**University of Minnesota**
**Masonic Cancer Center**
**Cancer Experimental Therapeutics Initiative (CETI)**

# A Randomized, Double-Blind Phase II Study of Sipuleucel-T (Provenge®) Followed by Indoximod or Placebo in the Treatment of Patients with Asymptomatic or Minimally Symptomatic Metastatic Castration Resistant Prostate Cancer

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# Revision History

| Revision # | Version Date | Details of changes | Consent change? |
|---|---|---|---|
| | 11/01/2011 | Original to CPRC | |
| | 11/23/2011 | In response to CPRC deferral | |
| | 12/15/2011 | In response to CPRC stipulations, original version to FDA | 12/15/2011 |
| | 02/08/2012 | In response to FDA initial review<br>Streamline patient visits during 1-MT/study drug<br>Permit Provenge to be given by local physician with the understanding that patient must sign consent at the study center and return to the study center the day after the 3rd Provenge infusion for blood collection and to start Study Drug;<br>Other minor edits/clarifications | 02/08/2012 |
| 1 | 09/10/2012 | Replace 1-MT with newer name of indoximod throughout protocol including title;<br>Add affiliate names and contact information;<br>Update research related lab instruction; increase blood volume from 60 ml to 90 ml; add a 2nd baseline collection, move week 8 time point to week 10 to match schema;<br>Section 8.3 – add SAE reporting to Dendreon and NewLink;<br>minor edits throughout | 09/10/2012 |
| 2 | 10/15/2012 | Update dose of indoximod to 2400 mg in a divided dose twice a day as it represents the current phase II dosing (the dose currently being used in clinical trials) – increase # of placebo capsules to match the new dose;<br>Section 3.7 and appendix I - Relax baseline serum creatinine to < 2.0 mg/dL to align with other similar trials and lack of renal toxicity in either drug. | 10/15/2012 |
| 3 | 07/15/2013 | Schema and section 4.2 - Change randomization from at time of enrollment to week 4<br>Schema and section 6.2 - Add to SOC - serum collection for circulating tumor cells (CTCs) at baseline and week 14<br>Schema and section 6 - Permit 2nd baseline research blood sample to be drawn at any time prior to the first spiuleucel-T infusion<br>Schema and section 6.2 - Separate research related serum collection (all patients) and tumor biopsy at pre and at week 14 (optional requiring additional consent)<br>Section 5.2.2 – clarify positive ANA must be > 5 times upper limit of normal before additional testing/treatment modification is required<br>Title page and Key Contact Info - Update affiliates sites and investigators<br>Other minor updates throughout protocol | no changes |

| Revision # | Version Date | Details of changes | Consent change? |
|---|---|---|---|
| 4 | 09/02/2014 | Title page and Key Contact Info – update affiliate sites and investigators<br>Section 3.7 and appendix I – delete ANC eligibility requirement, add CD4 count > 400 eligibility requirement if WBC </= 3,000<br>Section 8.4 table - Update telephone number for Dendreon Corporation Serious Adverse Event reporting<br>Update table of contents to show 2 levels of headings<br>Other minor edits as tracked | minor updates |
| 5 | 03/10/2015 | Title page and Key Contact Info – update affiliate sites and investigators<br>section 3.4 and checklist – change castration level of testosterone for </= 30 ng/dL to </= 50 ng/dL to be consistent with other studies; clarify several other criteria<br>section 5.2 0 revise how the indoximod tablets are to be taken – with water on an empty stomach, previously with food acceptable<br>section 5.2.1 – update indoximod adverse event section based on updated IB<br>schema and section 6.1 – consent for optional biopsy to be included in main treatment consent;<br>section 6.2 – add drug reconciliation to each visit<br>section 7.1 updated indoximod/placebo packing information<br>section 7.2 updated indoximod/placebo manufacturing information<br>other minor edits as tracked<br>Consent related changes –<br>update risks of indoximod based on updated IB | yes including merging of treatment and biopsy consents |
| 6 | 9/30/2015 | Change Principal Investigator from Gautam Jha, MBBS to Shilpa Gupta, MBBS | yes |

## Table of Contents

# Protocol Synopsis

## A Randomized, Double-Blind Phase II Study of Sipuleucel-T (Provenge®) Followed by Indoximod or Placebo in the Treatment of Patients with Asymptomatic or Minimally Symptomatic Metastatic Castration Resistant Prostate Cancer

**Study Design:** This is a randomized, double blind, multi-institutional phase II therapeutic study of indoximod or placebo after the completion of standard of care sipuleucel-T (Provenge®) in men with asymptomatic or minimally symptomatic metastatic prostate cancer that is castration resistant (hormone refractory). Patients are randomized to receive either twice daily oral indoximod or placebo for 6 months beginning the day after the third and final sipuleucel-T infusion.

Research related correlatives will include serial blood sampling for immune monitoring and an optional prostate or metastatic site biopsy at enrollment and at week 14.

**Primary Objective:** To assess the augmentation of immune response to sipuleucel-T measured at 14 weeks from first leukapheresis, in response to twice daily oral indoximod at a dose of 2400 mg/day or an identical looking placebo

**Secondary Objectives:**

- To assess the safety of indoximod when administered post sipuleucel-T therapy
- To assess efficacy as measured by improvement in time to disease progression, objective response rate, overall survival
- To assess health related quality of life improvement on therapy

**Inclusion Criteria:**

- Metastatic castration resistant prostate cancer
- Serum PSA ≥ 2.0 ng/ml at study enrollment
- Planned standard of care treatment with sipuleucel-T
- Asymptomatic or minimally symptomatic disease as demonstrated by ECOG Performance Status 0 or 1 and no need for opiate pain medications to control pain/symptoms
- Adequate organ function within 14 days of study enrollment

**Study Population:** Men with asymptomatic or minimally symptomatic castration resistant prostatic adenocarcinoma

**Sample Size:** Approximately 50 subjects will be enrolled (1:1 indoximod vs placebo) at up to 5 sites

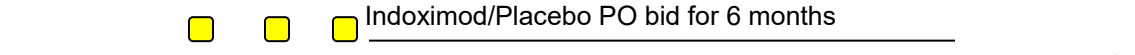
**Duration of Treatment:** Sipuleucel-T will be administered as standard of care either at the study center or by the referring physician. Oral indoximod /placebo will be self-administered twice daily for 6 months starting after the last infusion of sipuleucel-T. Patients will be treated for a minimum of 12 weeks of indoximod /placebo before disease progression can be declared and indoximod /placebo will not be discontinued for increasing PSA in the absence of symptomatic clinical progression.

# Schema

## Enrollment Plan:

Eligible, consenting patients will be enrolled to the study prior to the first leukapheresis (week 0). Randomization to either indoximod or placebo will occur at the beginning of week 4 (the week of the 3rd leukapheresis/sipuleucel-T infusion).

## Treatment Plan:




| Week | pre | 0 | 2 | 4 | 6 | 10 | 14 | 28 | follow for |
|---|---|---|---|---|---|---|---|---|---|
| Immune Monitoring | X | X | | X | X | X | X | X | survival |
| Biopsy (Optional) | | X | | | | | X | | |

**Sipuleucel-T (Provenge®) -** leukapheresis at weeks 0, 2, and 4 with sipuleucel-T infused 3 days later per Standard of Care

**Indoximod 2400 mg/day or Placebo** – begin 1 day after last sipuleucel-T infusion, continue twice daily for 6 months (24 weeks)

**Immune Monitoring/Indoximod Levels:**

1. At the time of screening/consent signature (1st baseline sample)
2. Any time prior to the first sipuleucel-T infusion on week 0 (2nd baseline sample)
3. After 3rd sipuleucel-T infusion on week 4
4. 2 weeks from initiation of treatment with indoximod/placebo on week 6
5. 6 weeks from initiation of treatment with indoximod/placebo on week 10
6. 10 weeks from initiation of treatment with indoximod/placebo on week 14
7. 24 weeks from initiation of treatment with indoximod/placebo on week 28

**Immune Response Biomarkers - Serum Sample:**

1. Any time prior to the first sipuleucel-T infusion on week 0
2. 10 weeks from initiation of treatment with indoximod/placebo on week 14

**Biopsy (optional):**

1. Prior to first leukapheresis on week 0
2. 10 weeks from initiation of treatment with indoximod/placebo on week 14

# 1 Objectives

## 1.1 Primary Objective

The primary objective of this study is to assess the augmentation of immune response to sipuleucel-T measured at 14 weeks from first leukapheresis, in response to twice daily oral indoximod at dose of 2400 mg/day or an identical looking placebo.

## 1.2 Secondary Objectives

- To assess the safety of indoximod when administered post sipuleucel-T therapy
- To assess efficacy as measured by improvement in time to disease progression, objective response rate, overall survival
- To assess health related quality of life improvement on therapy

## 1.3 Correlative Objectives

- To assess immune response at subsequent time points through week 28 and validate detection of PA2024 antibody response
- To assess other immune monitoring data including immunophenotyping

# 2 Background and Rationale

## 2.1 Prostate Cancer

Prostate cancer is the most common solid tumor malignancy in men in the United States. It is estimated that 217,730 men will be diagnosed with and 32,050 men will die of cancer of the prostate in 2010.(1)The vast majority of men are diagnosed at a localized stage and treated with prostatectomy or radiation therapy. While the overall five-year relative prostate cancer survival rate for 2001-2007 was 99.4 percent(1); approximately 1 in 3 men with early stage prostate cancer will experience a rise in the PSA levels within 5 years after initial treatment. At this point androgen ablation either through surgical or medical castration is the standard treatment for metastatic or recurrent disease. However this is only a temporary fix as most men who survive long enough (as the median age of diagnosis is 67 years) eventually develop castration resistant disease. The offer of chemotherapy with docetaxel suggests a survival benefit, but due to the associated “quality of life” side effects (alopecia, fatigue, neutropenia, and neuropathy) most men with asymptomatic disease will delay treatment until symptomatic. Thus, alternate treatment options are needed for this group of men with metastatic castration

resistant prostate cancer who, despite their disease maintain a good performance status with little or no disease associated symptoms.

### 2.2 Sipuleucel-T (Provenge)

After decades of promise and research, sipuleucel-T (Provenge) has been the first vaccine therapy approved for treatment of any cancer in the United States. Sipuleucel-T involves *ex-vivo* sensitization of peripheral blood mononuclear cells to a custom prostatic acid phosphatase and granulocyte monocyte – colony stimulating factor (GM-CSF) fusion protein (PA 2024) followed by autologous transfusion. Sipuleucel-T is very well tolerated with mostly grade 2 side effects consistent with cytokine release. It has shown to improve survival by 3-4 months as compared to placebo in randomized, double blinded phase III clinical trials.(2, 3) Besides this modest improvement in survival, there has been no improvement in time to objective disease progression or an objective response rate (>25% decline in PSA).(2, 3) Although this has been a huge first stride in development of immunotherapies and first proof of principle, additional progress needs to be made before this technology has its fullest and most widely-applicable impact in treating cancers of prostate and other malignancies.

### 2.3 1-methyl-D-tryptophan (1-MT, indoximod)

Indoleamine 2,3-dioxygenase (IDO) is a key immune-modulatory enzyme that degrades tryptophan to bioactive kynurenine metabolites. The process and effects of tryptophan depletion and kynurenine metabolism together form the immuno-modulatory IDO pathway(4), which promotes peripheral immune tolerance by direct inhibition of effector T cells, activation of pre-existing Foxp3+ Tregs, and conversion of naïve T cells to Tregs. 1-MT is a competitive inhibitor of the immunoregulatory enzyme, IDO, a critical regulator of immunosuppressive responses.

In the preclinical studies, 1-MT was readily absorbed following oral administration in mice, rats, and dogs and the bio-availability ranged from 85 to 100%(6). It was determined to be safe in rats and pigs at doses as high as 3000 mg/m$^2$/day (500 mg/kg/day) administered for 4 weeks and no significant clinical, hematology or chemistry abnormalities were noted.
In preclinical studies severity of toxoplasmosis was increased and activation of latent toxoplasmosis was noted in mice (unpublished data/7).
Experimental colitis and encephalitis in preclinical studies were worsened by administration of 1-MT, although colitis and encephalitis have not been noted by administration of 1-MT alone. (8,9).

Seventeen patients with advanced/metastatic solid tumors having progressed on established salvage therapy have been studied in phase I clinical trial at dose escalating from 200 mg once daily to 600 mg twice daily continued till disease progression or 3 months with 3 patients treated

at each dose level. Pharmacokinetics for 1-MT has been linear within this dose range (7). This has been well tolerated in the patient groups so far and most patients had only grade I or II toxicities consistent with advanced disease in a heavily pretreated population (7). The most frequently reported adverse events (regardless of attribution), occurring in ≥ 30% of patients, were fatigue, nausea and dyspnea (shortness of breath), muscle weakness (lower extremities), and pain in the lower extremities. The most frequently reported laboratory abnormalities (regardless of attribution), occurring in ≥ 30% of patients, were lymphopenia, anemia, hypoalbuminemia, hyperglycemia, hypokalemia, and hyponatremia. In the higher dose cohorts two cases of mild hypophysitis were noted during therapy with D-1MT which resolved on its own without any pharmacologic intervention. The most frequently observed adverse event which is possibly related to D-1MT is muscle weakness of the lower extremities (25%). Lymphopenia (43.75%) is the most frequently observed laboratory abnormality possibly related to 1-MT. There have been two CTCAE grade 3 adverse events of hyponatremia and dizziness which were possibly related to 1-MT were reported.

In a separate phase I dose-escalation study, 48 patients have been treated to a maximal dose of 2000 mg bid without attaining a MTD (7). The pharmacokinetics on this study was very similar to the earlier phase I study except that AUC values did not show a proportional increase with dose at the highest dose. This is in line with experience in rats and dogs where plasma concentrations of drug plateau due to finite intestinal absorptive area. Based on pharmacokinetics of indoximod tested in phase I trial, a dose of 1200 mg bid has been proposed for the phase II trials. Twelve patients have been treated at this dose of 1200 mg bid or higher in the phase I clinical trial without any notable toxicity. Indoximod is currently being studied in an ongoing phase II clinical trial for patients with breast cancer at this dose of 1200 mg bid along with docetaxel.

When indoximod (1-MT) used immediately post sipuleucel-T as in this clinical trial, it might increase the side effects of cytokine release from last infusion of sipuleucel-T.

## 2.4 Rationale

It has long been established that the tumors cause local immune-suppression that leads to tolerance toward various tumor antigens. This is primarily mediated by a linked set of inhibitory mechanisms involving regulatory T cells (Tregs), which dominantly inhibit other T cells(5), and by inhibitory check-points including IDO, CTLA4 and PD-1. Vaccine therapy by itself is limited in its ability to overcome this anergy and immunosuppressive microenvironment, without somehow interrupting suppression by Tregs or one of the key inhibitory checkpoints.

The IDO pathway is an attractive target because it sits at a nexus between immunosuppressive checkpoint blockade and functional Treg inhibition. In Phase I trials, 1MT has had little toxicity (especially in patients who have not received prior immunotherapy). We hypothesize that inhibition of the IDO pathway by indoximod (1-MT) will permit a robust and possibly more sustained immune response to sipuleucel-T, which may lead to further improvement of anti-cancer effects. Importantly, preclinical mouse studies show that tumor-bearing hosts are primed to express high levels of IDO, and this host IDO actively suppresses anti-tumor T cell responses. Thus, indoximod when combined with sipuleucel-T would primarily target the IDO expressed by the host, which inhibits optimal anti-tumor T cell responses to sipuleucel-T. This means that it is not necessary or beneficial to screen patients for IDO expression in their tumors, or their sipuleucel-T preparation, because these are not the primary target of the therapy.

In this randomized double blind phase II trial, indoximod or placebo will be administered following standard of care sipuleucel-T therapy to assess the augmentation of immune response to sipuleucel-T. Indoximod /placebo will be self-administered orally twice daily starting after the last sipuleucel-T infusion on week 4 (with first leukapheresis being week 0) and will be continued for 6 months in the absence of disease progression.

We plan to offer trans-rectal biopsy of prostate prior to initiating therapy with sipuleucel-T and at 14 weeks from start of therapy for all patients who have an intact prostate and have not received radiation to the prostate. We will also offer biopsies to patients who have an easily accessible metastasis that can be biopsied before and after treatment. Biopsy of the primary tumor or metastatic site will help understand local immune response to treatment in individual patients. Simultaneous assessment of the immune response within the peripheral blood and within the tumor will help understand immune response to treatment and possibly establish markers of response. The information gained from this study would help devise strategies to better develop sipuleucel-T, indoximod and other immunotherapies for prostate cancer.

# 3 Patient Selection

Study entry is open to adult men regardless of race or ethnic background. While there will be every effort to seek out and include minority patients, the patient population is expected to be similar to that of other prostate cancer studies at the University Of Minnesota and other participating institutions.

Patients with metastatic castration resistant prostate cancer with minimally symptomatic or asymptomatic disease (the clinical indication for use of sipuleucel-t) will be considered for enrollment in this clinical trial.

**Inclusion Criteria**

**3.1** Histologically documented adenocarcinoma of the prostate with metastatic disease as evidenced by soft tissue (e.g. lymphoid) and/or bony metastases on baseline CT scan of the abdomen and pelvis and/or bone scan

**3.2** Castration-resistant based on a current or historical evidence of disease progression despite surgical or medical castration as demonstrated by one or more of the following:

- PSA progression (defined as two consecutive PSA measurements at least 14 days apart ≥ 2.0 ng/ml and ≥ 50% above the minimum PSA during castration therapy or above pre-treatment value if no response)
- progression of measurable disease based on RECIST (≥ 20% increase in the sum of the diameters of all target lesions or the development of any new lesions – appendix III)
- progression of non-measureable disease based on imaging studies pre section 9.4

**3.3** Serum PSA ≥ 2.0 ng/ml at study enrollment

**3.4** Castration levels of testosterone defined as ≤ 50 ng/dL at study enrollment

Must be at least 3 months from surgical castration or must have received medical castration therapy for at least 3 months and be receiving such therapy at the time of confirmed disease progression as defined in section 3.2

**3.5** Asymptomatic or minimally symptomatic disease as demonstrated by ECOG Performance Status 0 or 1 (appendix II) and no need for opiate pain medications to control pain/symptoms

**3.6** Age 18 years and older

**3.7** Adequate bone marrow, renal and hepatic function within 14 days of study enrollment defined as:

- Bone marrow: WBC >3,000/ mcL or CD4 count >400 cells/$mm^3$; platelets >100,000/ mcL
- Renal: creatinine <2.0 mg/dL OR creatinine clearance >60 mL/min/1.73 $m^2$
- Hepatic: total bilirubin <1.5 X institutional ULN; AST(SGOT) and ALT(SGPT) <2.5 X institutional ULN

**3.8** Voluntary written consent

**Exclusion Criteria**

**3.9** Visceral metastases (e.g. lung, liver, brain, kidney, spleen) as the safety and efficacy of sipuleucel-T has not been established in this patient population

**3.10** Use of systemic corticosteroids or other immunosuppressive agents within the previous 4 weeks of study enrollment

**3.11** HIV-positive patients and those with other acquired/inherited immunodeficiency

**3.12** Active hepatitis including hepatitis B or C

**3.13** History of gastrointestinal disease causing malabsorption or obstruction such as, but not limited to Crohn's disease, celiac sprue, tropical sprue, bacterial overgrowth/blind loop syndrome, gastric bypass surgery, strictures, adhesions, achalasia, bowel obstruction, or extensive small bowel resection

**3.14** Inability to take medications by mouth

**3.15** History of allergic reactions attributed to compounds of similar chemical or biologic composition of those used in this study

**3.16** Active autoimmune disease, chronic inflammatory condition, conditions requiring concurrent use of any systemic immunosuppressants or steroids. Mild-intermittent asthma requiring only occasional beta-agonist inhaler use or mild localized eczema will not be excluded.

**3.17** Previous allo-transplant of any kind

**3.18** History of prior treatment with anti-CTLA4 blocking antibody

# 4 Patient Registration/Randomization

Registration will occur after the patient has signed the subject consent form and eligibility is confirmed, but before the 1st leukapheresis has been performed.

To be eligible for registration to this study, the patient must meet each criteria listed on the eligibility checklist (appendix I) based on the eligibility assessment documented in the patient's medical record. A copy of the eligibility checklist is also under attachments within the study in The Online Enterprise Research Management Environment (OnCore™).

## 4.1 Registration with Masonic Cancer Center Clinical Trials Office

Upon completion of the screening evaluation and obtaining written consent, the site study coordinator or designee will enroll the patient into OnCore. A copy of the signed consent and completed eligibility checklist must be uploaded as an attachment under the patient record in OnCore.

OnCore will notify key study personnel of the registration via a system generated email.

### 4.2 Patients Who Are Registered and Do Not Receive Sipuleucel-T

If a patient is registered to the study and is later found not able to begin sipuleucel-T, for whatever reason, he will be removed from study and treated at the physician's discretion. The patient will be considered a screen/baseline failure and the reason for removal from study will be clearly indicated in OnCore.

### 4.3 Patient Randomization

Each site will do their own randomization through the institutional investigational pharmacist using a randomized packet provided by the study statistician at the time of study site activation.

To be eligible for randomization a patient must have receive all 3 doses of spiuleucel-T.

Patients will be randomized 1:1 to either indoximod or an identical looking placebo by notifying the institutional investigational pharmacist at the beginning of week 4 (the week of the 3rd leukapheresis/sipuleucel-T infusion).

Patients who are not randomized (ineligible or refuses) will be deemed unevaluable, removed from study and followed per standard of care, independent of this study.

Patients/research staff will not be un-blinded for the duration of the study except in the event of a medical emergency per section 7.5.

## 5 Treatment Plan

In order to provide optimal patient care and to account for individual medical conditions, the treating physician's discretion may be used in the prescribing of all supportive care drug therapy.

### 5.1 Sipuleucel-T

Sipuleucel-T will be administered per standard of care in this study at either the study center or by the local referring physician. The information in this section is provided for reasons of continuity and only serves as standard of care guidelines.

#### 5.1.1 Leukapheresis and Product Manufacturing

Patients will undergo leukapheresis at weeks 0, 2, and 4 with sipuleucel-T infused 3 days later (i.e. Monday/Thursday; Tuesday/ Friday); however the 3rd infusion must be done on a schedule that allows a clinic visit at the study center the following day.

Leukapheresis will be performed at the American Red Cross who will ship the cells to the facility where sipuleucel-T is manufactured. The cell product will then be shipped to the clinical center for infusion. Since the product is shipped from the manufacturer prior to completion of quality control (QC) testing, **the cell product must not be infused until the Cell Product Disposition Form has been received by the clinical center and is marked "Approved."**

If a cell product does not meet Dendreon quality specifications, the center will be contacted by telephone and the Cell Product Disposition Form indicating that the product is not approved will be faxed to the center. Dendreon will provide instructions for the return or destruction of cell products that are not approved. Refer to section 5.1.3 regarding repeat leukapheresis procedures.

Note that if the leukapheresis appointment is delayed or rescheduled for any reason, the physical exam must also be re-scheduled for completion within the 7 days preceding the leukapheresis procedure.

### 5.1.2 Sipuleucel-T Administration

Approximately 30 minutes prior to infusion, patients must be pre-medicated with acetaminophen (650 mg) and diphenhydramine (50 mg).

Infusion of sipuleucel-T must begin prior to the labeled expiration time. Sipuleucel-T must be maintained in its refrigerated shipping package or stored at 2 to 8ºC until the cells are infused.

Sipuleucel-T must be administered over approximately 60 minutes through a large bore IV line suitable for blood transfusion. **DO NOT USE A FILTER**. Start and stop times of the product infusion will be recorded.

Common treatment-emergent AEs such as pyrexia and/or rigors may warrant reduction of the infusion rate. If such adverse reactions occur, subsequent infusions should be administered over the shortest period that is well tolerated, but not less than 60 minutes. Patients must be observed for at least 30 minutes after the infusion.

### 5.1.3 Sipuleucel-T Product Release Failure

In the event that a patient's leukapheresis procedure fails or the cell product does not meet quality specifications, the patient may undergo a repeat leukapheresis procedure**.** There is a small possibility that a patient's cell product will fail to meet quality requirements more than once. In such instances, the patient may not receive all 3 infusions.

In rare instances, it may be determined that it is not possible to make the investigational product from a patient's leukapheresis product that will pass the quality specifications, and he will not be able to receive any infusions of sipuleucel-T after multiple failed attempts.

Patients receiving fewer than 3 doses of sipuleucel-T will not continue on study and receive indoximod/placebo.

## 5.2 Indoximod/Placebo

The day after the 3rd and final sipuleucel-T infusion, the patient will begin indoximod 2400 mg/day or an identical appearing placebo. The study drug will be continued twice daily, approximately 12 hours apart for 6 months. The capsules should be taken with water on an empty stomach one hour before breakfast and one hour before dinner. Antacids are to be avoided.

The patient will be provided with a daily medication log to record times of administration, side effects, and missed doses, if any, through week 14 (immune monitoring endpoint). After week 14, the patient will be asked to record only events such as missed doses or side effects, rather than keeping a daily medication log.

The patient will be instructed to bring the medication log and study drug bottles (including any empties) to each appointment for reconcilement.

### 5.2.1 Expected Side Effects

All of the subjects in the indoximod clinical trials had at least one adverse event. The most frequently reported adverse events (regardless of attribution), occurring in ≥ 20% of patients were fatigue, nausea, headache, and alopecia. The most frequently reported laboratory abnormalities (regardless of attribution), occurring in ≥ 20% of patients were lymphopenia, anemia and hyperglycemia.

The most frequently observed adverse event which is possibly related to indoximod is fatigue (12%). Lymphopenia (16%) is the most frequently observed laboratory abnormality possibly related to

indoximod. The collective safety data from the clinical studies so far indicates indoximod has an acceptable safety profile and is safe for the treatment of patients with solid tumors.

Toxicities as updated with version 6 of the indoximod investigator's brochure (February 2015) are as follows:

**Likely: Likely to happen to 20% or more of patients**
- Fatigue or feeling tired
- Nausea
- Anorexia or loss or appetite
- Decrease in red blood cells (anemia)
- Diarrhea

**Less Likely: Likely to happen to 10 to 19% of patients**
- Decrease in white blood cells (neutrophils and lymphocytes)
- Abdominal pain
- Feeling short of breath or breathless (dyspnea)
- Rash
- Vomiting
- Constipation
- Decrease in platelets
- Headache
- Hair loss

**Rare: Likely to happen to 1% than 10% of patients**
- Dizziness
- Fever associated with low white blood cells
- Lung infection
- Increase in blood potassium, glucose, and creatinine levels
- Sleeplessness (insomnia)
- Low blood levels of sodium
- Multi-organ failure
- Low blood pressure
- Dehydration
- Ringing in ears
- Fever associated with low white blood cells (febrile neutropenia)
- Mouth Sores (Oral mucositis)
- Decrease in white blood cells

This drug is being employed in human clinical trials for solid tumors, breast cancer, melanoma, and pancreatic cancer. The profile of adverse events appears similar to that predicted for the study

subjects enrolled in these studies, e.g., a patient population with life-threatening disease. (7).

The data obtained from the Phase 1 studies performed under IND78060 suggest that certain patients with a history of exposure to targeted biologics involving components of the IDO pathway may be adversely impacted following administration of indoximod. However, these same patients were observed to have a clinical response after management of the toxicity. Therefore, the combination of indoximod with biologic agents including ipilimumab is being carefully evaluated in the clinical trial setting as described above.

The drug has not shown evidence of significant drug interactions. It is now being systematically tested in combination with docetaxel for metastatic breast cancer, in combination with ipilimumab for metastatic melanoma, in combination with temozolomide for glioblastoma, and in combination with gemcitabine/nabpaclitaxel for metastatic pancreas cancer in clinical trials under IND78189 and IND120813.

Based on phase I testing no serious toxicity is anticipated. Therefore, no specific supportive care measures are expected to be required for the drug administration itself; however dose withholding will occur for Grade 3 and 4 treatment related toxicity per section 5.2.3. Unexpected adverse events will be treated as medically indicated by the involved physicians.

Specific attention to development of autoimmune events or activation of latent infections will be given as trials using other immune-modulatory agents such as CTLA-4 blocking antibodies have shown a correlation between disease responses and so called autoimmune breakthrough events (ABEs) like hypophysitis, colitis, autoimmune hepatitis, or dermatitis. It is for this reason that they are distinguished from other adverse events. When used immediately post sipuleucel-T as in this clinical trial, it might increase the side effects of cytokine release from last infusion of sipuleucel-T. Refer to section 6.2 for study specific monitoring. Section 5.2.2 provides management of selected events.

**Placebo**
Placebo is a look-alike capsule containing no active ingredients and therefore no serious side effects are expected.

### 5.2.2 Management of Selected Events During Indoximod/Placebo

**Autoimmune Events**
Patients will be evaluated for autoimmune events by a checklist provided in Appendix IV every 2 to 8 weeks according to the schedule in section 6.2. This checklist, in addition to serologic tests, will be used by the study physicians to determine if further evaluation for autoimmune disease is warranted by an appropriate specialist in the organ system affected. This will be done to avoid misinterpretation of spurious autoimmune test results.

Treatment with indoximod can be withheld for up to four weeks while the appropriate workup/supportive care is performed and a determination made by the primary investigator whether the patient can remain on trial or should discontinue treatment.

Resuming treatment with indoximod after the autoimmune event has resolved or is stable in a patient who demonstrated an objective disease response may be entertained on a case by case basis if the principal investigator (Dr. Gupta), the treating investigator, and the patient agree to do so.

**Toxoplasma Serology**
There is some data supporting the role of Indoleamine 2,3-dioxygenase (IDO) in the suppression of latent chronic infections. New headaches, mental status changes, neurological deficits, or visual changes should be evaluated immediately for possible CNS or ocular toxoplasmosis reactivation and evaluated/treated as needed.

All patients will be screened at study entry for toxoplasma.

Toxoplasma serology positive patients who do not have a sulfa allergy will be offered prophylaxis with Septra DS one tablet daily on Monday, Wednesday, and Friday. Toxoplasma serology positive patients with a sulfa allergy who still want to enroll will be allowed to use atovaquone 750 mg twice daily administered with meals. Patients who cannot tolerate or choose not to take prophylaxis will not be excluded from the study, but they should do so only after clear informed consent has been obtained about the possible risks of toxoplasma reactivation.

Toxoplasma serology negative patients should be counseled on avoiding exposure to toxoplasma by avoiding direct skin contact with soil, cat feces, and raw meats. Domestic cats should be kept indoors and be fed pet food to prevent ingestion of contaminated soil or meat. Patients should thoroughly wash their hands after encountering any of these sources prior to eating or food

preparation. All utensils and surfaces that come into contact with raw meats should not touch cooked or prepared food without being washed first. Produce should be washed well prior to eating. Meats should be cooked completely until they are not pink and their juices run clear.

Toxoplasmosis IgM and IgG titers will be checked at baseline and rechecked at the final treatment visit for serology negative patients. In addition, IgM anti toxoplasma titers will be checked if acute infection in serology negative patients is suspected while on study.

**Proteinuria**
Urine analysis will be performed every 2 weeks for 6 weeks then every 4 to 8 weeks thereafter. Any protein ≥ 2+ on dipstick or new urine active sediment/ eosinophils should be evaluated.

**Positive ANA Panel or Symptoms of an Autoimmune Condition**
ANA will be drawn every four weeks. Any positive panel (> 5 times the upper limit of normal) should reflex over to a titer panel to determine the specific type. Any antibody titer > 5 times the ULN with symptoms consistent with an autoimmune condition should prompt withholding of indoximod and a rheumatologic evaluation. Also if inflammatory arthritis develops CCP and RF antibody titers will be evaluated.

**TSH > 5**
TSH will be monitored every 4 to 8 weeks and if it increases above a TSH of 5 a workup for autoimmune thyroiditis will be performed (anti-TG and anti-TPO Ab tests, thyroid uptake scan, FNA of the thyroid if warranted).

Also baseline and every 4 to 8 weeks, LH, FSH, ACTH, cortisol will be used to monitor for hypophysitis. These labs should be drawn between 7-8 AM due to the natural circadian variation of ACTH and cortisol. If any of these tests are lower than the reference lab values at the clinical institution and the primary investigator suspects hypopituitarism then study treatment should be held and a workup performed. This includes an MRI of the brain with attention to the sellar area to evaluate for hypophysitis.

**Ophthalmologic Complaints**
Any ophthalmologic complaints (including new ocular pain/inflammation, photosensitivity, or diminished vision) will be evaluated by an ophthalmologist if the treating investigator deems it necessary.

**Symptoms of Myositis**
CPK will be checked if any symptoms of myositis occur.

### 5.2.3 Indoximod /Placebo Dose Modifications (toxicity related)

Should a patient experience a Grade 3 toxicity that is possibly, probably, or definitely related to the study drug as determined by the treating investigator, the study drug will be held.

- If the toxicity resolves to Grade 2 or less within 7 days, the study drug may be resumed. If the toxicity recurs the event will count toward the early study stopping rule for excessive toxicity (section 12.2).

- If the toxicity does not improve to a grade 2 or less within 7 days or recurs, the patient will be permanently discontinued from treatment and the event will count toward the early study stopping rule for excessive toxicity (section 12.2).

If the patient experiences any Grade 4 toxicity, the study drug will be stopped and the event will count toward the early study stopping rule for excessive toxicity (section 12.2). If all toxicities resolved to Grade 2 or less, resumption of the study drug may be considered but must be discussed and agreed to by the investigator and Principal Investigator (Dr. Gupta).

### 5.2.4 Dosing Delays/Missed Doses (non-toxicity related)

If a dose is delayed or missed for reasons unrelated to toxicity issues (i.e. patient forgets, social or employment issues, holidays, unrelated inter-current illness), the patient will be instructed to take the dose as soon as possible. If more than 6 hours from the planned dosing time has passed, the dose will be skipped. The patient will resume his usual dosing schedule with the next dose. Patients must report missed doses on the provided dose tracking sheet.

## 5.3 Supportive Care

Optimal supportive care will be provided for all participants.

## 5.4 Duration of Indoximod/Placebo

Indoximod/placebo will continue twice daily for 24 weeks unless any one of the following occurs:

- Treatment related toxicity results in a discontinuation of indoximod /placebo for more than 7 days or a toxicity recurs despite delay
- indoximod/placebo is discontinued for more than 4 weeks for any reason
- The patient is non-compliant or withdraws consent

- Disease progression occurs, although the intent is to treat all patients for a minimum of 12 weeks with indoximod/placebo before declaring progression. In addition, treatment will not be discontinued solely based on early PSA progression in the absence of clinical or definite radiologic progression.
- Inter-current illness interferes with study drug administration
- Unacceptable adverse events
- The treating investigator or Principal Investigator feels the patient's continuing participation is not in the best interest of the patient

### 5.5 Duration of Study Participation

Patients who begin indoximod/placebo will be followed for disease response until progression and then survival only for 2 years from study enrollment.

# 6 Clinical Evaluations and Procedures

Scheduled evaluations may be performed +/-3 days from the targeted date to allow for holidays and other scheduling conflicts. The final post treatment visit may be performed +/- 2 weeks. Follow-up visits may be performed +/- 4 weeks. In addition, targeted days may be altered as clinically appropriate.

## 6.1 Baseline and Post Treatment

| Study | baseline | Weeks 0-28 | Post rx visit | F/U |
|---|---|---|---|---|
| Evaluation | Prior to 1st leukapheresis | Refer to table in 6.2 | 4 weeks after last dose of indoximod /placebo | Every 3 months from post-rx visit until 2 years from enrollment[8] |
| Consent | X | | | |
| Medical history | X | | | |
| Physical exam | X | | | |
| Assessment of symptoms and analgesic needs | X | | X | X |
| Weight | X | | X | |
| Vital signs | X | | X | |
| ECOG PS | X | | X | |
| CBC/diff/plt, CD4 count | X | | X | |
| Bun/creatinine, Na, K, Ca, Mg, tot. bili, AST, ALT, alkaline phosphatase, LDH, albumin, total protein | X | | X | |
| Circulating Tumor Cells (CTCs) | X | | | |
| PT/INR, CPK | X | | | |
| Urinalysis[1] | X | | | |
| Testosterone | X | | X | |
| HIV 1 & 2, hepatitis B, Hepatitis C, HTLV-1 | X | | | |
| β-HCG | X | | | |
| ESR | X | | | |
| EKG | X | | | |
| CT of chest, abd, pelvis | X | | | X |
| Bone scan | X | | | X |
| PSA | X | | | X |
| Research Related | | | | |
| FACT-P questionnaire | X | | X | |
| TSH, Free T4, LH, FSH, ACTH, Cortisol[4] | X | | | |
| Toxoplasma Ab titer | X | | X[5] | |
| Rheumatoid Factor | X | | | |
| C-Reactive Protein | X | | | |
| ANA panel[3] and auto-immune symptom checklist (app IV) | X | | | |
| C3, C4, CH50 | X | | | |
| Samples for immune monitoring, K/T ratio and indoximod level (9 – 10 ml green tops, 1-10 ml red top) | X, X[6] | | | |
| immune response biomarker (1-10 ml red top) | X | | | |
| Optional bx[7] | X | | | |

1- Proteinuria – any protein ≥ 2+ on dipstick or new urine active sediment/EOS should be evaluated per section 5.2.2
2- Toxoplasma serology positive patients will be offered prophylaxis with Septra DS per section 5.2.2
3- Refer to section 5.2.2 for positive ANA panel or symptoms of an autoimmune condition
4- Refer to section 5.2.2 for TSH > 5 or evidence of hypopituitarism
5- Retest sero-negative patients per section 5.2.2
6- Two separate sets of baseline samples to be done (i.e. at screening and prior to 1st spiuleucel-T infusion)
7- Biopsy for immune response biomarker only for those who provided additional consent within the treatment consent
8- Once disease progression is confirmed follow for survival status only

## 6.2 During Treatment

| Treatment | Week | Standard of Care | | | Research funded lab work to be performed by local (institutional) lab | Research Related Samples | indoximod / placebo count |
|---|---|---|---|---|---|---|---|
| Leukapheresis followed by sipuleucel-T infusion | 0 | | | | | | |
| | 1 | | | | | | |
| Leukapheresis followed by sipuleucel-T infusion | 2 | | | | | | |
| | 3 | | | | | | |
| Leukapheresis followed by sipuleucel-T infusion, start indoximod /placebo day after infusion | 4 | Prior to indoximod /placebo Physical exam, FACT-P | | | | 9 – 10 cc green, 1 – 10 cc red (pre indoximod/ placebo) | |
| indoximod /placebo twice daily continuously for 6 months | 5 | | | | | | |
| | 6 | PE, review of side effects | | CBC/diff/ plt, chem[1], U/A[2] | Thyroid function, C-reactive protein, ANA panel, Auto-immune symptom list | 9 – 10 cc green, 1 – 10 cc red | Reconcile Drug |
| | 7 | | | | | | |
| | 8 | PE, review of side effects, FACT-P | PSA | CBC/diff/ plt, chem[1], U/A[2] | Thyroid function, C-reactive protein, ANA panel, Auto-immune symptom list | | Reconcile Drug |
| | 9 | | | | | | |
| | 10 | PE, review of side effects | | CBC/diff/ plt, chem[1], U/A[2] | Thyroid function, C-reactive protein, ANA panel, Auto-immune symptom list | 9 – 10 cc green, 1 – 10 cc red | Reconcile Drug |
| | 11-13 | | | | | | |
| | 14 | PE, review of side effects, FACT-P | PSA, CT of chest, abd, pelvis, bone scan | CBC/diff/ plt, chem1, CTCs[3], U/A[2] | Thyroid function, C-reactive protein, ANA panel, Auto-immune symptom list | 9 – 10 cc green, 2 – 10 cc red, opt biopsy | Reconcile Drug |
| | 15-19 | | | | | | |
| | 20 | PE, review of side effects, FACT-P | PSA | CBC/diff/ plt, chem[1], U/A[2] | Thyroid function, C-reactive protein, ANA panel, Auto-immune symptom list | | Reconcile Drug |
| | 21-23 | | | | | | |
| | 24 | PE, review of side effects | | CBC/diff/ plt, chem[1], protein, U/A[2] | | | Reconcile Drug |
| | 25-27 | | | | | | |
| | 28 | PE, review of side effects, FACT-P | PSA, CT of chest, abd, pelvis, bone scan, | CBC/diff/ plt, chem[1], U/A[2] | Thyroid function, C-reactive protein, ANA panel, Auto-immune symptom list | 9 – 10 cc green, 1 – 10 cc red | Final Reconcile Drug |

1- chem to include Bun/creatinine, Na, K, Ca, Mg, tot. bili, AST, ALT, alkaline phosphatase, LDH, albumin, total protein
2- Proteinuria – any protein ≥ 2+ on dipstick or new urine active sediment/EOS should be evaluated per section 5.2.2
3- CTCs - circulating tumor cells

### 6.2.1 Immune Monitoring Studies

At each time point in the previous table nine 10 cc green top tubes and one 10 cc red top tube will be collected. An additional serum sample (one 10 cc red top tube) will be collected at week 14.

All blood samples will be sent to Translational Therapy Laboratory (TTL) at University of Minnesota. Refer to the affiliate lab manual for the specimen specific shipping instructions.

T, NK, Treg by immunophenotype, NK cell function [CD107a and IFN production] measurements will be done in peripheral blood and tumor tissue at the Translational Therapy Laboratory (TTL) at University of Minnesota.

ELISPOT to PA2024, ELISA to measure antibody to PA2024 will be done at above specified time points from the peripheral blood by Dendreon.

Serum kynurenine, tryptophan, K/T ratio, and indoximod levels will be measured from peripheral blood at the specified time points by Newlink.

The pre and week 14 serum sample will be analyzed for immune biomarkers by Newlink.

If the patient consents at time of enrollment, aliquots of leftover serum will be stored from each blood draw at -80 degrees C in the Masonic Cancer Center's TTL for future testing. Permission to store leftover samples will be embedded in the treatment consent.

### 6.2.2 Optional Biopsies

Patients with an intact prostate or a metastatic site that can be easily biopsied will be invited to participate in this optional component of the research at the time of consent.

Biopsy solely for research would be done prior to first leukapheresis and at 14 weeks from the first infusion of sipuleucel-T. Patients with an intact prostate that has not received prior radiation will be preferred over a metastatic site.

The core biopsy will be assessed for expression of Treg, T cells (CD4+ /CD8+), and NK markers. Part of the formalin-fixed paraffin embedded tumor tissue will be sent by the University of Minnesota to the laboratory of Dr. David Munn for IDO expression by immunohistochemistry (IHC).

Refer to the affiliate lab manual for the specimen specific shipping instructions to the University of Minnesota BioNet.

# 7 Study Drug (Indoximod/Placebo) Information

In this section, study drug is used as a general term referring to both indoximod and the identical looking placebo.

## 7.1 How Supplied

Indoximod is sterile tan powder compounded in capsule form of 200 mg. The capsules are packaged 175 capsules per bottle in white opaque HDPE bottles. The placebo consists of 313 mg of Microcrystalline Cellulose, NF in the identical #0el capsule used for indoximod capsules.

## 7.2 Manufacture and Control

Indoximod is manufactured according to current Good Manufacturing Practice guidelines and NewLink Genetics Corporation specifications by a contracted manufacturing facility. Indoximod is tested against established quality specifications by the contractor and released for clinical use by NewLink Genetics Corporation Quality Assurance. Indoximod components intended for use in the clinic are placed on stability testing according to International Conference on Harmonization (ICH) guidelines to ensure that it meets specifications during the course of the clinical trial.

The placebo product is manufactured according to current Good Manufacturing Practice guidelines and NewLink Genetics Corporation specifications by a contracted manufacturing facility. The placebo products are tested against established quality specifications by the contractor and released for clinical use by NewLink Genetics Corporation Quality Assurance. Placebo components intended for use in the clinic are placed on concomitant stability testing according to International Conference on Harmonization (ICH) guidelines to ensure that it meets specifications during the course of the clinical trial.

## 7.3 Drug Procurement

Indoximod (drug product) and placebo is shipped directly to the clinical sites at the direction of NewLink Genetics Corporation. Storage and audit of all Quality Control and Quality Assurance documentation will be performed by NewLink Genetics or designee. Indoximod/placebo is shipped by a carrier to the clinical site at room temperature. Each shipment is accompanied by a Drug Shipment Receipt Form.

## 7.4 Drug Accountability

As required by FDA regulations, all drug storage, procurement and usage will be carefully monitored and documented. The Principal Investigator and Sponsor will oversee this process and delegate responsibility as needed. A careful inventory will be maintained at NewLink Genetics Corporation and at the clinical sites.

### 7.4.1 Drug Receipt and Inventory:

The PI or designated individual will:

- Complete a Drug Request Form and send to NewLink Genetics. NewLink will make the appropriate arrangements for shipment of the drug from the manufacturer.
- Upon receipt of the investigational drug, inventory the shipment ensuring that the information on the packing slip matches exactly with what has been sent to the site, including the amount, lot numbers provided inventory form.
- Promptly bring any discrepancies, breakage or evidence of tampering to the attention of NewLink Genetics.
- Retain a copy of the shipping inventory, packing slips, and documentation of inventory in the study's records.

### 7.4.2 Drug Storage

The study drug must be stored in a secure environment, with access limited to essential and appropriate research personnel. The drugs should be kept locked in a cabinet in a locked/secure area. The study drugs should be stored at controlled room temperature (within the range of 18º –25º C or 64º – 75º F) and a storage area daily temperature log should be maintained and available for monitoring at all times. Shelf-life surveillance of the intact bottles is on-going.

### 7.4.3 Drug Labeling

The study drug bottles are pre-labeled and the labels should not be defaced or changed in any way without written permission of NewLink Genetics. It is recommended that an additional label be placed to include the subject initials, subject study number, date dispensed, name of institution, study staff contact name and phone number. NewLink will provide these labels for the clinical site.

### 7.4.4 Drug Dispensing

Study drugs will be dispensed only by those who are authorized by the IRB approved protocol, principal investigator, state and federal regulations, and NewLink Genetics.

Study drugs will be dispensed according to the dose, route, and frequency written in the clinical protocol. The PI shall dispense or

administer the study drug only to subjects under his/her personal supervision or under the supervision of a co-investigator. The investigator shall not dispense or supply the study drug to any person not authorized to receive it.

A study medication binder will be created to include specific dispensing instructions, drug accountability form, record of drug dispensing, drug shipment form, and drug return form and labels.

Study drug will be properly accounted for and tracked with adequate documentation (study medication diary). Each time the study drug is dispensed; there should be documentation as to the amount dispensed, to whom it is dispensed, and the date and signature or initials of the person dispensing the drug.

Subjects will be instructed in the proper storage, use and precautions, and potential known risks of the study drug. Subjects should be advised to return all used and unused containers/units to the site of original dispensing. Study personnel should record the amount (number of bottles and pills, etc.) and date of return. Attempts to retrieve the containers/units from subjects who have not returned them should be documented. Any discrepancies between the amounts used by subjects (actual or suspected) and the amount returned should be documented, as well as the reasons for the discrepancies.

## 7.5 Breaking the Blind

The blind shall be maintained throughout the conduct of the trial unless it is felt necessary to break the blind in a specific case in the interest of patient safety. In general, the blind will be broken after all the data are recorded, locked, and analyzed. The study statistician (Dr. Koopmeiners) will provide each site's investigational pharmacy with the treatment code key. Any request to break a blind will be discussed with the sponsor/investigator (Dr. Gupta) and NewLink.

## 7.6 Return/Destruction of Study Drug

At the conclusion of the study ensure that all documentation regarding receipt, storage, dispensing, return of used containers, and accountability is complete and accurate. Unused drug obtained from NewLink Genetics must be returned to NewLink or be destroyed on site using appropriate procedures upon written authorization from NewLink to do so.

# 8 Adverse Event Documentation and Reporting

Toxicity and adverse events will be classified according to NCI's Common Terminology Criteria for Adverse Events V 4.0 (CTCAE) and reported on the schedule below. A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

## 8.1 Definitions

The following definitions are based on the Code of Federal Regulations Title 21 Part 312.32 (21CFR312.32(a)).

**Adverse Event:** Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

**Suspected Adverse Reaction:** Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

**Life-Threatening Adverse Event Or Life-Threatening Suspected Adverse Reaction:** An adverse event or suspected adverse reaction 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.

**Serious Adverse Event Or Serious Suspected Adverse Reaction**: An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.

Important medical events 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 or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

If either the IND sponsor or the investigator believes the event is life-threatening or serious, the event must be evaluated by the sponsor for expedited reporting (21CRF 312.32(a)).

**Unexpected adverse event or unexpected suspected adverse reaction**: An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. Thus, adverse events that occur as part of the disease process or underlying medical conditions are considered *unexpected;* however, they will not be reportable per 8.3.

## 8.2 Adverse Event Documentation

Monitoring for adverse events will begin with the signing of the consent and continue through the final treatment visit approximately 30 days after the last dose of indoximod/placebo.

For the purposes of this study, adverse event documentation requirements will be determined based on grade, expectedness and relationship to study therapy as follows:

| | Grade 1 | Grade 2 | | Grade 3 | | Grade 4 and 5 |
|---|---|---|---|---|---|---|
| | **Expected or Unexpected** | **Expected** | **Unexpected** | **Expected** | **Unexpected** | **Expected or Unexpected** |
| **Unrelated Unlikely** | Not required | Not required | Not required | Not required | Required | Required |
| **Possible Probable Definite** | Not required | Not required | Required | Required* | Required* | Required* |

*any grade 3 treatment related event that does not resolve to a grade 2 or better within 7 days and any grade 4 and 5 events will be considered excess and count toward an early termination event per section 12.2. Such events must be reported on the early study stopping event form found in OnCore.

In addition, although not always a reportable event, deaths (date and cause) will be recorded in OnCore upon knowledge in the follow-up tab.

## 8.3 Required Reporting: Affiliates to the Masonic Cancer Center

Beginning with the signing of the consent and continuing through the final treatment visit, affiliate institutions will report all events meeting the definition of serious, regardless of attribution or expectedness, within 24 hours of knowledge of the event to the University of Minnesota Study Coordinator. After the final treatment visit, the investigator is obligated, upon knowledge of, to report any event that meets the definition of serious or life-threatening and is felt to be at least possibly related to the study drugs.

Reports are to be submitted to the Study Coordinator at the University of Minnesota Masonic Cancer Center (MCC) using the SAE reporting form found OnCore. The MCC Study Coordinator will facilitate reporting to the University Of Minnesota IRB and the FDA as required.

Affiliate institutions will be responsible for submitting reportable events to their institutional IRB and any other required local regulatory entities.

### 8.4 U of MN Required Reporting: FDA, IRB, MCC's SAE Coordinator, NewLink and Dendreon

The reporting period for this study is from initiation of any study treatment through the final treatment visit approximately 30 days after the last dose of indoximod/placebo; however after this point, the investigator must report upon knowledge any study treatment related event meeting the expedited reporting criteria below.

| Agency | Criteria for reporting | Timeframe | Form to Use | Submission address/ fax numbers | Copy to: |
|---|---|---|---|---|---|
| **U of MN IRB** | Events requiring prompt reporting including, but not limited to unanticipated death of a locally enrolled subject(s); new or increased risk; any adverse event that require a change to the protocol or consent form or any protocol deviation that resulting in harm<br>refer<br>to http://www.research.umn.edu/irb/guidance/ae.html#.VC7xral0-sh | within 5 business days of discovery | Report Form | irb@umn.edu | MCC SAE Coordinator mcc-saes@umn.edu |
| **FDA** | Unexpected and fatal or life threatening suspected adverse reaction | As soon as possible but no later than 7 Calendar-Day | UMCC SAE | Submit as an amendment to IND with a copy to all participating affiliate institutions, Dendreon, and NewLink | |
| | 1) Serious and unexpected suspected adverse reaction or<br>2) increased occurrence of serious suspected adverse reactions over that listed in the protocol or investigator<br>brochure or<br>3) findings from other sources (other studies, animal or in vitro testing) | As soon as possible but no later than 15 Calendar-Day | | | |
| | All other events per CFR 312.33 | At time of FDA annual report | Summary format | Submit as an amendment to IND | Not applicable |
| | **Note: Events due to the disease under treatment or an underlying medical condition will not require expedited reporting to the FDA for the purposes of this study** | | | | |
| **Dendreon and NewLink** (see details next page) | All SAEs that occur from the signing of the Study-specific consent through the duration of the post-therapy adverse event collection period (final treatment visit) | 24 hours of awareness of event | UMCC SAE | Dendreon Corporation<br>Attn: Safety Manager<br>Facsimile: (206) 829-1647<br>Phone: (206) 219-7899<br>After Hours: (206) 274-6774<br><br>NewLink Genetics<br>Attn: Safety Manager<br>Facsimile: (515) 296-3556<br>Phone: (515) 598-5020 ext 2876<br>After Hours: (515) 720-6296<br>Email: SAE_Reporting@linkp.com<br>with a copy to all participating affiliate institutions | SAE Coordinator mcc-saes@umn.edu |

| | | | | | |
|---|---|---|---|---|---|
| **Masonic Cancer Center SAE Coordinator** | Early stopping rule event per section 12.2 | Upon reporting | Early stopping rule form | SAE Coordinator mcc-saes@umn.edu | Not applicable |

In each IND safety report, the sponsor must identify all IND safety reports previously submitted to the FDA concerning a similar suspected adverse reaction and must analyze the significance of the suspected adverse reaction in light of the previous, similar reports.

The SAE Coordinator will provide the Masonic Cancer Center's Data and Safety Monitoring Council (DSMC) with the SAE in an appropriate format depending on the individual SAE (as reported or in a summary format).

**Dendreon and NewLink Serious Event Reporting**
Sponsor shall notify institution, investigator and IRB immediately during the conduct of the study and/or after the study is completed should it become aware of information related to the study that would impact participant safety or clinical care. Institution shall promptly disclose such information to study participants.

Significant new information regarding an ongoing SAE and the resolution must be sent to Dendreon and NewLinks within 3 business days of awareness of the new information.

# 9 Measurement of Effect

## 9.1 Immune Response to PA2024

The frequency of antigen specific, cytokine producing cells will be determined by an ELISPOT assay. ELISPOT assay will use whole PBMC to assess interferon gamma production in response to the immunizing protein PA2024. Increase in number of ELISPOT responses to PBMC in patients in the treatment arm will be compared to those in control arm.

## 9.2 Progression Free Survival

Progression free survival (PFS) is a composite endpoint defined as disease progression in bone or soft tissues, PSA progression, worsening pain, or death. PFS will be measured in months from the time of study enrollment until the date disease progression. During the first 12 weeks PSA progression alone will not be used as the sole criterion for clinical decision making to determine disease progression as per recommendations from Prostate Cancer Working Group -2 (PCWG2)(10).

### 9.3 PSA Progression

PSA measurements obtained during the first 12 weeks of indoximod/placebo will not be used as the sole criterion for establishing disease progression. Treatment will be discontinued if rapid disease progression is documented or the patient develops worsening symptoms of disease or toxicity. PSA progression is defined as the first PSA value that shows ≥ 25% increase from baseline and has a minimum absolute increase of ≥ 2 ng/mL after 12 weeks of treatment.

### 9.4 Imaging Progression

Progression based on CT scans, MRI or bone scan will be defined based on location/type of lesion present as defined below.

- Soft-tissue lesions – Progression will be determined by RECIST criteria (appendix III).
- Bone lesions – the appearance of ≥ 2 new lesions, with the additional requirement that progression at first assessment be confirmed by a second scan 6 or more weeks later. The confirmatory scan must document a minimum of 2 or more additional new lesions. The date of progression is the date of the first scan that shows the change.

## 10 Study Data Collection and Monitoring

### 10.1 Data Management

This study will report clinical data using The Online Enterprise Research Management Environment (OnCore™), a web based Oracle® database utilizing study specific electronic case report forms. Key study personnel are trained on the use of OnCore and will comply with protocol specific instructions embedded within the OnCore. Patient demographics, patient specific study treatment calendars, adverse events and other information required for IND annual reporting will be placed in OnCore.

### 10.2 Case Report Forms

Participant data will be collected using protocol specific electronic case report forms (e-CRFs) developed within OnCore based on its library of standardized forms. The e-CRF will be approved by the study's Principal Investigator and the Biostatistician prior to release for use. The Study Coordinator or designee will be responsible for registering the patient into OnCore at time of study entry, completing e-CRFs based on the patient specific calendar, and updating the patient record until the end of required study participation.

## 10.3 Data and Safety Monitoring Plan (DSMP)

The study's Data and Safety Monitoring Plan will be in compliance with the University of Minnesota Masonic Cancer Center's Data & Safety Monitoring Plan (DSMP), which can be accessed at http://www.cancer.umn.edu/prod/groups/ahc/@pub/@ahc/@mcc/documents/content/ahc_content_487799.pdf

Monitoring For the purposes of data and safety monitoring, this study is classified as high risk (under a locally held IND). Therefore the following requirements will be fulfilled:

- The PI (Dr. Gupta) will complete and submit a quarterly Trial Progress Report to the Masonic Cancer Center Data and Safety Monitoring Council (DSMC) with the understanding the Cancer Protocol Review Committee (CPRC) may require more frequent reporting.
- The PI will comply with at least twice yearly monitoring of the project by the Masonic Cancer Center monitoring services or designee.
- The PI will oversee the submission of all reportable adverse events per the definition of reportable in section 8.4.
- The PI will transfer affiliate site monitoring to NewLink and/or their designee who will, at a minimum, adhere to the University of Minnesota Masonic Cancer Center's DSMP.

In addition, at the time of the continuing review with the University of Minnesota IRB, a copy of the report with any attachments will be submitted to the Cancer Protocol Review Committee (CPRC).

**IND Annual Reports**

In accordance with regulation 21 CFR § 312.33, the IND sponsor (Dr. Jha) will submit a progress report annually. The report will be submitted within 60 days of the anniversary date that the IND went into effect. Affiliate sites will be notified approximately 60 days prior to the anniversary date of the data cut-off date and the data run date to ensure OnCore is current and eCRF's are complete.

## 10.4 Monitoring

The sponsor-investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University of Minnesota compliance groups in addition to the monitoring requirements of the Cancer Center's Data and Safety Monitoring Plan (section 10.3).

The investigator will make available all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data, etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory,

etc.) will be available for trial related monitoring, audits, or regulatory inspections.

### 10.5 Record Retention

Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

The investigator will retain study records including source data, copies of case report forms, consent forms, HIPAA authorizations, and all study correspondence in a secured facility for at least 6 years after the study file is closed with the IRB and FDA.

In addition, the Clinical Trials Office (CTO) will keep a master log of all patients participating in the study with sufficient information to allow retrieval of the medical records for that patient. Please contact the CTO before destroying any study related records.

## 11 Study Endpoints

### 11.1 Primary Endpoint

Augmentation of Tcell activation to PA2024 as measured by ELISPOT at 14 weeks from first leukapheresis

### 11.2 Secondary Endpoints

- Antibodies to PA2024 as measured by ELISA
- Progression free survival
- Objective response rate as defined by Prostate Cancer Working Group -2 (PCWG2)(6)
- Overall survival and survival at two years
- Safety and tolerability
- Health related quality of life

## 12 Statistical Considerations

Our primary analysis will compare Tcell activation to PA2024 as measured by ELISPOT at 14 weeks between treatment groups using the two-sample t-test for unequal variance. This analysis will be completed on log-transformed data in the event that Tcell activation is skewed. A secondary analysis will be completed adjusting for any potential confounders or baseline differences using linear regression.(11)

Secondary endpoints CD54 count, antibodies to PA2024 and Tcell proliferation will be compared between groups in an unadjusted analysis using the two-sample t-test and an adjusted analysis using linear regression. Response rate will be summarized by group using contingency tables and the odds ratio for response will be estimated using logistic regression. Time to disease progression and overall survival will be summarized by Kaplan-Meier Curves and the hazard ratio estimated using Cox regression. In addition, quality of life will be measured by the FACT-P (a validated questionnaire consisting of four subscales of well-being: Physical, Social/Family, Emotional and Functional) and compared between treatment groups using the two-sample t-test for univariate analyses and multivariate linear regression for multivariate analysis.

## 12.1 Power and Sample Size

Previous studies showed that subjects treated with Sipuleucel-T had an interferon-gamma ELISPOT response to PA2024 of ~24 spots per 3 x $10^5$ mononuclear cells at 14 weeks with a coefficient of variation of approximately 1.6. Assuming that we observe a similar coefficient of variation and a 2.5 fold increase in the ELISPOT assay (an average of ~60 spots per 3 x $10^5$ mononuclear cells) in those treated with Sipuleucel-T plus the addition of indoximod, a total sample size of 50 (25 subjects per group) will provide 80% power to reject the null hypothesis at the 0.05 level using a two-sample t-test to compare log-transformed expression levels between the two groups.

## 12.2 Early Termination for Excess Toxicity

O'Brian-Fleming group sequential stopping boundaries will be used to monitor for excess toxicity(11). Excess toxicity will be defined as CTCAE v4 grade 3 treatment related events that do not resolve to a grade 2 or better within 7 and any grade 4 and 5 events. We assume that a toxicity rate of 10% or lower is acceptable. The study will terminate for excess toxicity if 3 toxicities are observed in the first 5 subjects, 4 toxicities are observed in the first 15 subjects or 5 toxicities are observed at any point during the study. This stopping boundary has a type-I error rate of 0.1 (i.e. the probability of concluding excess toxicity when the true rate of toxicity is only 10%) and has 90% power to stop for excess toxicity if the true rate of toxicity is 30%.

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# Appendix I – Eligibility Checklist

**A Randomized, Double-Blind Phase II Study of Sipuleucel-T (Provenge®) and Followed by Indoximod or Placebo in the Treatment of Patients with Asymptomatic or Minimally Symptomatic Metastatic Castration Resistant Prostate Cancer**



Patient initials ☐☐☐ Enrolling Institution _____sequence #☐☐☐
assigned by ONCORE at enrollment

**INCLUSION CRITERIA**

**A "NO" response to any of the following disqualifies the patient from study entry.**

| | | Yes | No |
|---|---|---|---|
| 1- | Histologically documented adenocarcinoma of the prostate with metastatic disease as evidenced by soft tissue (e.g. lymphoid) and/or bony metastases on baseline CT scan of the abdomen and pelvis and/or bone scan | ☐ | ☐ |
| 2- | Castration-resistant based on a current or historical evidence of disease progression despite surgical or medical castration as demonstrated by one or more of the following:<br>☐PSA progression defined as two consecutive PSA measurements at least 14 days apart ≥ 2.0 ng/ml and ≥ 50% above the minimum PSA during castration therapy or above pre-treatment value if no response<br>☐progression of measurable disease based on RECIST (≥ 20% increase in the sum of the diameters of all target lesions or the development of any new lesions)<br>☐progression of non-measureable disease by imaging per section 9.4 of protocol | ☐ | ☐ |
| 3- | Serum PSA ≥ 2.0 ng/ml at study enrollment PSA ☐☐.☐ ng/ml Date☐☐/☐☐/☐☐ | ☐ | ☐ |
| 4- | Castration levels of testosterone defined as ≤ 50 ng/dL at study enrollment<br>Testosterone level ☐☐.☐ ng/dL Date☐☐/☐☐/☐☐<br>Must be at least 3 months from surgical castration or must have received medical castration therapy for at least 3 months and be continuing on such therapy at the time of confirmed disease progression | ☐ | ☐ |
| 5- | Asymptomatic or minimally symptomatic disease as demonstrated by ECOG Performance Status 0 or 1 (appendix II) and no need for opiate pain medications to control pain/symptoms PS ☐ | ☐ | ☐ |
| 6- | Age 18 years and older | ☐ | ☐ |
| 7- | Adequate organ function within 14 days of study enrollment defined as: | ☐ | ☐ |

| Test or evaluation | Required Value | Patient's Value | Date of Result |
|---|---|---|---|
| WBC or CD4 count | >3,000/mcL OR | ☐☐,☐☐☐ | ☐☐/☐☐/☐☐ |
| | >400 cells/$mm^3$ | ☐,☐☐☐ | ☐☐/☐☐/☐☐ |
| PLT | >100,000/mcL | ☐☐☐,☐☐☐ | ☐☐/☐☐/☐☐ |
| Creatinine or Creatinine Clearance | < 2.0 mg/dL<br>Or<br>> 60 mL/min/1.73 $m^2$ | ☐.☐<br>Or<br>☐☐.☐ | ☐☐/☐☐/☐☐ |
| total bilirubin | < 1.5 x institutional ULN value ☐.☐ | ☐.☐ | ☐☐/☐☐/☐☐ |
| AST(SGOT) | < 2.5 x institutional ULN value ☐,☐☐☐ | ☐,☐☐☐ | ☐☐/☐☐/☐☐ |
| ALT (SGPT) | < 2.5 x institutional ULN value ☐,☐☐☐ | ☐,☐☐☐ | ☐☐/☐☐/☐☐ |

| | | | |
|---|---|---|---|
| 8- | Voluntary written consent | ☐ | ☐ |

## A Randomized, Double-Blind Phase II Study of Sipuleucel-T (Provenge®) Followed by Indoximod or Placebo in the Treatment of Patients with Asymptomatic or Minimally Symptomatic Metastatic Castration Resistant Prostate Cancer

**Eligibility Checklist – page 2 of 2**

Patient initials ☐☐☐ Enrolling Institution _____

**EXCLUSION CRITERIA**

**A "YES" response to any of the following disqualifies the patient from study entry.**

| | | Yes | No |
|---|---|---|---|
| 9- | Visceral metastases (e.g. lung, liver, brain, kidney, spleen) as the safety and efficacy of sipuleucel-T has not been established in this patient population | ☐ | ☐ |
| 10- | Use of systemic corticosteroids or other immunosuppressive agents within the previous 4 weeks of study enrollment | ☐ | ☐ |
| 11- | HIV-positive patients and those with other acquired/inherited immunodeficiencies | ☐ | ☐ |
| 12- | Active hepatitis including hepatitis B or C | ☐ | ☐ |
| 13- | History of gastrointestinal disease causing malabsorption or obstruction such as, but not limited to Crohn's disease, celiac sprue, tropical sprue, bacterial overgrowth/blind loop syndrome, gastric bypass surgery, strictures, adhesions, achalasia, bowel obstruction, or extensive small bowel resection | ☐ | ☐ |
| 14- | Inability to take medications by mouth | ☐ | ☐ |
| 15- | History of allergic reactions attributed to compounds of similar chemical or biologic composition of those used in this study | ☐ | ☐ |
| 16- | Active autoimmune disease, chronic inflammatory condition, conditions requiring concurrent use of any systemic immunosuppressants or steroids. Mild-intermittent asthma requiring only occasional beta-agonist inhaler use or mild localized eczema will not be excluded | ☐ | ☐ |
| 17- | Previous allo-transplant of any kind | ☐ | ☐ |
| 18- | History of prior treatment with anti-CTLA4 blocking antibody | ☐ | ☐ |

Date consent form signed: _____

Agrees to optional biopsy component yes ☐ no ☐

Having obtained consent and reviewed each of the inclusion/exclusion criteria, I verify that this patient is:

☐ Eligible ☐ Ineligible Date registered _____

_____

Signature of person verifying eligibility

# Appendix II - Performance Status Scales

## ECOG PERFORMANCE STATUS CRITERIA

| Grade | Performance Criteria | Karnofsky Scale equivalent |
|---|---|---|
| 0 | Normal activity. Fully active, able to carry on all pre-disease performance without restriction. | (90-100) |
| 1 | Symptoms but ambulatory. Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work). | (70-80) |
| 2 | In bed <50% of the time. Ambulatory and capable of self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. | (50-60) |
| 3 | In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. | (30-40) |
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. | (10-20) |
| 5 | Dead | (0) |

# Appendix III – RECIST v 1.1

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

**Disease Parameters**

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol*.

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

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

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

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

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

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

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

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

Chest x-ray Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

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

**Evaluation of Target Lesions**

| | |
|---|---|
| Complete Response (CR): | Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. |
| Partial Response (PR): | At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters |
| Progressive Disease (PD): | At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least |

5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

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

**Evaluation of Non-Target Lesions**

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)
Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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

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

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

**Evaluation of Best Overall Response**

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

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

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

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

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

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

| Non-Target Lesions | New Lesions | Overall Response |
|---|---|---|
| CR | No | CR |
| Non-CR/non-PD | No | Non-CR/non-PD* |
| Not all evaluated | No | not evaluated |
| Unequivocal PD | Yes or No | PD |
| Any | Yes | PD |
| * 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised | | |

**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 progressive 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, including the baseline measurements.

**Progression-Free Survival**

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

# Appendix IV - Auto-Immune Symptom Evaluation Checklist

**Patient ID: _____ Week #:___ Date: _____**

| Organ System | Present | Absent |
|---|---|---|
| **SKIN:** Any new rashes, itching, lesions, change in skin color, or hair loss? | | |
| **EYES:** Any change in vision, blurring, haloes, floaters, pain/sensitivity to light, pain with eye movement, eye irritation, dryness, discharge, or excessive tearing? | | |
| **NERVOUS SYSTEM:** Any new recurrent headaches, change in mental function, muscle weakness, or numbness? | | |
| **LUNGS:** Any new wheezing, shortness of breath, cough? | | |
| **CARDIAC:** Any new chest pain, palpitations, irregular heart beats, shortness of breath with exertion or lying flat, or swelling in the legs? | | |
| **GASTROINTESTINAL:** Any new abdominal pain, nausea/vomiting, diarrhea, blood or pus in the stool, jaundice? | | |
| **GENITOURINARY:** Any bloody or cloudy urine, pain with urination, flank pain, or new lesions/rashes the genital area? | | |
| **MUSCULOSKELETAL:** Any new swollen, painful, and warm joints? Any new muscle soreness/weakness? | | |
| **ENDOCRINE:** Do you constantly feel cold while others around you are not? Any coarsening of your hair, deepening/hoarseness of your voice, thickening of your skin in your face, arms, or legs? | | |
| **GENERAL:** Any worsening fatigue or fevers? | | |

_____ _____

Evaluator Signature Date

## Appendix V – FACT P (version 4)

**Patient ID: _____ Week #:___ Date: _____**

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

| | PHYSICAL WELL-BEING | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| GP1 | I have a lack of energy..... | 0 | 1 | 2 | 3 | 4 |
| GP2 | I have nausea ..... | 0 | 1 | 2 | 3 | 4 |
| GP3 | Because of my physical condition, I have trouble meeting the needs of my family ..... | 0 | 1 | 2 | 3 | 4 |
| GP4 | I have pain ..... | 0 | 1 | 2 | 3 | 4 |
| GP5 | I am bothered by side effects of treatment ..... | 0 | 1 | 2 | 3 | 4 |
| GP6 | I feel ill ..... | 0 | 1 | 2 | 3 | 4 |
| GP7 | I am forced to spend time in bed ..... | 0 | 1 | 2 | 3 | 4 |

| | SOCIAL/FAMILY WELL-BEING | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| GS1 | I feel close to my friends ..... | 0 | 1 | 2 | 3 | 4 |
| GS2 | I get emotional support from my family ..... | 0 | 1 | 2 | 3 | 4 |
| GS3 | I get support from my friends..... | 0 | 1 | 2 | 3 | 4 |
| GS4 | My family has accepted my illness ..... | 0 | 1 | 2 | 3 | 4 |
| GS5 | I am satisfied with family communication about my illness..... | 0 | 1 | 2 | 3 | 4 |
| GS6 | I feel close to my partner (or the person who is my main support)..... | 0 | 1 | 2 | 3 | 4 |
| Q1 | *Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.* | | | | | |
| GS7 | I am satisfied with my sex life..... | 0 | 1 | 2 | 3 | 4 |

**Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

| | EMOTIONAL WELL-BEING | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| GE1 | I feel sad | 0 | 1 | 2 | 3 | 4 |
| GE2 | I am satisfied with how I am coping with my illness | 0 | 1 | 2 | 3 | 4 |
| GE3 | I am losing hope in the fight against my illness | 0 | 1 | 2 | 3 | 4 |
| GE4 | I feel nervous | 0 | 1 | 2 | 3 | 4 |
| GE5 | I worry about dying | 0 | 1 | 2 | 3 | 4 |
| GE6 | I worry that my condition will get worse | 0 | 1 | 2 | 3 | 4 |

| | FUNCTIONAL WELL-BEING | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| GF1 | I am able to work (include work at home) | 0 | 1 | 2 | 3 | 4 |
| GF2 | My work (include work at home) is fulfilling | 0 | 1 | 2 | 3 | 4 |
| GF3 | I am able to enjoy life | 0 | 1 | 2 | 3 | 4 |
| GF4 | I have accepted my illness | 0 | 1 | 2 | 3 | 4 |
| GF5 | I am sleeping well | 0 | 1 | 2 | 3 | 4 |
| GF6 | I am enjoying the things I usually do for fun | 0 | 1 | 2 | 3 | 4 |
| GF7 | I am content with the quality of my life right now | 0 | 1 | 2 | 3 | 4 |

**Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

| | ADDITIONAL CONCERNS | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| C2 | I am losing weight | 0 | 1 | 2 | 3 | 4 |
| C6 | I have a good appetite | 0 | 1 | 2 | 3 | 4 |
| P1 | I have aches and pains that bother me | 0 | 1 | 2 | 3 | 4 |
| P2 | I have certain parts of my body where I experience pain | 0 | 1 | 2 | 3 | 4 |
| P3 | My pain keeps me from doing things I want to do | 0 | 1 | 2 | 3 | 4 |
| P4 | I am satisfied with my present comfort level | 0 | 1 | 2 | 3 | 4 |
| P5 | I am able to feel like a man | 0 | 1 | 2 | 3 | 4 |
| P6 | I have trouble moving my bowels | 0 | 1 | 2 | 3 | 4 |
| P7 | I have difficulty urinating | 0 | 1 | 2 | 3 | 4 |
| BL2 | I urinate more frequently than usual | 0 | 1 | 2 | 3 | 4 |
| P8 | My problems with urinating limit my activities | 0 | 1 | 2 | 3 | 4 |
| BL5 | I am able to have and maintain an erection | 0 | 1 | 2 | 3 | 4 |