue steroids until symptoms are grade 1, then taper over at least one month If persists for $>3-5$ days or recurs after improvement, add infliximab 5mg/kg if no contraindication (Note: infliximab should not be used in cases of perforation or sepsis)

5.2.1.3 Endocrinopathy:

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue protocol therapy. Consider visual field testing, endocrinology consultation and imaging.

Endocrinopathy	Management	Follow-up
Asymptomatic thyroid-stimulating hormone (TSH) elevation	<ul style="list-style-type: none"> Continue nivolumab If TSH $<0.5 \times$ LLN or TSH $>2 \times$ ULN, or consistently out of range in subsequent measurements, include free T4 in subsequent measurements as clinically indicated Consider endocrinology consult 	
Symptomatic Hypothyroidism	<ul style="list-style-type: none"> Initiate thyroid replacement 	
Symptomatic Hyperthyroidism	<ul style="list-style-type: none"> Delay nivolumab Consider endocrinology consult 	<ul style="list-style-type: none"> Resume nivolumab and IL-2 when symptoms of hyperthyroidism are

Endocrinopathy	Management	Follow-up
	<ul style="list-style-type: none"> Initiate anti-thyroid drug 	controlled and thyroid function is improving
Hypophysitis	<ul style="list-style-type: none"> Administer corticosteroids and hormone replacement as clinically indicated Delay nivolumab for grade 2 or 3 hypophysitis Permanently discontinue nivolumab and IL-2 for grade 4 hypophysitis 	
Symptomatic Adrenal Insufficiency	<ul style="list-style-type: none"> Delay nivolumab Administer methylprednisolone 1-2 mg/kg/day IV followed by oral prednisone 1-2mg/kg per day or equivalent once symptoms improve 	<ul style="list-style-type: none"> If improves to \leq grade 1, taper steroids over at least one month Resume nivolumab and IL-2 if the vent improves to grade 0 or 1 within 12 weeks and corticosteroids have been reduced to the equivalent of ≤ 10 mg oral prednisone per day and the patient is on stable replacement therapy if required

5.2.1.4 Hepatic:

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue protocol therapy. Consider imaging for obstruction.

Grade of Liver Test Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 AST or ALT >ULN to 3x ULN and/or total bilirubin >ULN to 1.5x ULN	<ul style="list-style-type: none"> Continue nivolumab 	<ul style="list-style-type: none"> Continue liver function test monitoring per protocol If worsening, treat as grade 2,3, or 4
Grade 2 AST or ALT >ULN to 3-5x ULN and/or total bilirubin >ULN to 1.5-3x ULN	<ul style="list-style-type: none"> Delay nivolumab Administer corticosteroids at a dose of 1-2mg/kg/day prednisone 	<ul style="list-style-type: none"> Resume nivolumab and IL-2 if returns to baseline If persists >5-7 days or worsens, treat as grade 3 or 4

Grade 3 or 4 AST or ALT >5x ULN and/or total bilirubin >3x ULN	<ul style="list-style-type: none"> • Discontinue nivolumab • Increase frequency of monitoring to every 1-2 days • 1-2mg/kg/day methylprednisolone IV or IV equivalent for grade 3 and 2 mg/kg/day methylprednisolone IV for grade 4 • Add prophylactic antibiotics for opportunistic infections like PCP • Consult gastroenterologist 	<ul style="list-style-type: none"> • If improves to grade 2, taper steroids over at least one month • If does not improve within 3-5 days or worsens after improvement: <ul style="list-style-type: none"> ○ Add mycophenolate mofetil 1g twice daily ○ If no response within an additional 3-5 days, consider other immunosuppressive agents per local guidelines
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5.2.1.5 Neurological:

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue protocol therapy.

Grade of neurological toxicity (NCI CTCAE v 4)	Management	Follow-up
Grade 1 <ul style="list-style-type: none"> • Asymptomatic or mild symptoms • Intervention not indicated 	<ul style="list-style-type: none"> • Continue nivolumab 	<ul style="list-style-type: none"> • Continue to monitor the patient, if worsening treat as grade 2, 3, or 4
Grade 2 <ul style="list-style-type: none"> • Moderate symptoms • Limiting instrumental ADLs 	<ul style="list-style-type: none"> • Delay nivolumab • Treat symptoms per institutional guidelines • Consider 0.5-1mg/kg per day methylprednisolone IV or oral equivalent 	<ul style="list-style-type: none"> • If returns to baseline, resume nivolumab and IL-2 • If worsens, treat as grade 3 or 4
Grade 3 or 4 <ul style="list-style-type: none"> • Severe symptoms • Limiting self-care ADLs 	<ul style="list-style-type: none"> • Discontinue nivolumab • Consult Neurology • Treat symptoms per institutional guidelines • 1-2mg/kg per day IV methylprednisolone or IV equivalent • Add prophylactic antibiotics for opportunistic infections 	<ul style="list-style-type: none"> • If improves to grade 2, taper steroids over at least one month • If worsens, consider IVIG or other immunosuppressive therapies per institutional guidelines
Meningitis or Encephalitis	<ul style="list-style-type: none"> • Discontinue nivolumab • 1-2mg/kg per day IV methylprednisolone or IV equivalent 	<ul style="list-style-type: none"> • If improves, convert to oral steroids (prednisone 60mg/day or equivalent) • When symptoms

		improve to \leq grade 1, taper steroids over at least one month
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5.2.1.6 Skin:

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue protocol therapy

Grade of Rash (NCI CTCAE v4)	Management	Follow-up
Grade 1-2 Covering \leq 30% body surface area (BSA)	<ul style="list-style-type: none"> • Symptomatic therapy (such as antihistamines, topical steroids) • Continue nivolumab 	<ul style="list-style-type: none"> • If persists 1-2 weeks or recurs <ul style="list-style-type: none"> ○ Consider skin biopsy ○ Delay nivolumab and IL-2 ○ Consider 0.5-1mg/kg/day methylprednisolone IV or oral equivalent ○ Once improving, taper steroids for at least one month ○ Consider prophylactic antibiotics for opportunistic infections like PCP ○ Resume nivolumab and IL-2 if rash improves to \leq grade 1 within 12 weeks and corticosteroids have been reduced to \leq 10 mg oral prednisone or equivalent per day • If worsens, treat as grade 3 or 4
Grade 3-4 Covering $>$ 30% BSA or life threatening consequences	<ul style="list-style-type: none"> • Delay or discontinue nivolumab. • Consider skin biopsy • Consult dermatology • 1-2mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections 	<ul style="list-style-type: none"> • If improves to grade 1: <ul style="list-style-type: none"> ○ Taper steroids over at least one month ○ Resume nivolumab and IL-2 if rash improves to \leq grade 1 within 12 weeks and corticosteroids have been reduced to \leq 10 mg oral prednisone or equivalent per day

5.2.1.7 Renal:

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue protocol therapy

Grade of elevation in serum creatinine (NCI CTCAE v4)	Management	Follow-up
Grade 1 Serum creatinine >ULN and >baseline but ≤1.5x baseline	<ul style="list-style-type: none"> Continue nivolumab Monitor serum creatinine weekly 	<ul style="list-style-type: none"> If returns to baseline, resume creatinine monitoring per protocol If worsens, treat as grade 2, 3, or 4
Grade 2 or 3 Serum creatinine 1.5x baseline to ≤ 6 x ULN	<ul style="list-style-type: none"> Delay or discontinue nivolumab Monitor serum creatinine every 2-3 days 0.5-1 mg/kg/day methylprednisolone IV or oral equivalent Add prophylactic antibiotics for opportunistic infections Consider renal biopsy 	<ul style="list-style-type: none"> If improves to grade 1 <ul style="list-style-type: none"> Taper steroids over at least one month Resume nivolumab and IL-2 if improves to ≤ grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day If elevation persists >7 days or worsens, treat as grade 4
Grade 4 Serum creatinine <6x ULN	<ul style="list-style-type: none"> Discontinue nivolumab Monitor serum creatinine daily 1-2mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections Consult nephrology Consider renal biopsy 	<ul style="list-style-type: none"> If improves to grade 1 <ul style="list-style-type: none"> Taper steroids over at least one month Resume nivolumab and IL-2 if improves to ≤ grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day

For nivolumab only with any grade 4 **hematologic toxicity**, hold nivolumab. If the adverse event improves to grade 3 or better with symptomatic management and/or supportive medications, nivolumab may be resumed in ≥2 weeks.

Discontinue both IL-2 and Nivolumab permanently for the following conditions:

- Guillain-Barre Syndrome (GBS)
- Myasthenia gravis
- Pituitary apoplexy or hypopituitarism (clinical including based on biochemical values).

5.3 Concomitant Medications/Treatments

Corticosteroids greater than the equivalent of 10mg daily of prednisone (except physiologic dose for adrenal replacement therapy), other immunosuppressive agents (such as cyclosporine or methotrexate) and any other medications that could potentially impact the efficacy or safety of the study as judged by the treating investigator are NOT permitted from time of registration to subjects completing protocol therapy unless clinically indicated to manage adverse events or life threatening or serious conditions as determined by the treating investigator.

5.4 Other Modalities or Procedures

Nivolumab should be held for any surgery or radiotherapy until subject is judged to be stable to resume by treating investigator as adequate information does not exist on its effects on wound healing and radio sensitization effects. When resumed, same dose level will be maintained. Percutaneous procedures like imaging guided biopsies and central line placements do not require Nivolumab to be held.

5.5 Duration of Protocol Specified Therapy (IL2 and/or Nivolumab)

In the absence of treatment delays due to adverse events, treatment may continue for up to 48 weeks or until one of the following criteria apply:

- Disease progression as defined in Section 7.0.
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient voluntarily withdraws from treatment
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

5.6 Off Protocol Specified Therapy Criteria

Patients will be removed from protocol specified therapy when any of the criteria listed in Section 5.5 apply. The reason for ending protocol therapy and the date the patient was removed from treatment should be documented. All patients who discontinue treatment should comply with protocol specific follow-up procedures as outlined in Section 6.3. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely.

5.7 Duration of Follow-Up

Patients will be followed for 2 years (counting from week 1) after completion of/removal from treatment or until death, whichever occurs first. Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse events.

5.8 Off Study Criteria

Patients can be taken off study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation from study will be documented and may include:

- 5.8.1 Patient withdraws consent (termination of treatment and follow-up);
- 5.8.2 Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment;
- 5.8.3 Patient is unable to comply with protocol requirements in the judgment of the treating investigator;
- 5.8.4 Treating physician determines continuation on the study would not be in the patients best interest;
- 5.8.5 Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);
- 5.8.6 Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;
- 5.8.7 Lost to Follow-up. If a research subject cannot be located to document survival in the follow-up period per protocol, the subject may be considered "lost to follow-up." All attempts to contact such a subject during the follow-up period must be documented
- 5.8.8 Termination of the study by The University of Michigan or other regulatory bodies;
- 5.8.9 Patient completes protocol treatment and follow-up criteria.

5.9 Patient Replacement

Subjects who are not evaluable will be replaced. Evaluable patients are those who receive at least 1 dose of HD IL2 and at least 1 dose of nivolumab.

6.0 STUDY PROCEDURES

6.1 Screening/Baseline Procedures (see Time and Events table section 6.4)

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 calendar days prior to registration unless otherwise stated. The screening procedures include:

6.1.1 Informed Consent

6.1.2 Medical history

To include complete medical and surgical history, history of infections, autoimmune diseases

6.1.3 Demographics

Age, gender

6.1.4 Review subject eligibility criteria

6.1.5 Review previous (within 28 calendar days) and concomitant medications

6.1.6 Physical exam including vital signs, height and weight

Vital signs (temperature, pulse, respirations, blood pressure), height, weight

6.1.7 Performance status

ECOG performance status

6.1.8 Adverse event assessment

Baseline adverse events will be assessed. See Section 8.0 for Adverse Event monitoring and reporting.

6.1.9 Hematology

CBC with diff includes total WBC, hemoglobin, hematocrit, platelet count and differential of the WBC including absolute counts

6.1.10 Blood draw for correlative studies and anti-drug antibody analysis

See Section 10.0 for details.

6.1.11 Serum chemistries

Comprehensive metabolic profile (COMP) includes sodium, potassium, chloride, bicarbonate, BUN, creatinine, AST, ALT, alkaline phosphatase, total bilirubin.

Magnesium, phosphorus, LDH.

TSH, free T3, free T4 (Only If Clinically Indicated: FSH, LH, ACTH).

6.1.12 Coagulation

PT/INR

6.1.13 Urine Tests

Urine protein/creatinine ratio

6.1.14 Pregnancy test (for females of child bearing potential)

Women of non-childbearing potential are defined as those who have no uterus, ligation of the fallopian tubes, or permanent cessation of ovarian function due to ovarian failure or surgical removal of the ovaries. All others are considered women of child bearing potential.

Either urine or serum pregnancy test is acceptable.

6.1.15 Tumor assessment

To be performed within 28 calendar days of registration: Computed tomography of the chest, computed tomography or magnetic resonance imaging of the abdomen and pelvis, computed tomography or magnetic resonance imaging of the brain

6.1.16 Other

- 12-lead Electrocardiography.

- High dose Interleukin-2 eligibility assessment: to be done within 4 weeks of registration, should include cardiac (including dobutamine stress echocardiogram or equivalent at the discretion of the treating investigator) and pulmonary function testing evaluation.
- An archived tissue block must be identified (but not needed to be submitted) to submit unstained slides from prior to registration.

6.2 Procedures During Treatment

All assessments have a window of ± 3 business days except for imaging/tumor measurements where a window of ± 7 business days will apply.

6.2.1 Each HD IL2 week (weeks 1 and 3)

- Physical exam, vital signs, ECOG Performance Status, Toxicity.
- Minimum of once daily: urine output measurement, pulse oximetry measurement.
- Hematology: CBC with diff includes total WBC, hemoglobin, hematocrit, platelet count and differential of the WBC including absolute counts
- Serum chemistries: Comprehensive metabolic profile (COMP) includes sodium, potassium, chloride, bicarbonate, BUN, creatinine, AST, ALT, alkaline phosphatase, total bilirubin.
- Magnesium, phosphorus, LDH
- Day 5 and Day 19 (N.B: these will occur during IL2 weeks): Total Creatinine Kinase, Troponin T
- Central line placement prior to any IL2 dose on days 1 and 15.
- HD IL-2 administration will start on Day 1 and continue every 8 hours until Day 5 (cycle 1), then resume on D15 and continue until D19 (cycle 2). HD IL2 dose strength (600,000 IU/kg/dose) will be calculated separately on Day 1 and Day 15 and not modified at other times during the IL2 week. IL2 dose will be administered over 15 minutes (± 5 minutes) via a central line.
- Other clinical, laboratory and imaging assessments during HD IL-2 administration as per institutional guidelines per treating investigator

6.2.2 Nivolumab administration days

- Physical exam, vital signs, ECOG Performance Status, Toxicity
- Hematology: CBC with diff includes total WBC, hemoglobin, hematocrit, platelet count and differential of the WBC including absolute counts
- Serum chemistries: Comprehensive metabolic profile (COMP) includes sodium, potassium, chloride, bicarbonate, BUN, creatinine, AST, ALT, alkaline phosphatase, total bilirubin.

- Magnesium, phosphorus, LDH
- Every 12 weeks until discontinuation/completion of nivolumab on trial: TSH, free T3, free T4 (Only If Clinically Indicated: FSH, LH, ACTH).
- Whole blood will be collected for correlative analysis at certain time points. See Section 6.4 Time and Events Table including footnote #8 for the time points and the Lab Manual for collection, labeling and shipping instructions
- Blood draw for ADA (anti-drug antibody) analysis will be collected at the time points listed in Section 6.4 Time and Events Table.
- Prior to dose # 1 (subsequently ONLY if clinically indicated): 12-lead Electrocardiography
- At week 12: Echocardiogram
- Nivolumab administration will be over 60 minutes (\pm 10 minutes) at a dose of 480 mg intravenously. Pre-medications or rescue medications are not specified by protocol and will be per institutional guidelines/treating investigator.
- Continue Nivolumab every 4 weeks until i) progression noted or ii) up to 48 weeks completed from start of protocol therapy (week 1) - refer to sections 5.4, 5.5. and 5.7. Nivolumab may be continued by treating investigator beyond this period off-study at his or her discretion and clinical judgment.
- Clinic visits: For patients who continue on nivolumab on trial nivolumab: every 4 weeks (from week1) with scans as in Section 6.4 Time and Events Table below.
- At week 12 and then every 12 weeks: Computed tomography of the chest, computed tomography or magnetic resonance imaging of the abdomen and pelvis, and only if clinically indicated: computed tomography or magnetic resonance imaging of the brain

6.2.3 In between clinic visits

- Study nurse or coordinator will call patient at least once a week in the first 12 weeks between clinic visits to evaluate for toxicity.

6.2.4 End of Treatment Visit after protocol specified therapy (IL2 and nivolumab) termination

- Physical exam, vital signs, ECOG Performance Status, Toxicity
- Hematology: CBC with diff includes total WBC, hemoglobin, hematocrit, platelet count and differential of the WBC including absolute counts
- Serum chemistries: Comprehensive metabolic profile (COMP) includes sodium, potassium, chloride, bicarbonate, BUN, creatinine, AST, ALT, alkaline phosphatase, total bilirubin

- Magnesium, phosphorus, LDH
- TSH, free T3, free T4 (Only If Clinically Indicated: FSH, LH, ACTH)

6.3 Follow-Up Procedures

For patients who have stopped all protocol specified therapy (IL2 and nivolumab for up to 48 weeks), follow up will be done every 12 weeks (counting from week 1) via phone or other forms of communication. In these patients, scans and/or labs will be per the treating investigator's discretion/per standard of care and not dictated by the protocol.

6.4 Time and Events Table

	Screen (<28d)	Week 1 IL2 Cycle #1	Nivolumab Dose #1 ¹²	Week 3 IL2 Cycle #2	Nivolumab Dose #2... ¹²	Week 12	Subsequent ¹¹	End of treatment visit ¹⁶	Follow-Up ^{9, 11}
Informed Consent	X								
History, PE, Con Meds, Weight, Vital Signs ¹	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X	X	X	X	X	X	X	
Toxicity Evaluation		X	X	X	X	X	X	X	
HD IL2 eligibility assessment	X								
Pregnancy Test for WOCBP ¹⁰	X								
CBC with diff and plt ²	X	X	X	X	X	X	X	X	
COMP ³	X	X	X	X	X	X	X	X	
Mag, Phos, LDH	X	X	X	X	X	X	X	X	
PT/INR	X								
Urine Protein/Creatinine Ratio	X								
Urine output measurement, pulse oximetry measurement.		X (qday)		X (qday)					

	Screen (<28d)	Week 1 IL2 Cycle #1	Nivolumab Dose #1 ¹²	Week 3 IL2 Cycle #2	Nivolumab Dose #2... ¹²	Week 12	Subsequent ¹¹	End of treatment visit ¹⁶	Follow-Up ^{9, 11}
TSH, free T3, free T4 (IF Clinically Indicated: FSH, LH, ACTH) ³	X						X (q 12 weeks)	X	
Total Creatinine Kinase, Troponin T		X (day 5)		X (day 19)					
12-lead ECG	X		X				X (IF clinically indicated)		
CT chest ⁴	X					X	X (q 12 weeks)		X ⁹
CT or MRI abdomen/pelvis ⁴	X					X	X (q 12 weeks)		X ⁹
CT or MRI brain ⁴	X					X	X ⁵		X ^{5,9}
Tumor Measurements	X					X	X (q 12 weeks)		X ⁹
Central line placement		X (day 1)		X (day 15)					
HD-Interleukin-2		X (D1-5)		X (D15-19)					
Nivolumab ¹²			X		X	X	X... ⁶		
Archived Tumor Tissue ⁷	X								
Blood draw for Anti-Drug Antibody Analysis ¹⁵	X		X		X	X	X (q12 weeks)		
Whole blood, ⁸	X		X	X	X	X			
Serum ⁸	X								
Echocardiogram ¹³	X					X			
Study RN/Coordinator Call ¹⁴		X	X	X	X	X			

All assessments have a window of ± 3 business days except for imaging/tumor measurements where a window of ± 7 business days will apply.

- 1: Vital signs will include temperature, pulse, respirations, blood pressure); height will be obtained at screening only.
- 2: CBC with diff includes total WBC, hemoglobin, hematocrit and differential of the WBC including absolute counts.
- 3: Comprehensive metabolic profile includes sodium, potassium, chloride, bicarbonate, BUN, creatinine, AST, ALT, alkaline phosphatase, total bilirubin. TSH, free T3, free T4 at baseline and then repeated every 12 weeks. (IF Clinically Indicated ONLY: FSH, LH, ACTH)
- 4: With or without intravenous contrast, before or on associated visit.
- 5: Only if clinically indicated
6. Continue Nivolumab on trial every 4 weeks until i) progression noted and no clinical benefit as determined by treating investigator or ii) up to 48 weeks completed from start of protocol therapy (week 1). Please note that nivolumab could be continued by the treating investigator off-trial beyond the 48-week duration at his or her clinical discretion.
7. An archived tissue block must be **identified** with intent to submit for analysis prior to registration. See the Lab Manual for collection, labeling and shipping instructions.
- 8: Whole blood is to be collected at 5 time points: pre-all study therapy, post first HD IL2 cycle but pre-nivolumab, after the first dose of nivolumab but before the second dose of nivolumab, post second HD-IL2 cycle (before the next dose of nivolumab) and at 12 weeks on days indicated prior to study drug being administered on that day. In some patients, due to the exact timing of dose #1 of nivolumab in that patient, two of these time points might coincide and in those patients, only 4 time points will be drawn. Serum will be collected at baseline only. See the Lab Manual for collection, labeling and shipping instructions.
- 9: For patients who have stopped all protocol specified therapy, follow up will be done every 12 weeks \pm 4 weeks x total of 24 months (counting from week 1) via phone or other form of communication. In those patients, scans and/or labs will be per the treating investigator's discretion/standard of care and will not be dictated by protocol.
10. WOCBP: urine or serum pregnancy test for women of child bearing potential, see section 6.1.12
11. For as long as subjects continue on nivolumab (i.e. up to 48 weeks on treatment, or beyond the 48 week duration of treatment per treating investigator's discretion): Survival status assessment at least every 12 weeks \pm 4 weeks x total of 24 months (counting from week 1) with scans as noted.
12. Nivolumab should optimally be started on week 2 (after the first 3 subjects, please see statistical section 11) but can be started up to 3 weeks after first dose of IL-2 but NOT be on the same week as any HD IL2 cycle.
13. At baseline, a dobutamine stress echocardiogram or equivalent will be performed. Standard 2-D transthoracic or surface echo cardiogram will be performed.
14. A call from the study nurse or coordinator will occur in between clinic/hospital visits once weekly for the first 12 weeks.
15. Blood draw for Anti-Drug Antibody Analysis to be collected: pre-all study therapy, prior to Nivolumab dose 1, prior to Nivolumab dose 2, at week 12 (prior to Nivolumab dose), and every 12th subsequent week (prior to Nivolumab dose) until the end of protocol treatment.
16. Within 60 days after protocol specified therapy (IL2 and nivolumab) termination.

7.0 MEASUREMENT OF EFFECT

7.1 Antitumor Effect- Solid Tumors

Response and progression will be evaluated in this study using the new 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.

7.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with study drug.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least 1 dose of HD IL2 and at least 1 dose of nivolumab, 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.)

7.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10mm by CT scan (irrespective of scanner type) for studies with a slice thickness of ≤ 5 mm or twice the slice thickness or MRI
- 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20mm by chest X-ray (if clearly defined and surrounded by aerated lung)

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

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.

Note: Tumor lesions that are situated in a previously irradiated area are not considered measurable.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm using CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total 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 organ, but in addition should be those that lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these

measures is the short axis. For example, an abdominal node which is reported as being 20mm x 30mm has a short axis of 20mm and qualifies as a malignant, measurable node. In this example, 20mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed. 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 as noted above, 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 pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

7.1.3 Guidelines for Evaluation of Measurable Disease

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start 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 should always be done rather than 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 and > 10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be

reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Cytology, Histology: These techniques can be used to differentiate between PR and CR in rare cases. When effusions are known to be a potential adverse effect of treatment, the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

7.1.4 Response Criteria

7.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started, or the appearance of one or more new lesions.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

7.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

Incomplete Response/Stable Disease (SD): 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.

7.1.4.3 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.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires:
CR	CR	No	CR	≥4 wks. confirmation
CR	Non-CR/SD	No	PR	≥4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	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	
* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.				
<u>Note:</u> 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 “ <i>symptomatic deterioration</i> ”. Every effort should be made to document the objective progression even after discontinuation of treatment.				

Note: If subjects respond to treatment and are able to have their disease resected, the patient's response will be assessed prior to the surgery.

7.1.5 Duration of Response

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

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

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

7.1.6 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression.

7.2 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 4.0 for reporting of adverse events (<http://ctep.cancer.gov/reporting/ctc.html>).

8.0 ADVERSE EVENTS

8.1 Experimental Therapy

For the most recent safety update on Contraindications, Special Warnings and Precautions for Use, Interaction with other medications and Adverse Reactions, please refer to the current Investigator's Brochure or package insert.

8.2 Adverse Event Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial and is done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Data on adverse events will be collected from the time of initial study treatment administration or intervention through 60 days after the last dose of **study treatment** (study treatment here refers to the two possible cycles of interleukin-2 and/or last dose of nivolumab up to 48 weeks of therapy, whichever is later). Any serious adverse event that occurs more than 60 days after the last study treatment and is considered related to the study treatment must also be reported. Serious Adverse Events (SAEs) will continue to be followed until:

- Resolution or the symptoms or signs that constitute the serious adverse event return to baseline;
- There is satisfactory explanation other than the study treatment or intervention for the changes observed; or
- Death.

The investigator is responsible for the detection, documentation, grading and assignment of attribution of events meeting the criteria and definition of an AE or SAE. The definitions of AEs and SAEs are given below. It is the responsibility of the principal investigator to ensure that all staff involved in the trial is familiar with the content of this section.

Any medical condition or laboratory abnormality with an onset date before initial study treatment administration or intervention is considered to be pre-existing in nature. Any known pre-existing conditions that are ongoing at time of study entry should be considered medical history.

All events meeting the criteria and definition of an AE or SAE, as defined in Section 8.3, occurring from the initial study treatment administration or intervention through 60 days following the last dose of the study treatment (study treatment here refers to the two possible cycles of interleukin-2 and/or last dose of nivolumab up to 48 weeks of therapy whichever is later) or study intervention must be recorded as an adverse event in the patient's source documents and on the CRF regardless of frequency, severity (grade) or assessed relationship to the study treatment or intervention.

In addition to new events, any increase in the frequency or severity (i.e., toxicity grade) of a pre-existing condition that occurs after the patient begins study treatment or intervention is also considered an adverse event.

8.3 Definitions

8.3.1 Adverse Event

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 be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

- *Diagnostic and therapeutic non-invasive and invasive (i.e., surgical) procedures will not be reported as adverse events. However, the medical condition for which the procedure was performed must be reported if it meets the definition of an adverse event unless it is a pre-existing (prior to protocol treatment) condition.*
- *Abnormal laboratory values or test results constitute adverse events if they induce clinical signs or symptoms or require therapy. They are to be captured under the signs, symptoms or diagnoses associated with them.*

8.3.2 Serious Adverse Event

An adverse event is considered “serious” if, in the view of either the investigator or Sponsor-Investigator, it results in any of the following outcomes:

- Death
If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
- A life-threatening adverse event
An adverse even is considered ‘life-threatening’ if, in the view of either the investigator [or sponsor], its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical event
Any event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition of “Serious Adverse Event”. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that do not result in inpatient hospitalization or the development of drug dependency or drug abuse.

Previously planned (prior to signing the informed consent form) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

Preplanned hospitalizations or procedures for preexisting conditions that are already recorded in the patient's medical history at the time of study enrollment should not be considered SAEs.

Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study therapy (e.g. HD IL2) or other protocol-required procedure) should not be considered SAEs. However, if the preexisting condition worsened during the course of the study, it should be reported as an SAE.

8.3.3 Expected Adverse Events

An adverse event (AE) is considered "expected" if:

- For approved and marketed drugs or devices, those adverse events are described in the approved Package Insert (Label).
- For investigational new drugs or devices, those adverse events are described in the FDA Investigator's Brochure.
- In clinical research studies, information on expected adverse events is also summarized in the protocol and in the consent document. See section 9.1 for the list of expected adverse events related to the drug under study.

8.3.4 Unexpected Adverse Event

An adverse event (AE) is considered "unexpected" if it is not described in the Package Insert, Investigator's Brochure, in published medical literature, in the protocol, or in the informed consent document.

8.4 Adverse Event Characteristics

8.4.1 CTCAE Term

(AE description) and grade: The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site. (<http://ctep.cancer.gov>)

8.4.2 Attribution of the AE

The investigator or co-investigator is responsible for assignment of attribution.

Definite – The AE *is clearly related* to the study treatment/intervention.

Probable – The AE *is likely related* to the study treatment/intervention.

Possible – The AE *may be related* to the study treatment/intervention.

Unlikely – The AE *is doubtfully related* to the study treatment/intervention.

Unrelated – The AE *is clearly NOT related* to the study treatment/intervention.

8.5 Serious Adverse Event Reporting Guidelines

- 8.5.1** The Sponsor-Investigator and Coordinating Center must be notified within **24 hours** of study team's knowledge of all events meeting the criteria and definition of a serious adverse event that are unexpected and possibly related (definite, probable or possible) to study treatment administration, occurring during the study or within 60 days of the last administration of the study treatment. All other SAEs not meeting the criteria of unexpected and possibly related should be reporting to the Sponsor-Investigator and Coordinating Center within 5 business

days of study team's knowledge. All SAEs should be reported using the CTO SAE Form.

- 8.5.2** The investigator must report all events meeting the criteria and definition of a serious adverse event that are unexpected and possibly related (definite, probable or possible) to study treatment administration or intervention to the local IRB within 5 business days of study team's knowledge if death or life threatening, and within 7 calendar days for all others or per local institutional guidelines.

- 8.5.3** A copy of the CTO SAE form as available in the study database should be sent to the Sponsor-Investigator (see below for contact info) and also to the Coordinating Center via email to CTSU-Oncology-Multisite@med.umich.edu.

Contact information for the PI for notification of SAEs:

Ajjai Alva, MBBS, MS
7316 Cancer Center,
University of Michigan,
1500 E. Medical Center Dr.
Ann Arbor, MI 48109

Ph: (734) 936-0091
Fax: (734) 615-2719
Email: ajjai@med.umich.edu

Follow-up information must also be reported within 7 business day of the site's knowledge of the information.

- 8.5.4** The Coordinating Center will disseminate information regarding SAEs to the participating sites within 5 days of review of the information by the Sponsor-Investigator (or designee in the event of extended absence) only in the case that the event(s) is believed to be related (i.e., possibly, probably, or definitely) to the study treatment. The Coordinating Center will be responsible for reporting of events to supporters, as appropriate (outlined below). The Michigan Institute for Clinical and Health Research (MICHR) MIAP group will be responsible for reporting any SAEs to the FDA as outlined below.
- 8.5.5** In this trial, serious unexpected adverse events believed to be definitely, probably or possibly related to the study treatment will be reported to the Food and Drug Administration via the MedWatch 3500A according to the reporting requirements in 21 CFR 312.32. The MICHR MIAP group, in cooperation with the Coordinating Center, will be responsible for correspondence regarding adverse events with the FDA for all participating sites.

8.6 Routine Reporting

All other adverse events- such as those that are expected, or are unlikely or definitely not related to the study participation- are to be reported annually as part of regular data submission.

8.7 Reporting of Unanticipated Problems

There are types of incidents, experiences and outcomes that occur during the conduct of human subjects' research that represent unanticipated problems but are not considered adverse events. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs.

Upon becoming aware of any incident, experience, or outcome (not related to an adverse event) that may represent an unanticipated problem, the investigator should assess whether the incident, experience, or outcome represents an unanticipated problem. The incident, experience or outcomes is considered unanticipated if it meets all of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency);
2. Related or possibly related to participation in the research; and
3. Suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

If the investigator determines that the incident, experience, or outcome represents an unanticipated problem, the investigator must report it to the IRB within 14 calendar days of the study team becoming aware of the problem.

8.8 Stopping Rules

Please refer to Section 11.1.

9.0 DRUG INFORMATION

9.1 Interleukin-2:

- Chemical Name: Recombinant human interleukin-2 (rhIL-2)
- Other names for the drug: Proleukin, Aldesleukin
- Description: Interleukin-2 is supplied as a sterile, white to off-white, lyophilized cake in single-use vials intended for intravenous (IV) administration
- Classification - type of agent: Cytokine, Antineoplastic Agent, Miscellaneous; Biological Response Modulator
- Mode of action: Immune-stimulator; Binds to IL-2-receptor and activates proliferation of lymphocytes. Interleukin-2 is a human recombinant interleukin-2 product which promotes proliferation, differentiation, and recruitment of T and B cells, natural killer (NK) cells, and thymocytes; causes cytolytic activity in a subset of lymphocytes and subsequent interactions between the immune system and malignant cells; can stimulate lymphokine-activated killer (LAK) cells and tumor-infiltrating lymphocytes (TIL) cells.
- Side effects: Please see the Interleukin-2 Guidance Document for information regarding side effects. For the most recent safety update, please refer to the current package insert(s).
- Drug Interactions: Please see the Interleukin-2 Guidance Document for information regarding drug interactions.
- Contraindications
Please see the Interleukin-2 Guidance Document for information regarding contraindications.
- Special Warnings and Precautions for Use

Please see the Interleukin-2 Guidance Document for information regarding special warnings and precautions for use.

- Storage and stability: Refrigerator at 2° to 8°C (36° to 46°F). Avoid exposure to heat and light. Stability after reconstitution—24 hours.
- Preparation and Dispensing:
Please refer to package insert for preparation of this medication.
- Handling and disposal of IL-2 should be per institutional guidelines for the handling and disposal of cytotoxic agents.
- Administration:
Route of administration for this study: IV infusion over 15 minutes via a central line

Precautions:

Please see the Interleukin-2 Guidance Document for information regarding precautions. For the most recent safety update, please refer to the current package insert(s).

- Availability: Commercially available from Prometheus. Standard of care.

9.2 Nivolumab:

- Chemical Name: Nivolumab
- Other names for the drug: Opdivo, BMS-936558, MDX-1106, ONO-4538
- Description: Nivolumab is supplied a sterile solution (Opdivo Intravenous) which comes in bottles of 40 mg/4 mL (4 mL) or 100 mg/10 mL (10 mL).
- Classification - type of agent: Immunomodulatory; checkpoint inhibitor
- Mode of action: Nivolumab is a fully human IgG4 programmed death 1 (PD-1) immune checkpoint inhibitor antibody that selectively blocks the interaction between PD-1, which is expressed on activated T cells, and PD-1 ligand 1 (PD-L1) and 2 (PD-L2), which are expressed on immune cells and tumor cells.
- Side effects: Please see the package insert(s) for nivolumab. For the most recent safety update, please refer to the current package insert(s).

Treatment-Related Adverse Events Reported in 10% or more of treated patients in either group in the randomized phase 3 trial of nivolumab versus everolimus.

Event	Nivolumab Group (N = 406)		Everolimus Group (N = 397)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	<i>number of patients (percent)</i>			
All events	319 (79)	76 (19)	349 (88)	145 (37)
Fatigue	134 (33)	10 (2)	134 (34)	11 (3)
Nausea	57 (14)	1 (<1)	66 (17)	3 (1)
Pruritus	57 (14)	0	39 (10)	0
Diarrhea	50 (12)	5 (1)	84 (21)	5 (1)
Decreased appetite	48 (12)	2 (<1)	82 (21)	4 (1)
Rash	41 (10)	2 (<1)	79 (20)	3 (1)
Cough	36 (9)	0	77 (19)	0
Anemia	32 (8)	7 (2)	94 (24)	31 (8)
Dyspnea	30 (7)	3 (1)	51 (13)	2 (1)
Peripheral edema	17 (4)	0	56 (14)	2 (1)
Pneumonitis	16 (4)	6 (1)	58 (15)	11 (3)
Mucosal inflammation	11 (3)	0	75 (19)	12 (3)
Dysgeusia	11 (3)	0	51 (13)	0
Hyperglycemia	9 (2)	5 (1)	46 (12)	15 (4)
Stomatitis	8 (2)	0	117 (29)	17 (4)
Hypertriglyceridemia	5 (1)	0	64 (16)	20 (5)
Epistaxis	3 (1)	0	41 (10)	0

Ref: Motzer RJ et al. N Engl J Med 2015;373:1803-1813

- Drug Interactions Please see the Investigator's brochure and package insert for Nivolumab for information regarding drug interactions.
- Contraindications: Please see the Investigator's brochure and package insert for Nivolumab for information regarding contraindications.
- Special Warnings and Precautions for Use: Please see the package insert(s) for nivolumab for information regarding special warnings and precautions for use.
- Storage and Stability: Nivolumab vials must be stored at a temperature of 2°C to 8°C and should be protected from light. If stored in a glass front refrigerator, vials should be stored in the carton.

For details on prepared drug storage and use time of Nivolumab under room temperature/light and refrigeration, please refer to the Investigator Brochure section for "Recommended Storage and Use Conditions" and/or pharmacy reference sheets. Briefly, Withdraw the required volume and transfer into an IV container. Dilute with either NS or D5W to a final concentration of 1 to 10 mg/mL. Mix by gentle inversion; do not shake.

Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent. No incompatibilities between Nivolumab and polyvinyl chloride (PVC), non-PVC/non-DEHP (di(2-ethylhexyl)phthalate) IV components, or glass bottles have been observed.

- Administration: Nivolumab is to be administered as a 60 (\pm 10 minute) intravenous infusion, using a volumetric pump with a 0.2 to 1.2 micron in-line filter at the protocol-specified dose. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of 0.9% Sodium Chloride Injection or 5% Dextrose Injection.
- Handling and disposal of nivolumab should be per institutional guidelines for the handling and disposal of biologic and cytotoxic agents. Recommended safety measures for preparation and handling of Nivolumab include laboratory coats and gloves.
- Availability: Commercially available from Bristol Myers Squibb (BMS). Standard of care in metastatic renal cell carcinoma.

10.0 CORRELATIVES/SPECIAL STUDIES

The planned laboratory correlative studies are to profile the circulating T-cell subsets before and during therapy with IL2 and nivolumab.

We will also archive patient tumor and serum samples for future unspecified testing including but not limited to PD-L1 and anti-drug antibody testing. Submission of samples for correlative studies is expected of all subjects.

10.1 Sample Collection Guidelines

An archived tissue block must be identified (to submit unstained slides from) prior to registration. Unstained slides from an archived formalin-fixed paraffin embedded tissue block are to be submitted for each subject from prior nephrectomy or biopsy of metastatic lesion (estimated tumor content >30% of nucleated cells in specimen). This tissue will be archived for future testing, including but not limited to PD-L1 expression and anti-drug antibody testing.

Whole blood samples (20 mL at each time point) will be collected at the time points listed in Section 6.4 Time and Events Table.

Serum samples (5-10 mL) will be collected at the time points listed in Section 6.4 Time and Events Table.

ALL samples should be labeled with the subject's de-identified study number and collection date. Samples should be overnighted via a courier service and delivered for analysis to:

**Lab of Weiping Zou, MD PhD
Charles B de Nacrede Research Professor of Surgery and Professor of Surgery
University of Michigan**



Phone [REDACTED]

Email: [REDACTED]

Specimen receiving times are limited to Monday to Friday 8am to 4pm. Specimens should not be shipped on a Friday or the day before a national holiday without prior permission

10.2 Assay Methodology

Whole blood Flow Cytometry:

PBMCs will be isolated from the whole blood sample by standard centrifugation. We will analyze the changes of different immune cell sub-population components before and during the course of treatment by FACS with flow cytometry analyzer. These include APC (Antigen Processing Cells) subsets, ILC and NK subsets and T cell subsets.

The staining parameters are as follows:

Staining 1	APC subsets
Staining 2	ILC/NK subsets
Staining 3	T cells subsets - surface
Staining 4	T cells subsets - intracellular

Staining 1	CD45, CD11c, CD14, CD33, HLA-DR
Staining 2	CD45, CD3, CD123, CD127, NKp46, NKp44, CD56, CD161, CD94
Staining 3	CD3, CD4, CD8, CD45RO, CD45RA, PD-1, CD57, CD127, CXCR5, CXCR3
Staining 4	CD3, CD4, CD8, CD57, KLRG1, Tim3, Foxp3, Ki67
Staining 5	CD45, CD3, CD8, IFN γ , IL-17, GranB, TNFb, IL-2, IL-22, GM-CSF

10.3 Immunogenicity Analysis

Immunogenicity assessment (ADA sampling [including ADA neutralizing antibodies] to identify ADA responses in patient circulation):

Time-points:

Samples for ADA (Anti-drug antibody) analysis will be collected at the time points listed in Section 6.4 Time and Events Table.

Analysis:

Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of patients who develop detectable ADAs against nivolumab.

The immunogenicity titer and presence of neutralizing ADAs will be reported for samples confirmed positive for the presence of ADAs. The effect of immunogenicity on efficacy, and safety will be evaluated, if the data allow.

Method:

The presence of ADAs will be assessed in serum samples taken according to the assessment schedules. At each time point, 20 mL of blood will be drawn for nivolumab ADAs and nivolumab neutralizing antibodies.

Samples will be measured for the presence of ADAs and ADA-neutralizing antibodies for nivolumab using validated electrochemiluminescent (ECL) immunoassays. Tiered

analysis will be performed to include screening, confirmatory, and titer assay components, and positive-negative cut points previously statistically determined from drug naïve validation samples will be used.

ADA samples, if not exhausted by analyses outlined herein, may be retained for 15 years from the patient's last visit date for research purposes.

ADA samples may be disposed of or destroyed and anonymized by pooling after planned analyses.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but will be reported separately in a Bioanalytical Validation Report.

10.4 Specimen Banking

Patient samples (tissue, blood, serum) collected for this study will be retained at the University of Michigan. De-identified specimens will be stored indefinitely or until they are used up. If consent for future use of specimens is withdrawn by the subject, best efforts will be made to stop any additional studies and to destroy the specimens.

Specimens being stored long-term for potential use not outlined in the protocol are subject to University Policy Governing Tissue Sample Collection, Ownership, Usage, and Disposition within all UMMS Research Repositories [<http://msa.med.umich.edu/policies/tissue-sample-collection-ownership-usage-disposition-within-all-umms-research-biorepositories>]

11.0 STATISTICAL CONSIDERATIONS

This is a single arm phase Ib/II trial of Nivolumab and IL-2 in patients with Renal Cell Carcinoma. The phase Ib has an endpoint of safety and the phase II primary endpoint is overall response rate (ORR = CR or PR) at 12 weeks. A recently reported trial of Nivolumab after 1 prior therapy in RCC reported had an ORR of 25%. With the addition of IL-2 treatment to nivolumab, we hypothesize an ORR of approximately 46% in this population.

11.1 Study Design/Study Endpoints/Sample Size and Accrual

For the phase 1b portion of the study: We will accrue an initial cohort of 3 patients who will be treated with sequential (rather than interspersed) treatment as follows: they will receive 2 cycles of HD-IL2 given in standard fashion (two 5-day cycles one week apart) followed by nivolumab starting the week after the second IL-2 cycle and continuing every 4 weeks as per standard nivolumab dosing. If 2 or more out of 3 of the first patients suffer a grade 3 or 4 immune related toxicity of interest (see 5.2.1) **within 28 days** from the first dose of nivolumab (**DLT period**) the study will stop. The 4th patient will not be enrolled until after the analysis of the 3 patient cohort is complete and submitted to the regulatory bodies.

If <2 patients suffer a grade 3 or 4 immune related toxicity in the cohort of 3 patients, the study will enroll 7 more patients treated with Nivolumab administered intravenously at 480 mg/dose over 60 minutes every 28 days, starting 1 to 3 weeks after the start date of the first cycle of IL2. We will monitor these patients **continuously** for immune mediated dose limiting toxicities **for 28 days** from the first dose of nivolumab (**DLT period**). Up to 10 total patients will be treated and observed for toxicity for 28 days from the first dose of Nivolumab in the phase 1b portion.

If, at any time during accrual to the phase 1 b portion, 6 patients or more have a grade 3 or 4 immune mediated event of interest (as described in section 5.2.1) we will pause the study and modify/discontinue the protocol in consultation with the site principal investigators and applicable regulatory authorities. If 5 or fewer patients experience grade 3 or 4 immune mediated toxicity of interest (see 5.2.1) during the toxicity window, then the study will continue to the phase II portion.

We choose to examine toxicity after 10 patients because if 6 patients or more are found to have a DLT then the 95% exact binomial confidence interval (26% - 88%) will be > 25% and be indicative that immune mediated toxicity with this regimen is too great.

Dose-Limiting Toxicity is defined as a grade 3 or 4 immune mediated event of interest (as listed and described in section 5.2.1). Please note: immune mediated events of interest do not include those that might occur during high dose IL-2 and are reversible.

DLT evaluable patients: All patients who receive at least 1 dose of HD IL2 and at least 1 dose of Nivolumab will be evaluable for the primary endpoint of toxicity in the phase Ib portion of the trial. Subjects who are not evaluable will be replaced.

The phase II portion of the trial will be a Simon mini-max 2-stage design. The first stage will accrue 12 patients (including any response evaluable patients accrued in the phase 1b portion). If more than 2 patients have a response (CR or PR) out of the 12 patients, then we will accrue 11 more patients for a total sample size of 23 evaluable patients. If more than 8 responses (CR or PR) are observed in the 23 evaluable patients, then we will recommend further study of the combination. This design has 80% power and 10% type I error. If the true ORR of the combined treatment is 25% or less, the probability of early termination of the trial is 39%. If the true ORR is 46% or greater, then the probability of stopping early is only 3.6%. Patients accrued in the Phase Ib portion of the trial will also be included in the Phase II if they are evaluable as defined below.

Response Evaluable Patients: All patients who receive at least 1 dose of Nivolumab and IL-2 will be evaluable for the primary endpoint of overall response proportion in the phase II portion of the trial. If response at 12 weeks is not recorded for the patient, then the patient will be considered a non-responder.

We expect accrual to the entire study to be completed over a period of 24 months.

11.2 Data Analyses Plans

Primary Endpoint Analysis:

Phase 1b: DLT count and proportion will be reported. Type, grade and attribution will be described by body system in the first 10 DLT evaluable patients. Number of IL-2 cycles and doses and Nivolumab doses will be summarized.

Phase II: Overall response rate at 12 weeks will be reported with the sample size and proportion of evaluable patients and the corresponding 95% exact binomial confidence interval.

Secondary Endpoint Analyses:

Safety will be defined by frequency of drug-related grade 3-5 adverse events including adverse events of interest within the duration of protocol, specified therapy and an additional 60 days following the last dose with the combination of HD IL2 and nivolumab, as assessed by NCI's CTCAE version 4.0. Counts and frequencies will be reported by body system, type and grade. Cycles and of each drug and doses/cycle of IL-2 will be described using descriptive statistics.

Survival endpoints are 24-month Overall Survival (OS) and 24-month Progression-Free Survival (PFS) as assessed by RECIST 1.1 criteria in subjects treated with the combination. Product-limit estimates from Kaplan-Meier methods will be used to report the 24-month OS and PFS proportions with 95% confidence intervals. Kaplan-Meier figures will be produced.

Interim Analysis for efficacy: An interim analysis for efficacy is planned after 12 response evaluable patients have been enrolled (total in the phase I b/II portions). If 2 or less patients have a response at 12 weeks then the trial will terminate. .

Analyses for correlative endpoints

Flow Cytometry to profile circulating T cell repertoire including Tregs (CD4+/CD25+/FoxP3+) will be described graphically for pre-therapy and post-therapy.

All study information should be recorded in an appropriate source document (e.g. clinic chart).

Immunogenicity Analysis:

Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of patients who develop detectable ADAs against nivolumab.

The immunogenicity titer and presence of neutralizing ADAs will be reported for samples confirmed positive for the presence of ADAs. The effect of immunogenicity on efficacy, and safety will be evaluated, if the data allow.

12.0 DATA AND SAFETY MONITORING

- The Data and Safety Monitoring Committee (DSMC) of The University of Michigan Rogel Cancer Center is the DSMC for this study. This committee is responsible for monitoring the safety and data integrity of the trial. The committee will meet monthly (during the phase Ib portion) or quarterly (during the phase II portion).
- **Until the phase Ib portion is completed i.e. the first 10 patients have been treated and monitored for 28 days from the first dose of nivolumab, a biweekly phone call/webinar involving site Principal Investigators/Sub-investigator(s) from each site and relevant research staff at each site will be conducted to exchange information about toxicity/safety, subject clinical course and discern trends if any. The site investigators are highly experienced in the administration of HD IL2 and also, with nivolumab therapy.**
- At each site the study team is required to meet monthly (during the phase Ib portion) or quarterly (during the phase II portion) to discuss matters related to:
 - >Enrollment rate relative to expectations, characteristics of participants
 - >Safety of study participants (Serious Adverse Event & Adverse Event reporting)
 - >Adherence to protocol (protocol deviations)
 - >Completeness, validity and integrity of study data
 - >Retention of study participants
- These meetings are to be documented by the site data manager or study coordinator using the Protocol Specific Data and Safety Monitoring Report (DSMR), signed by the site principal investigator or co-investigator. Each site is required to submit the completed DSMR to the Multi-Site Coordinator at the University of Michigan Coordinating Center on a monthly (during

the phase Ib portion) or quarterly (during the phase II portion) basis together with other pertinent documents.

- Similarly, protocol deviations are to be documented using the Coordinating Center Deviation specified form and requires the signatures of both the sites data manager or study coordinator and the site principal investigator or co-investigator. These reports are to be sent to the University of Michigan Coordinating Center within 7 calendar days of awareness of the event and on a monthly (during the phase Ib portion) or quarterly (during the phase II portion) basis with the Protocol Specific Data and Safety Monitoring Report.
- The Coordinating Center is responsible for collating all the Data and Safety Monitoring Reports from all the participating sites, and providing the information to the Data and Safety Monitoring Committee.

13.0 QUALITY ASSURANCE AND AUDITS

The Data and Safety Monitoring Committee can request a 'for cause' audit of the trial if the committee identifies a need for a more rigorous evaluation of study-related issues.

A regulatory authority (e.g. FDA) may also wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, the site investigator must immediately inform the Coordinating Center that such a request has been made.

14.0 CLINICAL MONITORING PROCEDURES

Clinical studies coordinated by The University of Michigan Rogel Cancer Center must be conducted in accordance with the ethical principles that are consistent with Good Clinical Practices (GCP) and in compliance with other applicable regulatory requirements.

This study will be monitored by a representative of the Coordinating Center. Monitoring visits will be made during the conduct of the study and at study close-out.

Prior to subject recruitment, a participating site will undergo site initiation meeting to be conducted by the Coordinating Center. This will be done as an actual site visit; teleconference, videoconference, or web-based meeting after the site's IRB approval and fully executed subcontract has been received by the Multi-Site Coordinator. The site's principal investigator and his study staff should make every effort in attending the site initiation meeting. Study-related questions or issues identified during the site initiation meeting will be followed-up by the appropriate Coordinating Center personnel until they have been answered and resolved.

Monitoring of this study will include both 'Centralized Monitoring', the review of source documents at the Coordinating Center and 'On-site Monitoring', an actual site visit. The first 'Centralized' visit should occur after the first subject enrolled completes first HD IL2 course (consisting of both weeks of IL2). The study site will send the de-identified source documents to the Coordinating Center for monitoring. 'Centralized' monitoring may be requested by the Coordinating Center if an amendment requires changes to the protocol procedures. The site will send in pertinent de-identified source documents, as defined by the Coordinating Center for monitoring.

The first annual 'On-site' monitoring visit should occur after the first five study participants are enrolled or twelve months after a study opens, whichever occurs first. The annual visit may be conducted as a 'Centralized' visit if less than three subjects have enrolled at the study site. The type of visit is at the discretion of the Coordinating Center. At a minimum, a routine monitoring visit will be done at least once a year, or once during the course of the study if the study duration is less than 12 months. The purpose of these visits is to verify:

- Adherence to the protocol
- Completeness and accuracy of study data and samples collected
- Proper storage, dispensing and inventory of study medication
- Compliance with regulations

During a monitoring visit to a site, access to relevant hospital and clinical records must be given by the site investigator to the Coordinating Center representative conducting the monitoring visit to verify consistency of data collected on the CRFs with the original source data. While most patient cases will be selected from patients accrued since the previous monitoring visit, any patient case has the potential for review. At least one or more unannounced cases will be reviewed, if the total accruals warrant selection of unannounced cases.

The Coordinating Center expects the relevant investigational staff to be available to facilitate the conduct of the visit, that source documents are available at the time of the visit, and that a suitable environment will be provided for review of study-related documents. Any issues identified during these visits will be communicated to the site and are expected to be resolved by the site in a timely manner. For review of study-related documents at the Coordinating Center, the site will be required to ship or fax documents to be reviewed.

Participating site will also undergo a site close-out upon completion, termination or cancellation of a study to ensure fulfillment of study obligations during the conduct of the study, and that the site Investigator is aware of his/her ongoing responsibilities. In general, a site close-out is conducted during a site visit; however, site close-out can occur without a site visit.

15.0 DATA MANAGEMENT

All information will be recorded locally and entered into Case Report Forms (CRFs) on the web-based data management system of the University of Michigan. Online access will be provided to each site by the Coordinating Center.

CRFs will be reviewed and source verified by the MSC during annual monitoring visits and prior to and between visits. Discrepant, unusual and incomplete data will be queried by the MSC. The investigator or study coordinator will be responsible for providing resolutions to the data queries, as appropriate. The investigator must ensure that all data queries are dealt with promptly.

The data submission schedule is as follows:

- At the time of registration
 - Subject entry into the database
 - Subject Status
 - Demographics
- During study participation
 - All data should be entered online within 10 business days of data acquisition. Information on Serious Adverse Events must be entered within the reporting timeframe specified in Section 8.5 of the protocol.

Long term data will be collected periodically either by chart review or by contacting the patients.

All study information should be recorded in an appropriate source document (e.g. clinic chart).

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17.0 APPENDICES

Appendix A. ECOG Performance Status and Karnofsky Performance Scale

Additional documents not included in the protocol:

- Laboratory Manual
- IL2 guidance document

Appendix A. ECOG Performance Status and Karnofsky Performance Scale

ECOG Performance Status developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair.*

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Percent	Karnofsky Performance Scale
100	Normal, no complaints, no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self, unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.