Clinical Trial Protocol
NLG-2103

A Phase 1/2 Study of the Concomitant Administration of Indoximod plus Immune Checkpoint Inhibitors for Adult Patients with Advanced or Metastatic Melanoma

IND #: [redacted]
Clinicaltrials.gov #: NCT02073123

Version 6 Dated: 02/06/2017
Replaces Version 5: 12/01/2016

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Investigational Agent:
Indoximod (1-methyl-D-tryptophan, D-1MT)

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Principal Investigators and Participating Sites

Multiple institutions throughout the United States will be conducting this study. For a full list of participating institutions please refer to the Clinicaltrials.gov website listing for this study (NCT02073123).

PROTOCOL SYNOPSIS

Title: A Phase 1/2 Study of the Concomitant Administration of Indoximod plus Immune Checkpoint Inhibitors for Adult Patients with Advanced or Metastatic Melanoma

Primary Objective:

Phase 1: To establish the recommended phase 2 dose of indoximod in combination with immune checkpoint inhibition in patients with unresectable melanoma and assess the safety and tolerability of the combined treatments

Phase 2: To evaluate the preliminary efficacy of the established dose of indoximod in combination with immune checkpoint inhibition as measured by the best overall response rate (ORR) (complete response (CR) + partial response (PR))across both standard of care agents administered sequentially in patients with unresectable stage III or stage IV melanoma

Population: Adult patients with unresectable stage III or IV advanced melanoma

Sample Size:

Phase 1: 9-12 subjects (depending on dose escalation)

Phase 2: 116 subjects (20 of these subjects will be enrolled in the expansion cohort for the purpose of obtaining matched pre-treatment and on-treatment tumor biopsies)

Investigational Drug: Indoximod (1-methyl-D-tryptophan, D-1MT)

Dosage/Treatment:

Phase 1: Table below summarizes dose levels of indoximod and ipilimumab for the Phase 1 portion of the study.

Dose Level	Indoximod Dose (oral)	Ipilimumab (IV)
1	600 mg BID x 28 days	3mg/kg q 3 weeks X 4 doses
2	1200 mg BID x 28 days	3mg/kg q 3 weeks X 4 doses

Dose-escalation, indoximod in combination with ipilimumab in four 21-day cycles (segment 1). As the immune mediated toxicities seen with immune checkpoint inhibition are similar, indoximod will be dose escalated against ipilimumab as these toxicities are most common and most severe with ipilimumab when compared to PD-1 immune checkpoints inhibitors.

Treatment with indoximod then continues in 28 day cycles (segment 2) at the appropriate dose level until toxicity or disease progression.

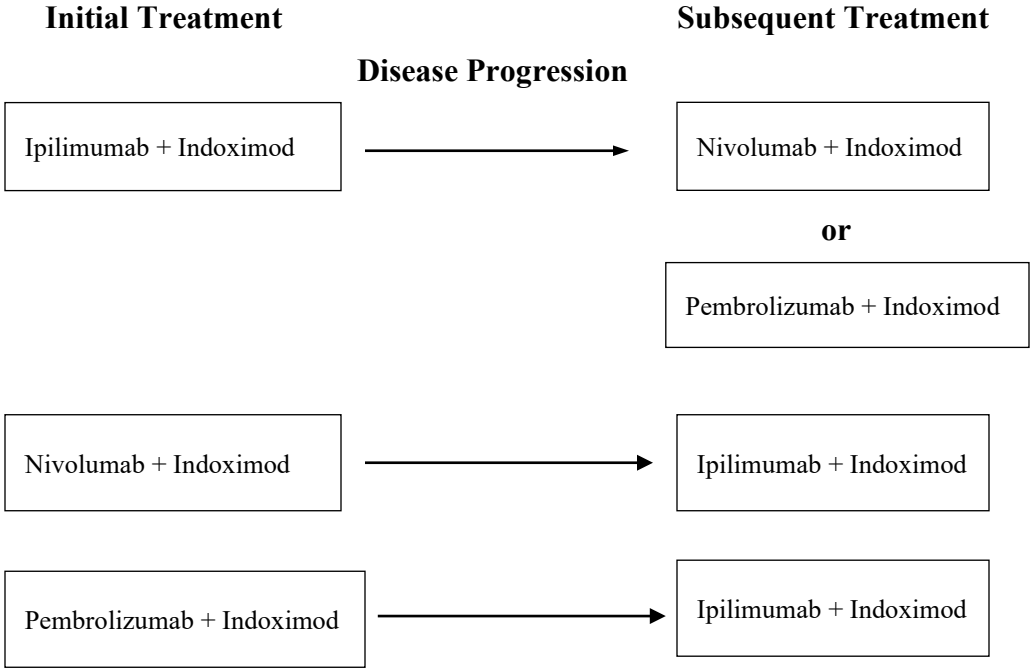
PHASE 2 COMPONENT

Once a dose for indoximod in combination with ipilimumab is established in phase 1, 116 patients will be enrolled in a single arm, fixed-dose phase 2 study. Treatment will be initiated using standard of care (SOC) immune checkpoint inhibition consisting of 4 cycles of concomitant ipilimumab, repeat cycles of nivolumab, or repeat cycles of pembrolizumab in combination with indoximod.

When given with ipilimumab as initial study treatment, indoximod will be administered concomitantly with the standard four doses of ipilimumab and then followed by indoximod given alone until disease progression or unacceptable toxicity occurs. If ipilimumab has to be stopped due to ipilimumab-related toxicity prior to administering all 4 doses, once the toxicities have resolved, indoximod is to be administered alone as long as there is clinical benefit (see secondary endpoints for definition). In the case of progression, either on the combination of ipilimumab and indoximod or with indoximod alone in maintenance, the regimen is to be changed to nivolumab or pembrolizumab plus indoximod.

When given in combination with nivolumab or pembrolizumab as initial study treatment, indoximod will be given concurrently with either checkpoint inhibitor until toxicity or disease progression occurs. If nivolumab or pembrolizumab is stopped due to toxicity, once resolved, indoximod is to be administered alone as long as there is clinical benefit. In the case of progression on combination therapy or indoximod alone, the regimen is to be switched to ipilimumab plus indoximod. See Section 11, Study Calendar, for treatment regimen cycles.

Phase 2 Doses: **Ipilimumab 3 mg/kg IV Q3 weeks x 4 doses**
Nivolumab 240 mg IV Q2 weeks
Pembrolizumab 2 mg/kg IV Q3 weeks
Indoximod 1200 mg PO BID



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1.0 OBJECTIVES

1.1 Primary Objectives Phase 1

1. To establish the safety of the combination of indoximod and ipilimumab when given concomitantly.
2. To establish the recommended phase 2 dose of indoximod in combination with immune checkpoint inhibition in patients with unresectable melanoma and assess the safety and tolerability of the combined treatments.

1.2 Primary Objectives Phase 2

To evaluate the preliminary efficacy of the established dose of indoximod in combination with immune checkpoint inhibition as measured by the best overall response rate (ORR) (complete response (CR) + partial response (PR)) across both standard of care agents administered sequentially in patients with unresectable stage III or stage IV melanoma.

1.3 Secondary Objectives Phase 2

1. To evaluate the adverse event profile and tolerability of immune checkpoint inhibition and indoximod in patients with unresectable stage III or stage IV melanoma.
2. To evaluate the median progression free survival (PFS) in patients with unresectable stage III or stage IV melanoma after the initiation of each agent in the sequential standard of care combination of CTLA-4 blockade and PD-1 blockade
3. To evaluate the clinical benefit of the combination of indoximod and checkpoint inhibition consisting of ipilimumab, nivolumab, or pembrolizumab as measured by observation and duration of disease control rate (CR + PR + stable disease (SD)).
4. To evaluate the overall survival of patients with unresectable stage III or stage IV melanoma receiving indoximod and immune checkpoint inhibition
5. To investigate mechanisms of activity/resistance to IDO/ immune checkpoint inhibitor therapy through correlative studies.

2.0 BACKGROUND

2.1 Study Disease

The incidence of melanoma is increasing. Based upon data obtained between 2004 and 2006, the lifetime probability of developing melanoma in the United States is estimated to be 1 in 37 for men and 1 in 56 for women. In the United States, melanoma is the fifth leading cancer in men and the seventh in women. An estimated 73,800 individuals will be diagnosed with melanoma and 9,900 will die of the disease in 2015 in the Unites States despite current therapy. Locally confined, fully-resectable disease may be curable with current therapy; but stage IV metastatic disease (or relapsed/recurrent disease) is highly refractory to therapy. Thus, experimental clinical trials provide an accepted treatment option for metastatic or relapsed/refractory melanoma.

2.2 Ipilimumab therapy for melanoma

Ipilimumab (Yervoy®) is a monoclonal antibody that blocks the immunosuppressive receptor CTLA-4 on T cells, thus enhancing (disinhibiting) immune responses against the tumor. Because of the role CTLA-4 plays in undermining antitumor T cell responses, the use of CTLA-4 blockade in combination with a range of cancer immunotherapies has been investigated in preclinical models and found to enhance antitumor T cell responsiveness. Ipilimumab has been approved by the FDA for unresectable and metastatic melanoma, and has demonstrated preliminary anti-tumor effect as a single agent in other solid tumors, including metastatic NSCLC and prostate carcinoma.

Treatment with ipilimumab increases median overall survival in both previously untreated and previously treated patients with metastatic stage III or IV melanoma (Hodi et al., 2010; Robert et al., 2011). Increase in median survival was approximately 2 to 4 months, but >90% of patients eventually progressed. Ipilimumab (Yervoy®) is currently approved for metastatic or unresectable melanoma at a dose of 3 mg/ kg every 3 weeks.

2.3 PD-1 Checkpoint inhibition for melanoma

Two anti–programmed death 1 (PD-1) antibodies, nivolumab (Opdivo®) and pembrolizumab (Keytruda®), were approved in 2014 by the Food and Drug Administration for the treatment of metastatic melanoma after progression during ipilimumab treatment and, in patients with BRAF-mutated melanoma, after progression during treatment with a BRAF inhibitor. These antibodies were associated with objective responses in 30 to 40% of patients. Two phase 3 trials have shown superior efficacy of nivolumab, as compared with chemotherapy, in previously untreated patients with wild-type BRAF tumors or in patients with either mutant or wild-type BRAF tumors after progression during ipilimumab therapy and, in patients with tumors positive for BRAF mutation, after progression during treatment with a BRAF inhibitor (Robert C, NEJM, 2015 and Weber JS, Lancet, 2015). Recently, pembrolizumab was associated with longer progression-free survival and overall survival and higher response rates than those associated with ipilimumab in a phase 3 trial involving patients with advanced melanoma (Robert C, NEJM, 2015).

In May 2015, results from the CheckMate 067 trial demonstrated that in patients with previously untreated advanced melanoma, treatment with nivolumab alone or with the combination of nivolumab and ipilimumab resulted in significantly longer progression-free survival and higher objective response rates than did treatment with ipilimumab alone. The incidence of adverse events in this study was lowest in the nivolumab group and highest in the combination group.

Pembrolizumab was first evaluated in the large, phase 1 KEYNOTE-001 study (Robert C, Lancet, 2014). In a pooled analysis of 411 patients with advanced melanoma enrolled in KEYNOTE-001 and after a median follow-up duration of 18 months, the response rate was 34%, the response was maintained in 81% of those patients, and median overall survival was 25.9 months (Ribas A, 2014)

In KEYNOTE-006 PD-1 inhibition is compared with CTLA-4 blockade in a controlled, randomized trial involving patients with advanced melanoma. The estimated 6-month progression-free survival rates were 47.3% for patients receiving pembrolizumab every 2 weeks, 46.4% for those receiving pembrolizumab every 3 weeks, and 26.5% for those receiving ipilimumab. Median estimates of progression-free survival were 5.5 months (95% confidence interval [CI], 3.4 to 6.9), 4.1 months (95% CI, 2.9 to 6.9), and 2.8 months (95% CI, 2.8 to 2.9), respectively. One-year estimates of survival were 74.1% for patients receiving pembrolizumab every 2 weeks (hazard ratio for death as compared with the ipilimumab group, 0.63; 95% CI, 0.47 to 0.83; P<0.0005), 68.4% for those receiving pembrolizumab every 3 weeks (hazard ratio for death as compared with the ipilimumab group, 0.69; 95% CI, 0.52 to 0.90; P=0.0036), and 58.2% for those receiving ipilimumab (Roberts C, NEJM, 2015).

Based on these data, many clinicians are changing practice patterns to use PD-1 inhibitors (nivolumab and pembrolizumab) as 1st line treatment in preference to ipilimumab. However, standard treatment of advanced melanoma is moving towards the use of both CTLA-4 blockade and PD-1 blockade. These two approaches to checkpoint blockade can be administered together as a combination or sequentially. Most utilization of PD-1 and CTLA-4 blockade as a therapeutic combination is currently confined to the clinical trial setting. The sequential use of these two approaches has become a standard approach and can essentially be considered on therapeutic regimen. Which checkpoint inhibitor (CTLA-4 blockade vs PD-1 blockade) and which PD-1 checkpoint inhibitor (nivolumab vs pembrolizumab) remains a question of treating physician discretion at this time.

2.4 Indoximod and the indoleamine 2,3-dioxygenase pathway

Although the effects of immune checkpoint inhibition have been encouraging, the impact on survival of these drugs as a single agent or in sequence remains limited. Thus, there is a need to enhance activity using synergistic and combinatory immune modulation. Indoleamine 2,3-dioxygenase (IDO) is the second of the three major negative immunoregulatory pathways in cancer for which therapeutic agents exist. IDO is a single chain oxidoreductase that was initially discovered by its ability to catalyze tryptophan degradation to kynurenine. The role of IDO in the mammalian immune system was first elucidated by Munn, Mellor and colleagues who correlated IDO activity with T cell suppression (Munn et al., 1998). IDO is expressed in antigen-presenting cells in the immune system and is inducible in many other non-immune cell types. Its immunoregulatory function is based on the relative sensitivity of T cells to tryptophan deprivation (Munn et al., 1999; Munn et al., 2005), along with the immunosuppressive effects of kynurenine metabolites on T cell activation and Treg generation (Fallarino et al., 2002; Fallarino et al., 2006; Mezrich et al., 2010). IDO is up-regulated in many human tumors and tumor-draining lymph nodes (Uyttenhove et al., 2003), including malignant melanoma (Gerlini et al., 2010; Lee et al., 2005; Lee et al., 2003; Munn et al., 2004). In preclinical animal models, the immunosuppressive function of IDO contributes to immune escape by tumors (Munn et al., 2004; Smith et al., 2012; Wainwright et al., 2012).

In a number of mouse studies models, the IDO inhibitor 1-methyl-D-tryptophan (indoximod) and other IDO inhibitors show cooperative effects with chemotherapy or anti-tumor vaccines, resulting in growth delay or regression of established tumors (reviewed in ref. (Munn, 2011)). In

these models, the anti-tumor effect of indoximod occurred in a T cell-dependent manner, and thus appeared mechanistically due to its specific immune-enhancing effects (Hou et al., 2007; Muller et al., 2005).

2.5 Safety data for the combination of ipilimumab and indoximod

The phase 1 trials of indoximod (IND#78060 and #78189) enrolled 65 patients with solid tumors (breast, colon, melanoma, sarcoma, pancreatic, lung). The highest dose of indoximod administered was 2000mg PO BID given in continuous 28 day cycles. Because no dose-limiting toxicity was reached, a maximally tolerated dose of the agent was not identified. The agent was well tolerated and good oral bioavailability was demonstrated. Five patients demonstrated prolonged stabilization of disease greater than six months, and there were instances of mixed responses observed. There were no confirmed objective responses.

In this study, 3 patients treated at the lowest dose level who had previously been treated with other experimental immunotherapy (two with ipilimumab, one with CD40-agonist antibody) developed autoimmune hypophysitis. These patients were managed by interrupting indoximod, treating with corticosteroids and hormone replacement therapy until stable, and then (with FDA approval and at the request of the patients) re-starting indoximod at the same dose. All three patients tolerated this well, and all had stable disease >6 months after re-starting therapy.

In the remainder of the phase 1 trial, patients were excluded if they had received prior immunotherapy, and no further cases of overt hypophysitis were observed. Elevations in CRP levels and increases in tumor-associated autoantibodies were observed. The conclusion was the drug was well tolerated, biologically active, and had modest activity as monotherapy.

Although IDO and CTLA-4 are closely related pathways, indoximod did not show the severe toxicities of ipilimumab (colitis, rash, hepatic dysfunction, etc.), with the exception of autoimmune hypophysitis. Importantly, the effect of indoximod on autoimmune hypophysitis was seen in patients who had previously received ipilimumab therapy (even though these patients had not developed known, overt hypophysitis during the treatment with ipilimumab itself). This “recall” flare of hypophysitis, which occurred at the lowest dose of indoximod (200 mg/day), suggests that indoximod may be able to activate and prolong a low-level immune reaction that had been initiated by ipilimumab. Thus, the design of the current trial is to treat with standard-regimen ipilimumab in combination with a concomitant administration of indoximod followed by a prolonged course of indoximod given as monotherapy.

In other, preclinical animal studies, the most significant interaction between ipilimumab and indoximod occurred in monkeys infected with simian immunodeficiency virus (SIV). These animals were treated concurrently with anti-retroviral chemotherapy (dideoxyadenosine + stavudine) plus MDX-010 (ipilimumab) and 1-methyl-D-tryptophan (Vaccari et al., 2012) for 3 cycles over 12 weeks. Animals receiving all 4 drugs developed progressive pancreatitis and eventual diabetes. The antiretroviral drugs (dideoxyadenosine and stavudine) are known to have a significant incidence of pancreatic dysfunction in both humans and monkeys, and this appeared to be markedly worsened by the addition of ipilimumab and indoximod. Thus, the current study

excludes patients with abnormal (> 1.5 ULN) amylase/lipase at baseline and carefully monitors amylase/lipase and glucose during therapy.

The phase 1 portion of this trial has been completed and dose escalated to 1200 mg po BID in combination with ipilimumab without any regimen limiting toxicities or observed increase in the rate or severity of known ipilimumab toxicities. The ready for phase 2 dose for indoximod in combination with immune checkpoint inhibitors is set at 1200 mg po BID. The toxicities seen with ipilimumab are similar to but more frequent and severe than those seen with nivolumab or pembrolizumab. The phase 1 dose escalation sets an expected phase 2 dose and toxicity profile for immune checkpoint inhibitors in combination with indoximod.

2.6 Rationale

The goal of the current study, based on pre-clinical data from studies conducted in rodents, is to enhance and prolong the immune response initiated by immune checkpoint inhibition by administering a sustained period of indoximod treatment concurrent with and after standard-dose immune checkpoint inhibition.

At the molecular level, the IDO and CTLA-4 and PD-1 pathways are closely linked. CTLA-4 causes induction of IDO gene expression and functional activity (Fallarino et al., 2003; Grohmann et al., 2002), and IDO contributes to the biologic effect of CTLA-4 as a downstream immunosuppressive pathway (Mellor et al., 2003; Sucher et al., 2012). Recently, preclinical data in mice showed synergistic activity and survival benefit when indoximod was combined with concurrent anti-CTLA-4 antibody, compared to either agent alone (Hoolmgard et al. 2013). Synergistic activity between PD-1 pathway inhibition and IDO pathway inhibition has also been demonstrated preclinically (Holmgaard et al, JEM 2013). These observations, combined with the close molecular links between the IDO pathway and the CTLA-4 and PD-1 pathways, provide the rationale for combination of immune checkpoint inhibitors with the IDO-inhibitor indoximod.

Additionally, a recent paper evaluating mechanisms of tumor resistance to CTLA-4 and PD-1 therapy in an animal model has highlighted the central role of IDO in mediating this resistance. In the setting of CTLA-4 and PD-1 blockade, tumor resistance was shown to be mediated by myeloid derived suppressor cells (MDSC's). These MDSC's are recruited into the tumor microenvironment by the actions of regulatory T-cells that express IDO. Treating the animals with indoximod precludes the IDO mediated upregulation of regulatory T-cells and the subsequent recruitment of MDSC's and renders resistant animals once again susceptible to treatment with CTLA-4 and PD-1 blockade. (Holmgaard et al., 2015). This mechanism demonstrated in an animal model provides further preclinical reasoning for the utilization of the combination therapy being evaluated in this study.

Given the primary objective of this study, the design chosen is an open-label, 2-segment, combination, single arm study. The study has determined the recommended phase 2 dose (RP2D) and associated toxicities of the combination by performing a phase 1 dose-escalation for indoximod in combination with standard fixed-dose ipilimumab. The study will then gather preliminary efficacy data in a single-arm expansion phase testing indoximod in combination with immune checkpoint inhibition.

Immune checkpoint inhibition will be defined within the scope of this study as the sequential administration of two of the three commercially available checkpoint inhibitors. One must be ipilimumab. One must be either nivolumab or pembrolizumab. The order in which the two are administered is left to treating physician discretion.

The intention in this study is to evaluate the benefit of adding indoximod to this regimen of immune checkpoint inhibition. Per design, the change from the initial checkpoint inhibitor to the second checkpoint inhibitor administered should only occur after definitive progression as defined by irRC or mWHO criteria. If a subject experiences an immune checkpoint inhibitor related adverse event that requires withdraw of that checkpoint inhibitor, once recovered, the subject should continue on indoximod as monotherapy until definitive evidence of progression. Once definitive progression occurs, either on combination therapy or indoximod monotherapy, the second checkpoint should be administered while indoximod continues.

An observation made during the course of the Phase 1 component was that once there was initial evidence of progression (increase in size or number of tumors below progression criteria or without confirmation by follow-up imaging), patients were taken off study and started on a second sequential checkpoint inhibitor (PD-1 blockade with nivolumab or pembrolizumab in the case of initial ipilimumab therapy) before definitive progression versus pseudo-progression with delayed response could be determined. This clinical practice limited the ability to determine the efficacy of the combination approach. The Phase 2 study design contained in this version of the protocol is intended to address that observation.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria

- Unresectable stage III or stage IV melanoma.

- Patients must have measurable disease, defined as lesions that can be accurately measured in 2 perpendicular diameters, with at least one diameter > 20 mm and the other dimension > 10 mm on MRI, or 10 mm x 10 mm for spiral CT. The area will be defined as the product of the largest diameter with its perpendicular. See Section 11 for the evaluation of measurable disease.

- No systemic treatment in the previous 28 days.

- Age ≥18 years. Because no dosing or adverse event data are currently available on the use of ipilimumab or indoximod in patients <18 years of age, children are excluded from this study.

- ECOG performance status ≤2 (Karnofsky ≥60%)

- Patient has adequate bone marrow and organ function as defined by the following laboratory values:

- Absolute Neutrophil Count (ANC) ≥ 1.0 x 10^9/L
- Platelets ≥ 100 x 10^9/L
- Hemoglobin ≥ 9.0 g/dL
- INR ≤ 2 x ULN

- Potassium, calcium, magnesium must be ≤ Grade 1 per CTCAE Version 4.03

- Serum Creatinine ≤ 1.5 x ULN

- Serum Bilirubin, amylase and lipase ≤ 1.5 x ULN (in patients with known Gilbert Syndrome, total bilirubin ≤ 3 x ULN, with direct bilirubin ≤ 1.5 x ULN)

- AST and ALT ≤ 3 x ULN (or ≤ 5.0 x ULN if hepatic metastases are present)

- Serum Albumin ≥ 3 g/dL

- Patients must have normal pituitary function as determined by investigator clinical judgment.

- Patients with known brain metastases will only be eligible after definitive treatment of brain metastases with SBRT provided that:
  - The subject did not require steroids for any significant duration (more than 5 days) as part of this treatment
  - The subject is neurologically stable and has had no persistent side effects / complications from the treatment.

- Patients that have received previous targeted therapies will only be eligible provided that 5 half-lives of the drug have passed and any/all side effects/adverse events experienced while on previous therapy have resolved to grade 1 or less.

- The effects of indoximod on the developing human fetus are unknown. For this reason and because indoximod may affect maternal immune tolerance of the fetus, sexually active women of child-bearing potential must agree to use two forms of contraception (hormonal and barrier method of birth control or abstinence) prior to study entry and for the duration of study participation. Use of contraception or abstinence should continue for a minimum of 1 month after completion of the study. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should discontinue the study drug and inform her treating physician immediately. A pregnancy test is required prior to study enrollment and monthly while on treatment with indoximod for all women of child- bearing potential. Also men should be discouraged from fathering children while on treatment.

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

- For the Phase 2 expansion cohort, patient must have a target tumor lesion that is easily amendable to percutaneous core needle biopsy. Lesions that can be imaged by ultrasound are strongly preferred. Only percutaneous biopsies are allowed, biopsies via endoscopic approaches are not allowed. Lung lesions are not allowed due to the high risk of complication (pneumothorax) with repeat core needle biopsy.

- For the Phase 2 expansion cohort, patient must receive pembrolizumab for the checkpoint inhibitor treatment.

3.2 Exclusion Criteria

- Patients who have had radiotherapy within 4 weeks prior to entering the study or those who have not recovered from adverse events due to radiotherapy administered more than 4 weeks earlier.

- Patients who have had prior therapy with immune checkpoint inhibition or indoximod are excluded from the trial. Pre-treatment with other immune modulators is allowed in the phase 1 component of the study only. For the phase 2 component, patients are excluded if they have had prior therapy with or immune-stimulating agents including, but not limited to, interleukin-2, interferons, CTLA-4 or PD1 antagonists, CD40 or CD137 agonist, or cancer therapeutic vaccines in any prior line for metastatic disease. Interferons used in the adjuvant setting are allowed (phase 1 or 2 component).

- Patients with known active, uncontrolled brain metastases should be excluded from this clinical trial.

- History of allergic reactions attributed to compounds of similar chemical or biologic composition to ipilimumab or tryptophan containing substances. This would include L-tryptophan or 5-hydroxy-tryptophan supplements. Also patients with a history of known hypersensitivity reactions to mouse or humanized monoclonal antibodies are excluded.

- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection (especially toxoplasmosis, which could potentially be worsened by indoximod (Divanovic et al., 2012)), symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

- Pregnant women are excluded from this study because indoximod is an immunoregulatory agent with the potential for abortifacient effects due to fetal rejection by the maternal immune system. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with indoximod, breastfeeding should be discontinued if the mother is treated with indoximod.

- Known HIV-positive patients and those with other acquired/inherited immunodeficiencies are ineligible due the possibility of affecting the response to indoximod, and the higher risk of active opportunistic infections.

- Any other cancer, unless the patient has been disease-free for ≥5 years (except treated and cured basal-cell or squamous-cell skin cancer, superficial bladder cancer, or treated carcinoma in situ of the cervix, breast, or bladder and treated localized prostate cancer with undetectable PSA for 2 years).

- Patients with laboratory evidence of pancreatitis are excluded.

- Patients with autoimmune disease (e.g., psoriasis, extensive atopic dermatitis, asthma, IBD, M.S., uveitis, vasculitis), chronic inflammatory condition, or any condition requiring concurrent use of any systemic immunosupressants or steroids for any reason are excluded from the study. Patients with isolated vitiligo remain eligible. Any patient with an allo-transplant of any kind would be excluded as well, including xenograft heart valve. Mild, intermittent asthma requiring only occasional beta-agonist inhaler use or mild localized eczema will not be excluded.

- Chronic use of immune-suppressive drugs (i.e., systemic corticosteroids used in the management of cancer or non-cancer related illnesses, e.g., COPD).

- Patients who are receiving or have received any other investigational agent within 30 days prior to enrollment into the study (or 5 half-lives of agent, whichever is longer).

3.3 Inclusion of Women and Minorities

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

3.4 Baseline Tests

- Baseline and Eligibility Tests will include (See Section 11.0, Study Calendar for details)

- Baseline history and complete physical examination (to include height and weight) within 28 days prior to initiating therapy. Confirmatory exam within 7 days prior to starting treatment.

- Serum chemistries including BUN, creatinine, albumin; electrolytes including sodium, potassium, magnesium, and calcium; liver function tests including total bilirubin, AST (SGOT), ALT (SGPT), and alkaline phosphatase, amylase, lipase, fasting glucose to be done within 7 days prior to initiating therapy. Liver function tests must be completed or repeated within 3 days prior to immune checkpoint inhibition administration per package insert.

- HCG pregnancy test (serum or urine) to be done within 7 days prior to first treatment for all women with child-bearing potential

- LH, FSH, free T4/TSH and ACTH to be drawn during screening (within 28 days of starting treatment), at baseline (on Cycle 1 Day 1 or within 3 days prior) and then at least monthly while on active treatment. Full endocrine analysis will be done if clinical suspicion and/or MRI data is suggestive of pituitary inflammation.

- CBC with platelets and 5-part differential (to include neutrophils, lymphocytes, eosinophils, basophils, and monocytes) to be done within 7 days prior to initiating therapy.

- Blood (approximately 4 mL) for measurement of [redacted] at baseline (Cycle 1 Day 1 prior to treatment)

- Baseline imaging performed within 28 days prior to initiating therapy

- For Phase 2 expansion cohort, pre-treatment biopsies are required. The lesion to be biopsied must be accessible via percutaneous core needle. No endoscopic or laparoscopic biopsies are allowed. No lung lesions are allowed. Lesions that can be imaged by ultrasound are strongly preferred. If a lesion can be imaged by both ultrasound and CT scan, ultrasound is required unless there are special circumstances. Such cases must be discussed in advance with the Medical Monitor. Each biopsy must consist of four individual core biopsies. Details of biopsy handling are included in the NLG2103 lab manual. A paired on-treatment biopsy of the same lesion performed in the same fashion is also required after the 3rd cycle of pembrolizumab treatment, prior to the start of the 4th cycle of pembrolizumab.

4.0 REGISTRATION PROCEDURES

4.1 Registration Process

All patients must be registered on study before beginning therapy. All patient will be enrolled in the study before receiving treatment. Treating physician must determine which standard of care immune checkpoint inhibitor is to be used first prior to registration.

[redacted]

[redacted]

5.0 TREATMENT PLAN

5.1 Experimental Design Synopsis

The current study is designed as a prospective trial to evaluate the combination of indoximod and immune checkpoint inhibition in adult patients with metastatic melanoma. The immune checkpoint inhibitors ipilimumab, nivolumab, and pembrolizumab will be used at the recommended approved dose for this indication.

The current trial has two phases: a phase 1b dose escalation of indoximod in combination with ipilimumab, starting at half the recommended single-agent dose, to establish the recommended phase 2 dose for the combination. The phase 1b trial has been completed, and the RP2D dose established for indoximod is 1200 mg po BID.

This is being followed by a single-arm phase 2 study testing a fixed dose of indoximod (at the recommended phase 2 dose of 1200 mg po BID) combined with standard-dose immune checkpoint inhibitors ipilimumab, nivolumab, or pembrolizumab. As sequential therapy with CTLA-4 and PD-1 checkpoint blockade is a standard approach to treating patients with advanced melanoma, this trial looks to evaluate the possibility of clinical benefit from adding indoximod across this treatment approach. The study is powered to a primary endpoint of best ORR after the sequential administration of the immune checkpoint inhibitors and indoximod. Secondary endpoints of clinical benefit (DCR and duration of DCR) will be evaluated for the combination of indoximod with the initial checkpoint inhibitor administered as well as for the second checkpoint combination. PFS after the initiation of each standard of care checkpoint inhibitor will be assessed. Overall survival will also be assessed. The Phase 2 expansion cohort will require paired biopsies prior to treatment and after Cycle 3 of pembrolizumab, prior to the start of Cycle 4. Drug dosing will be the same as in Phase 2.

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial cancer directed agents or therapies other than those described below may be administered.

Safety assessment will follow the guidelines provided in the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version.4.03.

Patients will be followed both clinically and radiographically starting 12 weeks after initiation of treatment then every 8 weeks for tumor evaluation. Post-treatment scans will be compared to the baseline scan and responses will be assessed based using immune related response criteria (irRC) described by Wolchok et al. and mWHO criteria (Wolchok et al., 2009).

“Combination” clinical trials of novel immunological agents assess the safety and/or efficacy of a combination of immunotherapeutic agents. While this begins to address understanding the

potential benefit of such combinations seen in pre-clinical models, it complicates the assessment of the safety and efficacy of the immunologic agents. Phase 1 dose-escalation trials are especially difficult, since patients are generally treated at the MTD of the backbone immunologic therapy, which, by definition, already induces significant toxicity in approximately 1/6 of patients (the target rate of the 3 + 3 dose-escalation trial design). We proposed a phase 1 dose escalation trial of combination immunotherapy that addresses these issues by escalating against the effect of regimen-limiting toxicity (RLT), i.e., toxicity induced by the immunological agents in combination that is not seen with either agent alone (or seen at severities or rates of occurrence above expected from existing data). Additionally, if one of the agents is already approved and considered a standard of care regimen for the indication being studied, additional toxicities (as for type, severity or timing) seen above those expected that limit the administration of the backbone therapy could also be considered a RLT.

Expected toxicity monitoring: In addition to the known side effects of immune checkpoint inhibitors, potential interactions between indoximod and these agents include the risk of pituitary inflammation (hypophysitis) and the possibility of pancreatitis. These have not been observed in the phase 1 portion of this study.

5.1.1 Phase 1 Portion

Choice of the phase 1 dose for indoximod: A single-agent phase 1 study of indoximod has already been conducted, as described in Section 2.4. Due to low toxicity, no MTD was determined up to a dose of 2000 mg p.o. BID. Based on pharmacokinetics, a dose of 1200 mg BID was chosen as the highest recommended dose for subsequent studies (giving essentially plateau drug level). For the current study, the phase 1 component started at one-half of that dose (600 mg BID) and progressed to a full dose of 1200 mg BID, which was established as the RP2D for the phase 2 portion of the study.

The phase 1 portion was designed to assess the safety of indoximod in combination with a fixed dose of ipilimumab, the potential regimen limiting toxicities (RLT) of the combination, and identify the recommended phase 2 dose (RP2D) of combination indoximod and immune checkpoint inhibition.

The goal of the trial was to find the maximum dose of indoximod that did not induce a regimen-limiting toxicity (RLT) in more than 1/6 of patients treated concurrently with ipilimumab. Two doses of indoximod were tested.

The standard regimen with ipilimumab is now one of the backbone regimens into which new agents will be integrated for patients with melanoma. To establish the safety and the RP2D of the new agent indoximod in combination with ipilimumab, it is necessary to determine the attribution of all toxicities. However, when ipilimumab is administered as standard regimen, it is associated with significant toxicities that may confound efforts to define the true toxicity of new agents added to this backbone. The danger is that the high rate of toxicity of the backbone regimen will result in an unacceptably high rate of rejecting all dose levels of new agents.

In our approach, patients were monitored for the acute toxicity of ipilimumab while the dose of indoximod was escalated. In the pivotal phase 3 study of ipilimumab, severe, life-threatening

immune-mediated adverse reactions have been reported in up to 10 % of the patients. Based on this study, permanent discontinuation of ipilimumab is recommended in these instances. This includes Grade 3-4 colitis, dermatitis, neuropathies or other immune-mediated adverse reactions, AST or ALT >5 x the upper limit of normal (ULN) or total bilirubin >3 the ULN. Investigators should follow all prescribing information contained in the ipilimumab package insert. If one of these toxicities occurs during either the phase 1 or phase 2 components of this study, ipilimumab will be permanently discontinued. Once an affected patient recovers (resolves to Grade 1 or less), they will be allowed to restart indoximod at the assigned dose as was done in the phase 1 indoximod trial as described in section 2.4.

Definition of a regimen-limiting toxicity: During dose-escalation, RLTs will be defined as any of the following events determined by the Investigator to be related to **treatment combination** (as opposed to an individual component) irrespective of outcome:

- Clinically significant non-hematologic toxicity of Grade 3 or greater not related to underlying malignancy (with the exception of fatigue and nausea and vomiting adequately managed medically).

- Severe hematological toxicity (Grade 3-4 febrile neutropenia, or Grade 4 thrombocytopenia) persisting for greater than 5 days.

- A Grade 3 or greater immune-related severe adverse event that meets the accepted criteria for permanent discontinuation of ipilimumab, as specified under the stopping-rules in Section 6.1.2, is considered a RLT.
    - **Note**, however, that less severe immune-related toxicity (Grade 2 or greater but not meeting the criteria for permanent discontinuation of ipilimumab), which resolves to Grade 1 or better with steroid therapy, is not considered a RLT. These toxicities are managed with a delay of dosing and administration of corticosteroids (orally or intravenously) until the event improved to Grade 1 or lower, as described in Section 6.1.1.
    - However, if, after this management, the event does **NOT** improve to Grade 1 or better, then indoximod will also be discontinued permanently, and the event considered as a RLT.

For purposes of the dose escalation in this trial, determination of toxicity for dose escalation purposes will be made after the third patient of any cohort has completed the first two cycles of combination immunotherapy.

AEs not known and expected from ipilimumab and not seen in phase 1 indoximod trials will be considered regimen toxicities initially. Any Grade 3 or higher regimen toxicity mandates a conference call within 3 business days between investigators and sponsor to discuss attribution and response.

Dosing regimen: Dosing cycles will be 21 days in length during the combination immunotherapy component (segment 1) and 28 days during indoximod monotherapy (segment 2).

Indoximod and ipilimumab will be dosed concurrently. Indoximod will be dosed twice daily on all days of each 21 day cycle. Ipilimumab will be dosed on the 1st day of each 21 day cycle for the first 4 cycles (segment 1). Indoximod dosing will continue after all 4 doses of ipilimumab are administered (segment 2, 28-day cycles).

The following doses for phase 1 were tested using the dose and schedule as described below:

Dose Level	Indoximod dose (oral)
-2	200 mg twice daily, until progression or limiting toxicity.
-1	400 mg twice daily, until progression or limiting toxicity
1 **(starting dose)**	600 mg twice daily, until progression or limiting toxicity.
2	1200 mg twice daily, until progression or limiting toxicity.

The starting dose was dose level 1 as defined above, and the dose escalation process was the following:

- If none of the three subjects forming the first cohort experience RLT, then dose level 2 cohort will be enrolled.
- If one of the three subjects in any cohort experiences a RLT, then enrollment into that cohort will be expanded to a total of 6 subjects.
- If > 1 of the 3-6 subjects experience a RLT, then the MTD for the combination has been exceeded and further enrollment into the cohort will cease.
- If >1 subject at dose level 1 experiences a RLT, then the dose will be de-escalated to dose level -1. If >1 subject at this level experiences a RLT, one additional de-escalation to dose level -2 is allowed.

The MTD will be considered the largest dose level at which at most 1 out of 6 patients experiences a RLT. If the MTD is not reached at level 2, no further dose-escalation will be allowed, based on the information (PK, PD) currently available on indoximod.

Delayed Toxicities: It is possible that some RLTs may not emerge until many months on therapy with indoximod (hence, after escalation has already occurred to the next dose step). Any such late RLT will still be considered an RLT, and will be dealt with as above. However, any patients who were already enrolled at the higher dose will be reduced to the dose that triggered the RLT. These patients will continue treatment at the lower dose, but will not be evaluable for definition of the RLT (because they received mixed dosing).

Restarting Indoximod: For immunotherapy, certain autoimmune AEs are an expected consequence of successful immune stimulation, and may even correlate with tumor response.

In the phase 1 trials of indoximod, administration of indoximod to patients who previously received ipilimumab caused isolated recall hypophysitis. This was managed safely, and all patients were successfully re-started on indoximod without other additional toxicity, and were treated for >6 months with stable disease. Therefore, it could be stated that the underlying hypothesis of this combination therapy is to treat to toxicity, manage that toxicity, and then

prolong the state of immune activation with indoximod, which is previously demonstrated to be less toxic, well tolerated, and titratable with a short half-life.

- Thus, patients with an "on-target", expected immune-related adverse event, which does not rise to the level of permanent discontinuation criteria for ipilimumab (as defined in Section 6.1.2) and which resolves (to Grade 1 or better) with corticosteroids, may be re-started on indoximod (same dose) if they meet all of the restarting criteria described in Section 6.1.
- Isolated hypophysitis, in the absence of other regimen-limiting toxicity, is an expected (on-target) toxicity of the combination. It is scored as a RLT for purposes of dose-escalation, but isolated hypophysitis will be managed by stopping all study medication, treating with corticosteroids and hormone replacement (thyroid and cortisol) until clinically stable, and then (at the judgment of the treating investigator) restarting indoximod at the same dose if clinically stable. This approach was well tolerated in the phase 1 trial of single-agent indoximod by patients who experienced recall hypophysitis. Patients with hypophysitis will remain on hormone replacement as long as needed.

Monitoring of Adverse Events: Monitoring of adverse events will continue until any ongoing event is resolved or stabilized. A data and safety monitoring committee will provide independent oversight of safety and the risk–benefit ratio.

Combination with PD-1 Inhibitors: The toxicities seen with immune checkpoint inhibitors are similar across CTLA-4 inhibitors (ipilimumab) and PD-1 inhibitors (nivolumab and pembrolizumab). These toxicities are observed with less severity and less frequency with PD-1 inhibitors than with ipilimumab. Therefore, we believe we can safely initiate the combination of nivolumab or pembrolizumab with indoximod at the RP2D of 1200 mg po BID determined by combination with ipilimumab. Patients initially enrolled on treatment with nivolumab or pembrolizumab in the phase 2 portion of the trial will be closely monitored after enrollment for any change in frequency or severity of expected immune mediated adverse reactions. Given the limited scope and open label nature of this trial, this is feasible and provides an adequate safety approach.

5.1.2 Phase 2

No patients will be enrolled in the Phase 2 portion until all patients in the dose-escalation component have completed the RLT determining portion of the Phase 1 aspect of the trial, and the recommended phase 2 dose determined. Investigators and representatives of the Sponsor will meet by teleconference to review all toxicity data from the dose-escalation component. When all agree on the safety and appropriateness of the indoximod RP2D, then the Phase 2 portion will begin. The teleconference was held July 24, 2015 and a Phase 2 dose of 1200 mg BID was set.

Immune checkpoint inhibition will be defined within the scope of this study as the sequential administration of two of the three commercially available checkpoint inhibitors. One must be ipilimumab. One must be either nivolumab or pembrolizumab. The order in which the two are administered is left to treating physician discretion.

The intention in this study is to evaluate the benefit of adding indoximod to this regimen of immune checkpoint inhibition. Per design, the change from the initial checkpoint inhibitor to the second checkpoint inhibitor administered should only occur after definitive progression as defined by irRC or mWHO criteria. If a subject experiences an immune checkpoint inhibitor related adverse event that requires withdraw of that checkpoint inhibitor, once recovered, the subject should continue on indoximod as monotherapy until definitive evidence of progression. Once definitive progression occurs, either on combination therapy or indoximod monotherapy, the second checkpoint should be administered while indoximod continues.

When given with ipilimumab as initial study treatment, indoximod will be administered concomitantly with the standard four doses of ipilimumab and then followed by indoximod given alone until disease progression or unacceptable toxicity occurs. If ipilimumab has to be stopped due to ipilimumab-related toxicity prior to administering all 4 doses, once the toxicities have resolved, indoximod is to be administered alone as long as there is clinical benefit (CR or PR or SD). In the case of progression, either on the combination of ipilimumab and indoximod or with indoximod alone in maintenance, the regimen is to be changed to nivolumab or pembrolizumab plus indoximod.

When given in combination with nivolumab or pembrolizumab as initial study treatment, indoximod will be given concurrently with either checkpoint inhibitor until toxicity or disease progression occurs. If nivolumab or pembrolizumab is stopped due to toxicity, once resolved, indoximod is to be administered alone as long as there is clinical benefit (CR or PR or SD). In the case of progression on combination therapy or indoximod alone, the regimen is to be switched to ipilimumab plus indoximod. See Section 11, Study Calendar, for treatment regimen cycles.

5.1.3 Phase 2 Expansion Cohort Treatment Plan

Up to 20 patients will be enrolled in an expansion cohort that requires paired pre-treatment and on-treatment biopsies of the same lesion. Biopsies must be done percutaneously, preferably by ultrasound guidance. No endoscopic or laparoscopic biopsies are allowed. No lung lesions are allowed due to the high risk of complication (pneumothorax) with multiple core needle biopsies.

Each biopsy is to consist of four core needle samples of tumor. No FNA's are allowed. Patients have to have a lesion that can be biopsied with a core needle to be eligible. Lesions that can be imaged by ultrasound are strongly preferred. If a lesion can be imaged by both ultrasound and CT scan, ultrasound is required unless there are special circumstances. Such cases must be discussed in advance with the Medical Monitor.

The first biopsy is to be done prior to study treatment. The second biopsy is to be done after the 3rd cycle of pembrolizumab treatment, prior to the start of the 4th cycle, on the same lesion, performed in the same fashion, as the baseline biopsy.

Patients who cannot undergo a second biopsy for compelling medical reasons (determined by discussion between the treating physician, PI, and Sponsor) may stay on study. In the case of significant clinical response, if a previously biopsied lesion is no longer available, an alternate

lesion may be biopsied as long as the alternate lesion is also regressing (documented objective response).

Details of biopsy handling are included in the NLG2103 lab manual.

Study treatment in the Phase 2 expansion will otherwise follow the treatment plan for Phase 2.

5.2 Indoximod Administration

Three or six 200 mg capsules (600 mg or 1200 mg) should be taken in the morning and evening. No food should be taken for at least 2 hours before and at least 1 hour after administration of the morning and evening doses. The medication should be taken twice daily in a continuous fashion. Patients should be told to swallow whole capsules without chewing with a full glass of water. Antacids are also not allowed to be taken for at least 2 hours before and 1 hour after administration of the indoximod. No specific premedications are required.

5.3 Immune Checkpoint Inhibitor Administration

The study is designed to evaluate the addition of indoximod to standard of care checkpoint immunotherapy. The administration of these agents (ipilimumab, nivolumab, and pembrolizumab) should be done at the direction of the treating physician according to the physician's usual standard of care practices.

Management of risk for autoimmune side effects:

- Tissue-specific inflammatory events (known as immune related adverse events or reactions) can be associated with indoximod and immune checkpoint inhibition treatment.
- Careful laboratory and symptom monitoring for pituitary dysfunction and pancreatitis is warranted based on the prior experience with patients treated with indoximod and ipilimumab.
- Careful monitoring for other potential inflammatory symptoms (including enterocolitis, skin reaction, hepatic toxicity, pneumonitis, nephritis, and uveitis) will be also performed.
- Management of immune-related adverse events from immune checkpoint inhibition and indoximod will include administration of corticosteroids (orally or intravenously), a delay in a scheduled dose, or discontinuation of therapy. Assigned doses will be delayed in case of immune-related adverse event of Grade 2 or higher until the event improves to Grade 1 or lower. Immune checkpoint inhibition will be restarted at this point and continue every 3 weeks until all 4 planned doses are administered or 16 weeks from first dose, whichever occurs earlier.
- For corticosteroid-refractory side effects, TNF-blocking agents (e.g. infliximab) or other immunosuppressive medications (e.g. mycophenolate mofetil) will be administered.
- Details of algorithmic management will be as described in the respective package inserts and Investigators should follow all prescribing information therein.

5.4 General Concomitant Medication and Supportive Care Guidelines

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient is permitted, except as specifically prohibited.

Anticancer therapy (chemotherapy, biologic or radiation therapy, and surgery) other than the study treatment(s) must not be given to patients while the patient is on the study. If such agents are required for a patient, then the patient must be withdrawn from the study. Exceptions may be made for limited interventions (radiation therapy or surgery) intended to palliate a specific medical problem (i.e. cord compression or bowel obstruction) on an individual basis.

Systemic corticosteroid use will not be permitted on this study with the exception of treating immune-mediated AEs or adrenal insufficiency (see section 5.1 and 5.3).

Subjects are allowed to receive palliative radiotherapy for painful bone lesions.

5.5 Duration of Therapy

The intention of this trial is to evaluate the preliminary efficacy of adding indoximod to immune checkpoint therapy, defined within the scope of this study as the sequential administration of two of the three commercially available checkpoint inhibitors. One must be ipilimumab. One must be either nivolumab or pembrolizumab. The order in which the two are administered is left to treating physician discretion. Once a patient progresses on or after the first administered checkpoint, the patient should be administered the second checkpoint inhibitor, all in combination with indoximod.

Patients whose tumors progress are to be switched to the second treatment combination. Mild progression (immunologic pseudoprogression) at the beginning of the treatment is expected in a portion of enrolled patients, given the usual delayed response in immunotherapy (Wolchok et al., 2009). Once a patient demonstrates definitive progression on or after the second treatment combination, they will be taken off study treatment. They will be followed for overall survival.

Patients who experience an AE requiring permanent discontinuation of the first administered checkpoint inhibitor, as described in sections 6.1.2, 6.2 or 6.3, should be restarted on indoximod alone as described in section 6.6. If they have a second incidence of an immune related SAE after re-initiation of indoximod or the administration of the second checkpoint therapy combination, they will be considered for removal from the study. Study medications will be held until a conference call to discuss any such patient can be held between the investigator and the medical monitor.

Isolated hypophysitis or pituitary dysfunction, in the absence of other regimen-limiting toxicity, is a possible expected (on-target) toxicity of the combination and does not require discontinuation from the study (even though it does not resolve). Such patients will be treated by stopping all study medication, treating with corticosteroids and hormone replacement (thyroid and cortisol) until clinically stable, and then (at the judgment of the treating investigator, and if the patient agrees) restarting indoximod at the same dose if clinically stable. This approach was

well tolerated in the phase 1 trial of indoximod. Patients with hypophysitis will remain on hormone replacement as long as needed.

Patients are also removed from study treatment who:

- experience intercurrent illness that prevents further administration of treatment
- decide to withdraw from the study
- experience general or specific changes in the patient's condition that render them unacceptable for further treatment in the judgment of the investigator
- have the inability to be compliant with study treatment in opinion of investigator defined as missing treatments or study visits for non-medical reasons or complying with oral treatments below an 85% threshold on two sequential study visits.

5.6 End of Treatment and Premature Withdrawal Visit

Once a participant discontinues study therapy for any reason, the participant will be asked to return to the clinic within 30 days for the assessments listed below.

- Update medical history including prior and concomitant medications
- Physical examination including vital signs, weight, and a review of body systems
- ECOG performance status
- CBC with differential and platelets
- Serum chemistries
- Concurrent medications and adverse events assessed at end of treatment

5.7 Duration of Follow Up

After the End of Treatment Visit, Follow up visits will be conducted every 3 months for 2 years, to include the following:

- Update medical history including current cancer therapy receiving every 3 months.
- Physical examination including vital signs, weight, and a review of body systems every 3 months.
- CBC with differential and platelets per SOC practices.
- Serum chemistries per SOC practices.
- Imaging per SOC practices.

Patients will be followed for survival and possible long-term toxicity from this treatment. Follow-up visits will continue for 2 years as per Section 11 (and as stated above). For those surviving longer than 2 years, follow-up will be performed using telephone contact, correspondence with treating physicians, and death records as necessary to update vital status at least every 6 months until death or lost to follow-up. Further therapy will be at the discretion of the treating physician.

5.8 Criteria for Removal from Study Treatment

Patients will be removed from study treatment when any of the criteria listed in Section 5.5 applies. If rapid life-threatening disease progression happens, or unacceptable adverse event(s) occur, or patient decides to discontinue the study, or patient becomes pregnant or starts breast-feeding, the patient will be removed from the study therapy. The reason for study removal and the date the patient was removed must be documented on the Case Report Form. Patients who discontinue study treatment will be followed for survival status until they are lost to follow up or death whichever occurs first.

6.0 DOSING DELAYS/MODIFICATIONS

The dosing delay and modification information contained in this section concerning ipilimumab, nivolumab, and pembrolizumab is provided for background purposes. Dosing delays and/or modification of these agents should be performed consistent with standard of care practice by the treating physician within the guidelines provided in the respective package inserts.

6.1 Dose Modifications for Ipilimumab

- Ipilimumab related toxicities must be resolved to baseline or ≤ Grade 1 prior to administering the next dose.
- No dose reductions for ipilimumab are allowed.
- Ipilimumab can be delayed if the reason for the delay is toxicity/AE and if resolved to Grade one or better can restart and continue every 3 weeks until all 4 planned doses are administered or 16 weeks from first dose, whichever occurs earlier.
- Please refer to the AE management algorithms provided by the package insert for ipilimumab on management of potentially ipilimumab-related adverse events.
- Liver function tests (AST, ALT total bilirubin) will be evaluated for every subject prior to administration of ipilimumab. **Blood samples must be collected and analyzed within 3 days prior to dosing.** Liver function test results must be reviewed by the principal investigator or designee prior to ipilimumab administration and meet dosing criteria specifications:
    - < 2.5 x ULN for AST and ALT and < 1.5 x ULN for total bilirubin
- If abnormal LFT values are detected, the subject must be managed using hepatotoxicity algorithm (see Appendix A).

6.1.1 Criteria to Resume Treatment with Ipilimumab

Treatment may resume when the AE(s) resolve(s) to Grade 1 or baseline value.

6.1.2 Rules for Permanent Discontinuation of Ipilimumab

During ipilimumab administration, ipilimumab must be permanently discontinued if the subject experiences any of the following toxicities. Events requiring permanent discontinuation are:

- Grade 3 or 4 motor or sensory neuropathy, regardless of causality
- Any AE which, in the judgment of the investigator, presents a substantial clinical risk to the subject with investigational drug dosing.

- Any ≥ Grade 2 eye pain or reduction of visual acuity that does not respond to topical therapy and does not improve to Grade 1 or better severity with topical therapy or requires systemic treatment.
- Any other ≥ Grade 3 non-skin related AE with the exception of laboratory abnormalities and Grade 3 nausea and vomiting.
- Any Grade 4 laboratory abnormalities
- Persistent Grade 2 adverse reactions (that push ipilimumab administration beyond the 16 week window from first dose) or inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day.
- Severe or life-threatening adverse reactions, including any of the following:
    - Colitis with abdominal pain, fever, ileus, or peritoneal signs; increase in stool frequency (≥ Grade 3)
    - AST or ALT > 5 times the ULN or total bilirubin > 3 times the ULN
    - Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous or hemorrhagic manifestations.
    - Severe motor or sensory neuropathy, Guillain-Barre syndrome, or myasthenia gravis.
    - Severe immune-mediated reactions involving any organ system (e.g. nephritis, pneumonitis, pancreatitis, myocarditis).
    - Severe infusion reaction (see Section 6.1.3)

6.2 Nivolumab dosing modifications

There are no recommended dose modifications for hypothyroidism or hyperthyroidism. Immune mediated adverse events should be treated with corticosteroids in accordance with the guidelines in the package insert.

Withhold nivolumab for any of the following:
- Grade 2 pneumonitis
- Grade 2 or 3 colitis
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3 and up to 5 times upper limit of normal (ULN) or total bilirubin greater than 1.5 and up to 3 times ULN
- Creatinine greater than 1.5 and up to 6 times ULN or greater than 1.5 times baseline
- Any other severe or Grade 3 treatment-related adverse reactions

Resume nivolumab in patients whose adverse reactions recover to Grade 0 to 1.

Permanently discontinue nivolumab for any of the following:
- Any life-threatening or Grade 4 adverse reaction
- Grade 3 or 4 pneumonitis
- Grade 4 colitis
- AST or ALT greater than 5 times ULN or total bilirubin greater than 3 times ULN
- Creatinine greater than 6 times ULN
- Any severe or Grade 3 treatment-related adverse reaction that recurs

- Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks
- Persistent Grade 2 or 3 treatment-related adverse reactions that do not recover to Grade 1 or resolve within 12 weeks after last dose of nivolumab

6.3 Pembrolizumab Dosing Modifications

For immune mediated adverse reactions administer corticosteroids based on the severity of the reaction. See package insert for guidelines.

Withhold pembrolizumab for any of the following:

- Grade 2 pneumonitis
- Grade 2 or 3 colitis
- Symptomatic hypophysitis
- Grade 2 nephritis
- Grade 3 hyperthyroidism
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3 and up to 5 times upper limit of normal (ULN) or total bilirubin greater than 1.5 and up to 3 times ULN
- Any other severe or Grade 3 treatment-related adverse reaction

Resume pembrolizumab in patients whose adverse reactions recover to Grade 0-1.

Permanently discontinue pembrolizumab for any of the following:

- Any life-threatening adverse reaction
- Grade 3 or 4 pneumonitis
- Grade 3 or 4 nephritis
- AST or ALT greater than 5 times ULN or total bilirubin greater than 3 times ULN
- For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week
- Grade 3 or 4 infusion-related reactions
- Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks
- Persistent Grade 2 or 3 adverse reactions that do not recover to Grade 0-1 within 12 weeks after last dose of pembrolizumab
- Any severe or Grade 3 treatment-related adverse reaction that recurs

6.4 Treatment of Checkpoint Inhibitor Related Infusion Reaction

Infusion reactions should be graded according to CTCAE version 4.03 Allergic reaction/ hypersensitivity criteria.

Severe infusion reaction requires permanent discontinuation for further treatment.

Appropriate medical therapy including fluids, epinephrine, corticosteroids, IV antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions.

In each case of an infusion reaction, the investigator should institute treatment measures according to the best available medical practice.

6.5 Management of Adverse Events of Interest

Adverse events of interest are AEs of unknown etiology, which may potentially be due to an immune phenomenon.

The investigator will refer to the algorithms on the management of these Adverse Events of Interest described in Appendix A.

6.6 Rules for Stopping and Restarting Indoximod

The half-lives of immune checkpoint inhibitors are long (>15 days), and the toxicity may be cumulative. In contrast, the half-life of indoximod is much shorter (10 hrs), and discontinuation of indoximod results in a prompt reduction in drug levels. Indoximod is a reversible inhibitor of the IDO pathway. In the indoximod phase 1 trial, patients did not show cumulative toxicity over many months of therapy.

The rules for stopping and restarting indoximod will follow the rules described for the checkpoint inhibitors as described in section 6.1, 6.2, and 6.3 and the applicable package inserts.

Follow the below recommendations for indoximod in addition to the recommendations outlined for each checkpoint inhibitor:

- When the AE is resolved to $\leq$ Grade 1 and the patient is stable and is off steroids, the patient may re-start indoximod at the same dose, if, in the judgment of the treating physician, restarting indoximod is not contraindicated for that patient.
- There is no time limit on when patients are allowed to re-start indoximod. As long as measurable tumor remains stable, patients may re-start indoximod whenever toxicity has resolved.
- Indoximod may be restarted even if a patient has experienced a SAE that requires permanent discontinuation of the checkpoint inhibitor.
- Patients with isolated hypophysitis or pituitary dysfunction who are stable on hormone replacement (thyroid and cortisol) are eligible to restart indoximod, as long as the endocrine dysfunction is stable on replacement therapy. These patients will remain on hormone replacement as long as necessary.
- No patient should be re-started on indoximod if, in the judgment of the treating investigator, this would be clinically contraindicated (e.g., due to the severity of the antecedent toxicity, or to the patient's medical condition).
- Indoximod may be continued as monotherapy if the patient can no longer tolerate checkpoint inhibitor treatment and if, in the judgment of the treating physician, is in the best interest of the patient.

- Once a patient has demonstrated a durable response of > 6 months on combination treatment, the treating physician, at his or her discretion may elect to hold the checkpoint inhibitor per their usual practice and continue on indoximod alone.

In general, indoximod was very well tolerated in previous phase 1 trials and seldom required any dose reductions. If a dose reduction is deemed necessary due to intolerance from taking the required number of pills or grade 3-4 nausea, one dose reduction by 200 mg per dose (1200mg BID to 1000mg BID) is permitted. Indoximod will not be restarted at full dose after a dose reduction. If this dose reduction is not tolerated then discontinuation of the study treatment is required.

7.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting in addition to routine reporting.

7.1 Most Common Adverse Events

7.1.1 Adverse Events for Indoximod

The most common adverse reactions ($\geq$ 10% incidence) are: fatigue, nausea, diarrhea, and anorexia.

The most common Grade 3 to 4 hematologic laboratory abnormalities that have developed during treatment with indoximod are: thrombocytopenia, neutropenia, lymphopenia, and leukopenia.

7.2 Definitions for Reporting Purposes

In this protocol the study drug indoximod is being combined with one of three different immune checkpoint immunotherapies, drugs with an established safety profile. Adverse events and serious adverse events observed during the course of this trial and previously reported as related to ipilimumab, nivolumab, or pembrolizumab will be attributed to such. Adverse events previously seen with indoximod will be attributed to indoximod. Novel serious adverse events not previously seen with any study agent will initially be considered regimen associated and will require an evaluation by the PI and the sponsor to determine attribution. This will be done via teleconference within three business days of the report.

Subject data accrued on this study will be reported in accordance with Code of Federal Regulations Title 21 (21CFR) 312.32.

This study will utilize the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 for grading all adverse events. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

The Site P.I. will notify the IRB and NewLink Genetics (Study Sponsor) who in turn will notify the FDA and other regulatory agencies of all serious adverse events as required by law or regulation. All participating investigators will be notified of IND Safety Reports by Investigator Alerts sent through email. Serious Adverse Event (AE) Reporting by investigators will be done as outlined below.

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Related/Attribution to the use of the drug: There is a reasonable possibility (more likely than not) that the experience may have been caused by the investigational drug.

Attribution Categories:

Unrelated	The AE *is clearly NOT related* to the intervention.
Unlikely	The AE *is doubtfully related* to the intervention.
Possible	The AE *may be related* to the intervention.
Probable	The AE *is likely related* to the intervention.
Definite	The AE *is clearly related* to the intervention.

Adverse events that are known and expected from checkpoint inhibition therapy per the package inserts for ipilimumab, nivolumab, and pembrolizumab are to be attributed to the relevant approved agent unless there is something specific about the individual adverse event (severity, timing, etc.) that compels the investigator to attribute the adverse event differently. Any adverse events that are observed that have been previously reported in Phase 1 and 2 trials of indoximod as likely due to indoximod are to be attributed as related to indoximod.

AEs not known and expected from ipilimumab and not seen in phase 1 indoximod trials nor expected per package insert from ipilimumab, nivolumab, or pembrolizumab will be considered regimen toxicities initially. Any Grade 3 or higher regimen toxicity mandates a conference call within 3 business days between investigators and sponsor to discuss attribution and response.

A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Reporting Requirements for **Serious Adverse Events** (21CFRPart312)

Investigators MUST immediately report to the sponsor ANY serious adverse events within 24 hours of learning of the SAE, whether or not they are considered related to the investigational agent(s)/intervention (21CFR312.64)

An adverse events is considered SERIOUS if it results in ANY of the following outcomes:

1. Death
2. A life-threatening adverse event
3. An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. A congenital anomaly/birth defect
6. Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon 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. (FDA21CFR312.32; ICHE2A and ICHE6).

SAE reporting timelines are defined as:

- "24 Hour; 5 Calendar Days" – The SAE must initially be reported within 24 hours of learning of the SAE, followed by a complete SAE report within 5 calendar days of the initial 24 hour report.

Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and are considered related to the investigational drug require reporting on the same timelines as noted above.

Deaths clearly due to progressive disease should **NOT** be reported expeditiously but rather should be reported via routine reporting (death report).

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.

- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

SAE Reporting Form and Content: For those events that meet the criteria for serious as listed above, please complete a Serious Adverse Event Reporting Form. This form will be provided by NewLink Genetics. [redacted]

Routine Adverse Event Reporting
All Adverse Events must be reported in routine study data submissions. AEs reported through expedited SAE reports must also be reported in routine study data submissions (CRFs).

Adverse Event Case Report Form
All adverse events (regardless of grade and attribution) observed while on study and for 30 days after last dose of treatment, must be recorded on the adverse event case report form. After 30 days from last dose of treatment, only adverse events that are attributed to the study drug/combination (possible, probable, or definite) are required to be recorded on the adverse event forms.

Reporting Requirements for Baseline Adverse Events:
A pertinent positive finding identified on baseline assessment is to be documented as a Baseline Adverse Event using CTCAE terminology and grade on the provided Baseline CRF. An expedited AE report is not required if a patient is entered on to the study with a pre-existing condition (e.g., elevated laboratory value, diarrhea). The baseline AE must be re-assessed throughout the trial and reported if it fulfills expedited AE reporting guidelines.

1) If the pre-existing condition worsens in severity, the investigator must reassess the event to determine if an expedited report is required.
2) If the AE resolved and then recurs, the investigator must re-assess the event to determine if an expedited report is required.
3) No modification in grading is to be made to account for abnormalities existing at baseline.

7.3 Pregnancy

The teratogenic potential of indoximod is unknown. During the course of the study, all women of childbearing potential who are participants and all spouses of participants must be instructed to contact the Principal Investigator immediately if pregnancy is suspected. Pregnancy in a participant or partner of a participant who is receiving treatment will be reported following procedures for a SAE (although it will not be coded as a SAE). The event will be recorded in the pregnancy CRF. If pregnancy is suspected in a participant or partner of a participant prior to study drug administration, the study drug will be withheld until the β-hCG test result is available. If pregnancy is confirmed, the patient will not receive study drug and will be withdrawn from the study. If pregnancy is suspected while the patient is receiving study drug, the study drug will be

immediately withheld until the result of a β-hCG test result is available. If pregnancy is confirmed, the patient will be permanently discontinued from the study in an appropriate manner. Protocol-required procedures for study discontinuation will be performed unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate follow-up procedures should be considered, if indicated. In addition, the Principal Investigator will report pregnancy-related follow-up information, including perinatal and neonatal outcomes to the IRB. Infants will be monitored for a minimum of eight weeks.

8.0 PHARMACEUTICAL INFORMATION

8.1 Indoximod (1-methyl-D-tryptophan IND # 78060/78189/120813 (NSC-721782) pharmaceutical information

Chemical Name: 1-methyl-[D]-tryptophan

Other Names: indoximod, D-1MT

Classification: Immunomodulatory

CAS Registry Number: 110117-83-4

Molecular Formula: $C_{12}H_{14}N_2O_2$ M.W.: 218

Approximate Solubility: Approximately 4 mg/mL at pH 2 and 2 mg/mL at pH 2.5 to 9

Mode of Action: Inhibition of IDO pathway activity.

How Supplied: Indoximod is supplied by NewLink Genetics as 200 mg capsules. The capsules contain the inactive ingredients lactose monohydrate, microcrystalline cellulose, sodium croscarmellose, colloidal silicon dioxide, and magnesium stearate. The capsules are packaged 175 capsules/bottle in white opaque HDPE bottles.

The 200 mg capsules are white opaque hard gelatin capsules.

Storage: Stored at controlled room temperature (59 - 77°F)

Stability: Shelf-life surveillance of the intact bottles is on-going. Initial lots have been stable at 48 months.

Route of Administration: Oral

Agent Ordering and Agent Accountability: Indoximod is supplied and shipped by NewLink Genetics Corporation to the study site. Each shipment is accompanied by a Clinical Investigational Material Shipment Receipt Form. Upon receipt, at the clinical site, the product is stored in the clinical site's Investigational Pharmacy or designated area.

As required by FDA regulations for all drug storage, procurement and usage are carefully monitored and documented. The Principal Investigator will oversee this process and delegate responsibility as needed to conduct the trial under Good Clinical Practices. A careful inventory is maintained at each of the clinical sites.

8.2 Ipilimumab (Yervoy®) pharmaceutical information

Description: Ipilimumab is a recombinant, human monoclonal antibody that binds to the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). Ipilimumab is an igG1 kappa immunoglobulin with an approximate molecular weight of 148 kDa. Ipilimumab is produces in mammalian (Chinese hamster ovary) cell culture.

Mechanism of Action: CTLA-4 is a negative regulator of T-cell activation. Ipilimumab binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation. The mechanism of action of ipilimumab's effect in patients with melanoma is indirect, possibly through T-cell medicated anti-tumor immune responses.

Pharmacokinetics
The pharmacokinetics of ipilimumab was studied in 499 patients with unresectable or metastatic melanoma who received doses of 0.3, 3, or 10 mg/kg administered once every 3 weeks for four doses. Peak concentration (C_{max}), trough concentration (C_{min}), and area under the curve (AUC) of ipilimumab were found to be dose proportional within the dose range examined. Upon repeated dosing of ipilimumab administered every 3 weeks, ipilimumab clearance was found to be time-invariant, and minimal systemic accumulation was observed as evident by an accumulation index of 1.5-fold or less. Ipilimumab steady-state concentration was reached by the third dose. The following mean (percent coefficient of variation) parameters were generated through population pharmacokinetic analysis: terminal half-life of 14.7 days (30.1%); systemic clearance (CL) of 15.3 mL/h (38.5%); and volume of distribution at steady-state (Vss) of 7.21 L (10.5%). The mean (±SD) ipilimumab C_{min} achieved at steady-state with the 3-mg/kg regimen was 21.8 mcg/mL (±11.2).

Specific Populations: Cross-study analyses were performed on data from patients with a variety of conditions, including 420 patients with melanoma who received single or multiple infusions of ipilimumab at doses of 0.3, 3, or 10 mg/kg. The effects of various covariates on ipilimumab pharmacokinetics were assessed in population pharmacokinetic analyses.

Ipilimumab CL increased with increasing body weight; however, no dose adjustment of ipilimumab is required for body weight after administration on a mg/kg basis. The following factors had no clinically meaningful effect on the CL of ipilimumab: age (range 26 to 86 years), gender, concomitant use of budesonide, performance status, HLA-A2*0201 status, positive anti-ipilimumab antibody status, prior use of systemic anticancer therapy, or baseline lactate dehydrogenase (LDH) levels. The effect of race was not examined as there were insufficient numbers of patients in non-Caucasian ethnic groups.

Renal Impairment: Creatinine clearance at baseline did not have a clinically important effect on ipilimumab pharmacokinetics in patients with calculated creatinine clearance values of 29 mL/min or greater.

Hepatic Impairment: Baseline AST, total bilirubin, and ALT levels did not have a clinically important effect on ipilimumab pharmacokinetics in patients with various degrees of hepatic impairment.

Pharmaceutical Data
Ipilimumab is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution for intravenous infusion, which may contain a small amount of visible translucent-to-white, amorphous ipilimumab particulates. It is supplied in single-use vials of 50 mg/10 mL and 200 mg/40 mL. Each milliliter contains 5 mg of ipilimumab.

Supply: Ipilimumab is commercially available.

Storage: Ipilimumab injection (5 mg/ml) must be stored refrigerated (2° - 8°C) with protection from light and from freezing. Ipilimumab may be stored (5 mg/ml) in PVC, non-PVC or glass containers for up to 24 hours at room temperature or refrigerated (2°C - 8°C). This would include any time in transit and the total time for infusion. Drug must be completely delivered to the subject within 24 hours of preparation.

Administration: Ipilimumab is to be administered as an IV infusion using a volumetric pump through an in-line, sterile, non-pyrogenic, low-protein-binding filter with a pore size of 0.2micrometer to 1.2 micrometer (supplied by site) at the 3 mg/kg dose. The infusion must be completed in 90 minutes, followed by a normal saline (NS) flush with an adequate amount of NS to completely flush the residual fluid (dead space) in the administration set (approximately 30 - 50 mL). The total dose must be calculated using the most recent subject weight available. If the subject weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated and the amount of ipilimumab should be adjusted accordingly by the pharmacist. Doses can be rounded per institutional practice.

8.3 Nivolumab (Opdivo®)

Description
Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. Nivolumab is an IgG4 kappa immunoglobulin that has a calculated molecular mass of 146 kDa.

Pharmacokinetics
The pharmacokinetics (PK) of nivolumab was studied in patients over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. Based on a population pharmacokinetic (PK) analysis using data from 909 patients, the geometric mean (% coefficient of variation [CV%]) clearance (CL) is 9.5 mL/h (49.7%), geometric mean volume of distribution at steady state (Vss) is 8.0 L (30.4%), and geometric mean elimination half-life (t1/2) is 26.7 days (101%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was approximately 3-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks.

Specific Populations: Based on a population PK analysis using data from 909 patients, the clearance of nivolumab increased with increasing body weight supporting a weight-based dose. The population PK analysis suggested that the following factors had no clinically important effect on the clearance of nivolumab: age (29 to 87 years), gender, race, baseline LDH, PD-L1 expression, tumor type, tumor size, renal impairment, and mild hepatic impairment.

Renal Impairment: The effect of renal impairment on the clearance of nivolumab was evaluated by a population PK analysis in patients with mild (eGFR 60 to 89 mL/min/1.73 m2; n=313), moderate (eGFR 30 to 59 mL/min/1.73 m2; n=140), or severe (eGFR 15 to 29 mL/min/1.73 m2; n=3) renal impairment. No clinically important differences in the clearance of nivolumab were found between patients with renal impairment and patients with normal renal function.

Hepatic Impairment: The effect of hepatic impairment on the clearance of nivolumab was evaluated by population PK analyses in patients with mild hepatic impairment (total bilirubin [TB] less than or equal to the upper limit of normal [ULN] and AST greater than ULN or TB less than 1 to 1.5 times ULN and any AST; n=92). No clinically important differences in the clearance of nivolumab were found between patients with mild hepatic impairment and patients with normal hepatic function. Nivolumab has not been studied in patients with moderate (TB greater than 1.5 to 3 times ULN and any AST) or severe impairment (TB greater than 3 times ULN and any AST).

Pharmaceutical Data
Nivolumab is a clear to opalescent, colorless to pale-yellow solution. Discard the vial if the solution is cloudy, is discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake the vial. It is supplied in 40 mg/4 mL (10 mg/mL) and 100 mg/10 mL (10 mg/mL) solution in single-use vials.

Supply
Nivolumab is commercially available.

Specific Risk/Adverse Events
Nivolumab can cause severe and fatal immune mediated adverse effects. Many organs systems can be involved. The most common severe adverse events include pneumonitis, colitis, hepatitis, nephritis, and thyroid disease (either hypothyroidism or hyperthyroidism). Additional immune

mediated reactions observed include adrenal insufficiency, pancreatitis, neuropathies, hypophysitis, and Guillain-Barre syndrome.

Management of these conditions includes withholding of nivolumab, administration of high-dose corticosteroids, and if appropriate, initiation of hormone replacement therapy.

8.4 Pembrolizumab (Keytruda®)

Description
Pembrolizumab is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 149 kDa. Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response.

Pharmacokinetics
The pharmacokinetics of pembrolizumab was studied in 479 patients who received doses of 1 to 10 mg/kg every 2 weeks or 2 to 10 mg/kg every 3 weeks. Based on a population pharmacokinetic analysis, the mean [% coefficient of variation (CV%)] clearance (CL) is 0.22 L/day (28%) and the mean (CV%) elimination half-life (t1/2) is 26 days (24%). Steady-state concentrations of pembrolizumab were reached by 18 weeks of repeated dosing with an every 3-week regimen and the systemic accumulation was 2.1-fold. The peak concentration (C_{max}), trough concentration (C_{min}), and area under the plasma concentration versus time curve at steady state (AUCss) of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg every 3 weeks.

Specific Populations: The effects of various covariates on the pharmacokinetics of pembrolizumab were assessed in population pharmacokinetic analyses. The CL of pembrolizumab increased with increasing body weight; the resulting exposure differences were adequately addressed by the administration of a weight-based dose. The following factors had no clinically important effect on the CL of pembrolizumab: age (range 18 to 94 years), gender, renal impairment, mild hepatic impairment, and tumor burden. The effect of race could not be assessed due to limited data available in non-White patients.

Renal Impairment: The effect of renal impairment on the CL of pembrolizumab was evaluated by population pharmacokinetic analyses in patients with mild (eGFR 60 to 89 mL/min/1.73 m2; n=210), moderate (eGFR 30 to 59 mL/min/1.73 m2; n=43), or severe (eGFR 15 to 29 mL/min/1.73 m2; n=2) renal impairment compared to patients with normal (eGFR greater than or equal to 90 mL/min/1.73 m2; n=221) renal function. No clinically important differences in the CL of pembrolizumab were found between patients with renal impairment and patients with normal renal function.

Hepatic Impairment: The effect of hepatic impairment on the CL of pembrolizumab was evaluated by population pharmacokinetic analyses in patients with mild hepatic impairment (TB less than or equal to ULN and AST greater than ULN or TB between 1 and 1.5 times ULN and any AST; n=59) compared to patients with normal hepatic function (TB and AST less than or equal to ULN; n=410). No clinically important differences in the CL of pembrolizumab were found between patients with mild hepatic impairment and normal hepatic function. Pembrolizumab has not been studied in patients with moderate (TB greater than 1.5 to 3 times ULN and any AST) or severe (TB greater than 3 times ULN and any AST) hepatic impairment.

Pharmaceutical Data
Pembrolizumab for injection is a sterile, preservative-free, white to off-white lyophilized powder in single-use vials. Each vial is reconstituted and diluted for intravenous infusion. Each 2 mL of reconstituted solution contains 50 mg of pembrolizumab and is formulated in L-histidine (3.1 mg), polysorbate 80 (0.4 mg), and sucrose (140 mg). May contain hydrochloric acid/sodium hydroxide to adjust pH to 5.5.

Supply
Pembrolizumab is commercially available.

Specific Risks / Adverse Events
Pembrolizumab can cause severe immune mediated adverse events and can involve multiple organ systems. Severe immune mediated adverse events include pneumonitis, colitis, hepatitis, hypophysitis, nephritis, and hypothyroidism and hyperthyroidism. Additional severe immune mediated adverse events can include dermatitis, uveitis, myositis, pancreatitis, and adrenal insufficiency. Pembrolizumab may also cause or increase the risk for Guillain-Barre Syndrome.

For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold pembrolizumab and administer corticosteroids.

9.0

[redacted]

10.0 VISIT SCHEDULE AND ASSESSMENTS

Section 11, Study Calendar, lists all of the assessments and indicates with an "X" the visits when they are performed.

10.1 Screening and baseline examination

Informed consent must be signed before any screening procedures. The details of the assessments can be found in Section 11.

The screening examination must start with the Informed Consent procedure. The investigator is obliged to give the patient thorough information about the study and the study related assessments, and the patient should be given ample time to consider his/her participation. The investigator must not start any study related procedure before ICF is signed and dated by both patient (and impartial witness, if applicable) and investigator.

Screening includes obtaining written informed consent, a physical exam, demography, medical history/current medical conditions, current concomitant medications/therapies, disease history and extent of disease, and prior anticancer therapies.

Patient demographics and other baseline characteristics

The following patient demographic and baseline characteristics will be collected:

- General demography
- Medical history/current medical conditions (including prior and concomitant medications)
- History and current disease status (including staging, diagnosis information, previous anti-cancer treatments, and sites of disease).
- Additionally, the following assessments will be performed:
  - Physical examination, weight and height
  - Vital signs including sitting blood pressure/pulse and heart rate, respiratory rate and temperature
  - ECOG performance status
  - ECG
  - Safety laboratory assessments: biochemistry, lipase, INR, PT, hematology and urinalysis
  - Pregnancy test (if applicable)
  - Chest, abdomen and pelvis CT-scan.
  - Brain MRI (if indicated).
  - Paired Core Needle Biopsies for those patients on the Expansion Cohort

10.2 Treatment period

Patients will be asked to visit the clinic every two to three weeks depending on which checkpoint inhibitor they receive. Treatment will continue until disease progression or significant toxicity.

The details of on-treatment assessments can be found in Section 11.

10.3 End of treatment and premature withdrawal visit

The details of end-of-treatment assessments can be found in Section 11.1.

10.4 Criteria for premature patient withdrawal

Patients may voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time.

10.5 Assessment types

10.5.1 Efficacy

Tumor response and progression will be assessed according to both irRC and mWHO criteria (see section 12).

At baseline, CT/MRI of chest, abdomen and pelvis will be performed to assess disease status.

Tumor assessment tests will be repeated (same method as used as baseline) after the first 12 weeks of treatment (or at the conclusion of ipilimumab treatment if there has been a treatment delay or discontinuation due to toxicity) and then every 8 weeks and whenever disease progression is suspected.

Whenever possible, clinical evaluation of superficial lesions should not be used as the sole form of measurement. However, when necessary, color photograph with metric caliper is acceptable.

A complete physical examination includes a major review of body systems (general appearance, skin, neck including thyroid, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities and a neurological examination).

10.5.2 Vital signs

Body temperature, sitting pulse rate, respiratory rate and sitting blood pressure will be measured (details of assessments can be found in Section 11).

10.5.3 Height and weight

Height in centimeters will be measured at baseline and body weight to the nearest 0.1 kilogram will be measured (details of assessments can be found in Section 11).

10.5.4 Performance status

The performance status will be assessed (details of assessments can be found in Section 11) according to the ECOG performance status scale (Oken et al. 1982).

10.5.5 Laboratory evaluations

Hematology
Hematology tests are to be performed by the local laboratory according to the Visit Schedule outlined in Section 11. The Hematology panel includes red blood cells (RBC), hemoglobin, hematocrit, platelet count, total white blood cells (WBC) count, and a WBC differential including neutrophils, lymphocytes, monocytes, eosinophils and basophils.

Clinical chemistry
Clinical chemistry tests are to be performed by the local laboratory according to the Visit Schedule outlined in Section 11. The Clinical chemistry panel includes creatinine, blood urea nitrogen (BUN), sodium, magnesium, potassium, chloride, calcium, phosphate, bicarbonate, glucose, amylase, lipase, LDH, direct, indirect and total bilirubin, Alkaline phosphatase, AST/SGOT, ALT/SGPT, total protein and albumin, free T4, TSH and ACTH.

Note: LFTs (ALT, AST, and T. bilirubin) must be performed within 3 days prior to each immune checkpoint inhibitor dosing visit. The results of these tests must be reviewed by the principal investigator (or designee) prior to dosing.

Coagulation
Coagulation testing will be measured (as outlined in Section 11) with INR and pro-thrombin time (PT).

Urinalysis
Urinalysis can include dipstick analysis and will be performed at screening visit. Additional urinalysis can be done during study if clinically indicated.

Pregnancy and assessments of fertility
All women of childbearing potential must undergo a serum pregnancy test at screening to confirm eligibility in the trial as well as at EOT. In case an additional pregnancy test is indicated throughout the trial a serum test should be performed. In case of pregnancy, the patient must immediately be withdrawn from the study, and the pregnancy must be reported.

11.0 STUDY CALENDARS

Study Calendar if receiving Ipilimumab (Q3 weeks x 4) or Pembrolizumab (Q3 weeks until toxicity/progression) Study visits may be performed +/- 3 days from the targeted study visit date to allow for holidays and other scheduling conflicts. Laboratory evaluations may be collected up to 24 hours prior to study visit without being a deviation.

Evaluations	Pre-Study	Cycle 1			Cycle 2			Cycle 3			Cycle 4 and Subsequent Cycles if receiving Pembrolizumab			Subsequent Cycles Indoximod Only				End of Tx Visit
		D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	D22	
		Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12					
Ipilimumab OR Pembrolizumab		A			A			A			A							
Indoximod		B			B			B			B			B				
Informed consent	X																	
Demographics	X																	
Medical history	X																	
Concurrent meds	X	X----------																X
Physical exam	X	X			X			X			X			X				X
Vital signs	X	X			X			X			X			X				X
Height	X																	
Weight	X	X			X			X			X			X				X
Performance status	X	X			X			X			X			X				X
CBC w/diff, plts	X	X			X			X			X			X				X
Serum chemistry	C	C			C			C			C			C				C
C-Reactive Protein		X			X			X			X			X				
INR, PT	X	X			X			X			X			X				
Amylase, lipase	X	X			X			X			X			X				
LH, FSH	X	X			X			X			X			X				
Free T4,TSH, ACTH	X	X			X			X			X			X				
Urinalysis	X	Completed if clinically indicated																
EKG	X																	
AE evaluation	X	X----------																X
Radiologic Tumor measurements	X	**Radiologic evaluations should be performed after the first 12 weeks then every 8 weeks and whenever disease progression is suspected.**																
B-HCG	D	Completed if clinically indicated and at the end of treatment.																D
[redacted]																		
Archival tumor tissue		F																
Core Needle BX	G									G								

Study Calendar if receiving Nivolumab (Q2 weeks until toxicity/progression) Study visits may be performed +/- 3 days from the targeted study visit date to allow for holidays and other scheduling conflicts. Laboratory evaluations may be collected up to 24 hours prior to study visit without being a deviation.

Evaluations	Pre-Study	Cycle 1				Cycle 2				Cycle 3 and Subsequent Cycles if Nivolumab Continues				Subsequent Cycles Indoximod Only				End of Tx Visit
		D1	D8	D15	D22	D1	D8	D15	D22	D1	D8	D15	D22	D1	D8	D15	D22	
		Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12					
Nivolumab		N		N		N		N		N		N						
Indoximod		B				B				B				B				
Informed consent	X																	
Demographics	X																	
Medical history	X																	
Concurrent meds	X	X----------															X	X
Physical exam	X	X		X		X		X		X		X		X				X
Vital signs	X	X				X								X				X
Height	X																	
Weight	X	X				X				X				X				X
Performance status	X	X		X		X		X		X		X		X				X
CBC w/diff, plts	X	X		X		X		X		X		X		X				X
Serum chemistry	C	C		C		C		C		C		C		C				C
C-Reactive Protein		X				X				X				X				
INR, PT	X	X				X				X				X				
Amylase, lipase	X	X				X				X				X				
LH, FSH	X	X				X				X				X				
Free T4,TSH, ACTH	X	X				X				X				X				
Urinalysis	X	Completed if clinically indicated																
EKG	X																	
AE evaluation	X	X----------															X	X
Radiologic Tumor measurements	X	**Radiologic evaluations should be performed after the first 12 weeks then every 8 weeks and whenever disease progression is suspected.**																
B-HCG	D	Completed if clinically indicated and at the end of treatment.															D	
[redacted]																		
Archival tumor tissue		F																

Calendar Notes:

A: **Ipilimumab** 3 mg/kg Q3 weeks x 4 doses or **Pembrolizumab** 2 mg/kg Q3 weeks **N: Nivolumab** 240 mg Q2 weeks

B: **Indoximod:** 600 mg or 1200 mg po BID administered daily throughout study

C: Albumin, alkaline phosphatase, direct/indirect/total bilirubin, bicarbonate, BUN, calcium, magnesium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.

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

[redacted]

F: Archival tumor tissue is obtained if possible.
G: Paired Core Needle Biopsies completed pre-study and after Cycle 3 (prior to Cycle 4) for patients on Expansion Cohort receiving pembrolizumab

11.1 After Finishing Protocol Therapy

Required observations following the completion of protocol therapy Follow-up visits may be performed +/- 2 weeks from the targeted study visit date. Laboratory evaluations may be collected up to 24 hours prior to study visit without being a deviation.

Time after completion of protocol therapy (months)								
Observation	**3 mo**	**6 mo**	**9 mo**	**12 mo**	**15 mo**	**18 mo**	**21 mo**	**24 mo**
Medical history	X	X	X	X	X	X	X	X
Physical exam (VS, Wt, PS)	X	X	X	X	X	X	X	X
CBC/Chemistry	Per SOC schedule							
Disease Imaging	Per SOC schedule							
Adverse Events	Capture all AEs observed for 30 days after last dose of treatment. After 30 days, only AEs that are attributed to the study drug are required to be captured.							
Concomitant Medications	Capture all concomitant medications for 30 days after last dose of treatment.							

Patients will be followed for survival and possible long-term toxicity from this treatment. Every 3 month follow-up visits will continue for 2 years as per Section 5.7 (and as stated above). For those surviving longer than 2 years, follow-up will be performed using telephone contact, correspondence with treating physicians, and death records as necessary to update vital status at least every 6 months until death or lost to follow-up.

12.0 MEASUREMENT OF EFFECT

For the purposes of this study, patients should be re-evaluated after the first 12 weeks of treatment and then every 8 weeks. **In addition to a baseline scan, confirmatory scans will also be obtained between 4 and 6 weeks following initial documentation of an objective response (CR, PR) or progressive disease (PD).**

Primary efficacy endpoint is best ORR defined as the proportion of all treated subjects whose best response at any time during the study following initiation of therapy is confirmed CR or confirmed PR. This will be assessed according to irRC, as well as separately by mWHO criteria.

PFS, defined as the time between the first dose of study therapy and the earliest date of progression or death. Subjects who have neither progressed nor died will be censored at the last tumor assessment date for PFS. The endpoint PFS and will be assessed according to irRC and mWHO.

Additional efficacy endpoints will include the disease control rate (DCR) defined as the percentage of patients achieving CR + PR + SD at any time during the study following initiation of therapy. This will be assessed according to irRC, as well as separately by mWHO criteria. The duration of response (DOR), is defined as the time between the date that the criteria are first met for CR or PR or SD and the earliest date of progression or death.

PFS, defined as the time between the first dose of study therapy with each commercially immune checkpoint and the earliest date of progression or death, will be assessed. Subjects who have neither progressed nor died will be censored at the last tumor assessment date for PFS. The endpoint PFS and will be assessed according to irRC and mWHO

OS, defined as the time between the first dose of study therapy and death (subjects who have not died will be censored at the most recent last-known-alive date), will also be analyzed.
The tumor assessment (TA) performed during screening will be used as a baseline for efficacy assessments. CT/MRI imaging of the chest and abdomen is required at Screening and at each TA, regardless of the location of known metastases. In addition, CT/MRI scans must be obtained of anatomic regions not covered by the chest and abdomen scans in subjects where there is clinical suspicion of deep soft tissue metastases (e.g., lesions in the thigh). Such additional CT/MRIs will be required at Screening when deep soft tissue disease is known/suspected and must be consistently repeated at all TAs if a deep soft tissue lesion is identified during Screening. The same imaging modality must be used for all TAs, unless contraindicated.

Imaging-based evaluation is preferred to clinical examination. Helical (spiral) CT scans of the chest and abdomen are preferred. If not available, MRI can be used; however, a measurable lesion must not have the longest diameter smaller than 20 mm by MRI (10 mm on spiral CT). IV contrast should be used for all CT scans; if IV contrast is contraindicated, oral contrast maybe used, or MRI should be used at the Screening exam and at all TA time points. Subjects who develop contrast allergy after study enrollment must be followed by MRI for subsequent tumor measurements.

Sections should be contiguous, similarly sized and consistent from visit-to-visit. Section thickness must be based on institutional standards (e.g., from 5 to 8 mm, 10 mm cuts are not recommended). Chest x-rays and ultrasound are not acceptable methods to measure disease. Response and progression of disease must be documented by CT or MRI similar to the methods used at Screening.

If bone lesions are identified at any time during the study, additional imaging studies of the lesion(s) must be performed to confirm the malignant nature of the new findings on the bone scan. If an abnormal bone scan is observed at any time point throughout the study, a repeat bone scan must be performed prior to the confirmation of a CR (e.g., the remaining metastatic lesions must have resolved. In case of new lesions such as pleural effusion, cytology must be performed

to identify and confirm malignancy. Skin and soft tissue lesions will be captured as non-measurable lesions through physical examination only.

Any subject who develops an objective tumor response (CR or PR) or progression (PD) is required to undergo confirmatory scans between 4 and 6 weeks from the prior scan in order to verify the reliability of the radiologic finding. Sites are encouraged to collect additional CT scans after mWHO PD has been confirmed, as long as a subsequent line of therapy has not been initiated.

Definition of Measurable / Non-measurable Lesions

- Measurable lesions are lesions that can be accurately measured in 2 perpendicular diameters, with at least one diameter $\geq$ 20 mm and the other dimension $\geq$ 10 mm on MRI, or 10 mm x 10 mm for spiral CT. The area will be defined as the product of the largest diameter with its perpendicular.
- Non-measurable (evaluable) lesions are all other lesions, including unidimensional measurable disease and small lesions (lesions without at least 1 diameter $\geq$ 20 mm on MRI, or $\geq$ 10 mm on spiral CT), and any of the following: lesions occurring in a previously irradiated area (unless they are documented as new lesions since the completion of radiation therapy), bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusion, lymphangitis cutis/pulmonis, abdominal masses that are not pathologically/cytologically confirmed and followed by imaging techniques and cystic lesions. All measurable and non-measurable lesions should be assessed at Screening and at the defined TA time points. Extra assessments may be performed, as clinically indicated, if there is a suspicion of progression.

Definition of Index / Non-index Lesions

At Screening, measurable lesions, up to a maximum of 5 lesions per organ and 10 lesions in total, must be identified as index lesions to be measured and recorded on the CRF. The index lesions should be representative of all involved organs. In addition, index lesions must be selected based on their size (e.g., lesions with the longest diameters), their suitability for accurate repeat assessment by imaging techniques, and how representative they are of the subject's tumor burden. At Screening, a Sum of the Products of Diameters (SPD) for all index lesions will be calculated. This baseline SPD will be used as the reference point to determine the objective tumor response of the index lesions at each TA.

Measurable lesions, other than index lesions, and all sites of non-measurable disease, will be identified as non-index lesions. Non-index lesions will be recorded on the CRF and will be evaluated at the same assessment time points as the index lesions. In subsequent assessments, non-index lesions will be recorded as CR, stable, or progression.

Calculation of Sum of Products of Diameters (SPD)

SPD is an estimation of tumor burden based on the index lesions observed at baseline. The 2 greatest perpendicular diameters are used to estimate the size of each tumor lesion. The SPD is

calculated as the sum of the product of the diameters for index tumor lesions. Several variations of the SPD are identified for the purpose of classification of tumor responses.

SPD at Screening: The sum of the product of the diameters for all index lesions identified at screening assessment prior to randomization. This is considered the baseline SPD.

SPD at TA: For every post randomization TA collected, per protocol Section 5.1 or as clinically indicated. The SPD at TA will be calculated using tumor imaging scans. Only index lesions are included in the calculation.

SPD Nadir: For tumors that are assessed more than one time after baseline, the lowest value of the SPD (SPD Baseline or SPD at TA) is used to determine subsequent TAs for each subject.

Definition of Tumor Response Using mWHO
The mWHO criteria were developed as a hybrid tumor response classification system using elements of both the WHO and RECIST criteria in an attempt to more accurately measure tumor lesions and estimate tumor responses. In this study, the response per irRC as determined by the investigator will serve to guide clinical care, and as the basis of multiple exploratory endpoints.

However, to determine overall response per mWHO, all timepoint assessments are considered. The assessment performed during Screening will be considered as the baseline.

Overall response per mWHO will be calculated based on index lesion response, non-index lesion response, and new lesion response, as follows:

Definition of Index Lesion Response Using mWHO
- Complete Response: Complete disappearance of all index lesions.
- PR: At least 50% decrease in the SPD from baseline.
- Stable Disease: Does not meet criteria for CR or PR, in the absence of PD.
- Progressive Disease: At least 25% increase in the SPD from the nadir.
- Unknown: Response cannot be determined (e.g., due to image quality).

Definition of non-index Lesion Response Using mWHO (based on non-index lesions present at baseline)

- Complete Response: Complete disappearance of all non-index lesions.
- Stable Disease: A decrease or tumor stabilization of one or more non-index lesions in the absence of complete disappearance, PD.
- Progressive Disease: Unequivocal progression of non-index lesion(s).
- Unknown: Response cannot be determined (e.g., due to image quality).

Definition of New Lesion Response Using mWHO
- Absent: No unequivocal new lesion is present.
- Present: At least 1 unequivocal new lesion is present.
- Unknown: Response cannot be determined (e.g., due to image quality)

Definition of Overall Response (OR) using mWHO
All subjects will have the OVERALL RESPONSE classified based on timepoint index lesion response, non-index lesion response, and new lesion response, as outlined below:

- Complete Response: Disappearance of all known disease. CR for index lesions, CR for non-index lesions, and the absence of unequivocal new lesions.
- PR: An index lesion response of CR or PR, a non-index response of CR or SD, and the absence of unequivocal new lesions, provided the criteria for CR are not met.
- Stable Disease: An index lesion response of SD, a non-index lesion response of CR or SD, and the absence of unequivocal new lesions.
- Progressive disease (PD): Any of the following:
    - An index lesion response of PD.
    - A non-index lesion response of PD.
    - The presence of an unequivocal new lesion.
- Unknown (UN) Not classifiable above. Tumor assessments which cannot be evaluated (e.g., due to image quality, inability to assess all relevant lesions, etc.) will be reported as UN.

Progression Free Survival by mWHO is included as a secondary endpoint and is defined as: PFS by mWHO is the time from the date of the first dose to the time of disease progression per mWHO or death, whichever occurs first.

Immune-related Endpoints
The irRC incorporate several elements reflecting the complex tumor dynamics of immune checkpoint inhibitor treatment. Under these criteria, a measure of tumor volume is used that incorporates the contribution of new measurable lesions. Each net percentage change in tumor burden per assessment using irRC accounts for the size and growth kinetics of both old and new lesions as they appear. New lesions alone do not qualify as irPD.

In this study, irRC will be used to assess subject response to study treatment per investigator assessment. The secondary endpoint irPFS will be determined based on investigator assessment. In order to adequately address this secondary objective, investigators will obtain confirmatory scans beyond mWHO PD and follow the instructions in this section for the determination of immune-related response.

New Lesion Measurement
The irRC are tumor assessment criteria that have been developed to better capture the activity of immunotherapeutic agents. These criteria have been used with success in clinical studies that were performed with ipilimumab in advanced metastatic melanoma and in lung cancer.

Additional tumor response data will be collected, beyond what is required to apply the mWHO criteria. More specifically, the investigator will have to record in the CRF the bi-dimensional measurements for each new lesion which has become measurable in each tumor assessment.

Tumor Assessments Beyond mWHO Progression
To support evaluation of progression-free survival based on irRC criteria (irPFS) in this indication, investigators must perform tumor assessments (including new lesion measurements) during the Toxicity/Progression Follow-up Phase in subjects who have experienced mWHO

progression until the total sum of product diameters (SPD including new lesions) has increased 25% or more from the nadir or until subjects discontinue study therapy regardless of whether the subject is initiating subsequent therapy. All available post mWHO progression tumor imaging- based assessments during this phase in the study must be entered into the CRF, including any standard of care assessments and any assessments performed while under non-study subsequent cancer therapy.

Any subject who develops an objective tumor response (CR or PR) or progression (PD) is required to undergo confirmatory scans between 4 and 6 weeks from the prior scan in order to verify the reliability of the radiologic finding. Sites are encouraged to collect additional CT scans after mWHO PD has been confirmed, as long as a subsequent line of therapy has not been initiated.

Definition of Tumor Response Using irRC
Calculation of Immune-related Sum of Products of Diameters (irSPD)

The irSPD incorporates measurable new lesions that may have developed on-study, providing an assessment that includes both index and new lesions. The tumor assessment performed during Screening will serve as the baseline for determination of tumor response using irRC.

irSPD at Baseline: The sum of the product of the diameters for all index lesions identified prior to randomization. At baseline, irSPD and SPD are the same.

irSPD at TA: For every post-randomization TA collected, per protocol Section 5.1 or as clinically indicated including post mWHO PD TA, the irSPD at TA will be calculated using tumor imaging scans. Both index lesions and any measurable new lesions that have developed on study will be included.

irSPD Nadir: For tumors that are assessed more than one time after baseline, the lowest value of the irSPD (irSPD Baseline or irSPD at TA) is used to classify subsequent TAs for each subject. Because ipilimumab treatment may result in complex tumor dynamics in which index lesions may shrink while new lesions appear, the irSPD nadir may be different from the SPD nadir, and may occur either before or after the SPD nadir.

At baseline, the irSPD is measured and recorded.

At each subsequent assessment timepoint, a separate assessment of timepoint overall response will be obtained for that timepoint. The sum of products of perpendicular diameters calculated and recorded at each post-baseline timepoint for immune-related response purposes (irSPD) include measurements of index lesions and also include measurable new lesions which are not too small to measure at this timepoint. A value of 25 mm^2 (5 mm x 5 mm) is imputed for each index and previously measurable new lesion which is present but too small to measure.

Timepoint Overall Response Using irRC

- The overall assessment of immune-related response reported at each timepoint will be based on the following criteria:

- Immune-related CR (irCR): Complete disappearance of all tumor lesions (index and non-index together with no new measurable/unmeasurable lesions).
- Immune-related PR (irPR): A decrease, relative to baseline of the irSPD (as defined above) of 50% or greater is considered an irPR.
- Immune-related SD (irSD): irSD is defined as an evaluable response that fails to meet criteria for immune-related CR or immune-related PR, in the absence of irPD.
- Immune-related Progressive Disease (irPD): At least a 25% increase in the irSPD (based on irSPD of all index lesions and any measurable new lesions, as defined above) over the nadir irSPD, or the occurrence of any new measurable lesions if the SPD nadir is "0" (including when no measurable lesions are present at baseline.
- Immune-related Unknown Response (irUN): Tumor assessments which cannot be evaluated (e.g., due to image quality, inability to assess all relevant lesions, etc.) will be reported as irUN.

13.0 DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0.

13.1 Regulatory Compliance/Good Clinical Practices

This study will be conducted in accordance with the following regulations and guidelines, to include but not limited to:

- Declaration of Helsinki (October 2000)
- Current ICH Guideline for Good Clinical Practice
- 21 CFR 50: Protection of Human Subjects
- 21 CFR 54: Financial Disclosure by Clinical Investigators
- 21 CFR 56: Institutional Review Boards
- 21 CFR 312: Investigational New Drug Application

13.2 Regulatory Documentation

Prior to study start-up, investigators will submit the following documents to NewLink Genetics Corporation, as outlined in the Essential Documents Section 8.0 of the ICH Guidelines for Good Clinical Practice to include but not limited to:

- Signed Confidentiality Agreement
- Signed Clinical Trial Agreement, if applicable
- Up-to-date signed and dated Curriculum vitae and copies of medical licenses for Principal and sub-investigators to be submitted promptly
- Financial Disclosure forms for Principal and sub-investigators to be submitted promptly
- FDA Form 1572
- IRB approval to conduct the study: IRB-approved informed consent form,
- Name and address of the IRB with the statement that it is organized and operates according to GCP and the applicable laws and regulations

- IRB membership roster or Federal Wide Assurance (FWA) letter
- Local laboratory certifications, its name and address
- Local laboratory normal ranges (a dated copy for tests to be performed during the study)
- Financial agreement, if applicable
- Signed and dated Investigator Agreement page of the final protocol and amendments, where applicable

13.3 Institutional Review Board (IRB)

This trial will be undertaken only after full approval of the protocol and addenda has been obtained from an IRB and a copy of this approval has been received by the sponsor. The IRB must be informed of all subsequent protocol amendments issued by the sponsor. Reports on and reviews of, the trial and its progress will be submitted to the IRB by the investigator at intervals set forth in its guidelines.

13.4 Informed Consent

Each subject must give written consent and sign other locally required documents after the nature of the study has been fully explained. The informed consent form must be signed prior to performance of any study- related activity. The informed consent form that is used must be approved both by the sponsor and by the reviewing IRB. The Informed Consent should be in accordance of the Declaration of Helsinki, current International Conference on Harmonization (ICH) and Good Clinical Practices (GCP) guidelines.

13.5 Administrative Requirements

Protocol modifications
The investigator will not modify this protocol without obtaining permission from the sponsor. All protocol amendments must be issued by the sponsor, signed and dated by the investigator, and should not be implemented without prior IRB approval, except where necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s).

In situations requiring a modification, the investigator or other physician in attendance will contact the medical monitor by fax or telephone (see Contact Information page). This contact must be made prior to implementing any departure from protocol. Contact with the sponsor must be made as soon as possible in order to outline an appropriate course of action.

Record Retention
In compliance with the ICH/GCP guidelines the investigator/institution will maintain all CRFs and all source documents that support the data collected from each patient, and all trial documents as specified in Essential documents for the Conduct of a Clinical Trial and as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents. Essential documents must be retained until at least two years after the last approval of a marketing

application in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

Data Quality Assurance
Steps to be taken to assure the accuracy and reliability of data include the selection of qualified investigators, review of protocol procedures with the investigator and associated personnel prior to the study, and periodic monitoring visits by the sponsor. CRFs will be reviewed for accuracy and completeness by the sponsor during on-site monitoring visits and any discrepancies will be resolved with the investigator or designees per NewLink Genetics SOPs.

On-Site Audits
Representatives of the sponsor's Clinical Quality Assurance department or a contracted research organization may visit the site to carry out an audit of the study in compliance with regulatory guidelines and company policy. Such audits will require access to all study records, including source documents, for inspection and comparison with the CRFs. All efforts will be made to preserve patient privacy. Sufficient prior notice will be provided to allow the investigator proper preparation for the audit. Auditing procedures may also be conducted by any regulatory body. The investigator should immediately notify the sponsor about any audit.

Data Safety Monitoring Committee
This study will use a Data Safety Monitoring Committee (DSMC). The DSMC will review accrual information, and safety data such as listings and natures of adverse events. The DSMC will be provided with safety data listings, data summary and appropriate analysis for review at the completion of the phase I study. The DSMC will review the safety of the combination on a quarterly basis while any subject is still receiving study drug.

Use of Information and Publication
All information on indoximod, NewLink operations, patent application, manufacturing process, basic scientific data supplied by the sponsor to the investigator and not previously published is considered confidential and remains the sole property of NewLink Genetics. The investigator agrees to use this information only to accomplish this study and will not use it for other purposes without the sponsor's written consent.

The investigator understands that the information developed in the clinical study will be used by NewLink in connection with the continued development of indoximod and thus may be disclosed as required to other clinical investigators or government regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

Any publication or other public presentation of results from this study requires prior review of NewLink Genetics. Draft abstracts, manuscripts and materials for presentation at scientific meetings should be provided to the sponsor as outlined in the clinical trial agreement.

13.6 Human Subjects Protection

Rationale for subject selection
Advanced melanoma affects men and women from all racial/ethnic groups. Subjects from all racial/ethnic groups are eligible for this study if they meet the eligibility criteria. We will make an attempt at enrolling representative proportions of minorities on this study.

Efforts will be made to extend accrual to a representative population, but in this phase 1/2 study, a balance must be struck between subject safety considerations and limitations on the number of individuals exposed to potentially toxic and/or ineffective treatments on the one hand and the need to explore gender and ethnic aspects of clinical research on the other hand.

Participation of Children
There is no plan to allow the participation of children in this study.

Evaluation of Benefits and Risks
Advanced melanomas have a very poor overall prognosis. After failing currently available regimens, the chance of cure is rare if at all. The benefits of this approach are theoretical and it is hoped that the inhibition of IDO will lead to an effective anti-tumor immune response. By generating an immune response against the subject's tumor, their overall survival might be improved.

Given the safety demonstrated by indoximod in several clinical studies, and the poor prognosis of this patient population, it is believed that the possible benefits from improved survival probability far outweigh the risk to the patient. The information obtained in this study may be extremely valuable in the treatment of malignancies in the future. The chance of this experimental treatment to provide clinical benefit is unknown. All possible benefits and risks will be carefully explained to all subjects and the Informed Consent Document will be signed by the subject prior to entrance into the protocol.

There are no new anticipated severe adverse side effects to the treatment approach technique employed in this study other than those outlined above. Theoretical risks may include the induction of unanticipated autoimmune disease and/or liver, kidney, lung, heart and CNS damage. Expected risks and discomforts to the subjects are minimal and will be those of needle sticks for phlebotomy. Subjects will be treated as deemed medically appropriate for any immediate or delayed adverse event related to the treatment.

Blood and tissue specimens collected in the course of this research project may be banked and used in the future to investigate new scientific questions related to this study. Patients may withdraw this consent at any point in the future by informing the PI at their treatment site in writing. The PI will inform NewLink Genetics who will destroy any remaining samples.

Consent Processes and Documents
All subjects will be thoroughly screened prior to admission onto this study. During this time, the subject, along with family members, will be presented with a detailed description of the protocol treatment. The specific requirements, objectives, advantages and disadvantages will be presented. The Informed Consent document is given to the subject and they are asked to review it and ask questions prior to agreeing to participate in this protocol. The subject will be reassured that participation on this trial is entirely voluntary and that they can withdraw or decide against treatment at any time without adverse consequences. The Principal Investigator or their designee is responsible for completing the consent process and a copy of the completed Consent Document is offered to the subject.

Recruitment Strategy
Patients, their physicians or family members may contact the clinical sites directly. Information about the clinical trial can be obtained at clinicaltrials.gov. [redacted]

Patient Confidentiality
Strict patient confidentiality is standard policy at clinical research sites. Standard practices will be followed.

14.0 STATISTICAL CONSIDERATIONS

14.1 Introduction

This phase 1/2 trial is being conducted primarily to assess the safety and tolerability of indoximod when administered in combination with immune checkpoint inhibition in adult patients with metastatic melanoma, and to determine the MTD of the combined treatment. The dose escalation part (phase 1) will be followed by an expansion part (phase 2) to assess the preliminary efficacy of the combined regimen.

Descriptive statistics will be employed to evaluate the endpoint and analyze the data. Summary statistics for continuous variables will include mean, standard deviation, median and range.

Categorical variables will be presented as frequency counts and percentages; and time-to-event variables will be summarized by Kaplan-Meier medians and survival plots. Data listings will be created to support tables and present data. The preliminary efficacy analysis will be conducted on the efficacy evaluable population and safety analysis will be performed on the safety population. SAS 9.2 or higher will be used for data analysis. The data will be tabulated and analyzed with respect to patient enrollment and disposition, demographic and baseline

14.2 Study Objectives

The primary objectives of this study are:

a) To establish the recommended phase 2 dose (MTD) of a sequential administration of immune checkpoint inhibitors and indoximod in patients with melanoma and assess the safety and tolerability of the combined treatments.
b) To evaluate the preliminary efficacy of the established dose of immune checkpoint inhibitors followed by indoximod as measured by the best ORR in patients with unresectable stage III or stage IV melanoma.
c) To further asses the safety and tolerability immune checkpoint inhibitors followed by indoximod.

The secondary objectives are:

a) To evaluate the adverse event profile and tolerability of immune checkpoint inhibitors and indoximod in patients with unresectable stage III or stage IV melanoma.

b) To evaluate the median progression free survival (PFS) in patients with unresectable stage III or stage IV melanoma after the initiation of each agent in the sequential standard of care combination of CTLA-4 blockade and PD-1 blockade.
c) To evaluate the clinical benefit of the combination of indoximod and checkpoint inhibition consisting of ipilimumab, nivolumab, or pembrolizumab as measured by observation and duration of disease control rate (CR + PR + stable disease (SD)).
d) To evaluate the overall survival of patients with unresectable stage III or stage IV melanoma receiving immune checkpoint inhibitors and indoximod.

14.3 Analysis of study endpoints

14.3.1 Analysis of Primary endpoint

a) (Recommended phase 2 dose)
A minimum of nine patients will be treated depending on DLT. Each dose will be administered to a cohort of 3 patients. If 0 out of 3 or less than 2 out of 6 patients experienced a DLT at any given dose level, the dose escalation will proceed to the next dose level. The MTD is generally the largest dose level at which at most 1 out of 6 patients experiences a DLT. IF DLT is not reached at the highest dose level (1200mg twice daily), no further escalation will proceed and this dose level will be declared the recommended phase 2 dose (See dosing regimen table in section 5.1.1)

b) (Primary efficacy for phase 2 portion)
The preliminary efficacy will be measured by the best ORR in patients with unresectable stage III or stage IV melanoma.

The objective response rate for PD-1 inhibition with pembrolizumab after progression on ipilimumab is listed as approximately 25% in the pembrolizumab package insert. We will use this as a reference point for the benefit provided by immune checkpoint inhibitors used in sequence. We are expecting to increase the ORR from 25% to 35% by using immune checkpoint inhibition (defined as the sequential use of CTLA-4 blockade and PD-1 blockade in either order) with indoximod. Formal statistical testing will be performed using one-sided probability of Type-I error (α) =0.10. Ninety-six (96) patients will provide at least 80% power to detect the increase of ORR.

c) The safety and tolerability of immune checkpoint inhibitors followed by indoximod will be assessed by listing the overall incidence of AEs. The AEs will be summarized and classified by body system and by treatment group. The type, incidence, severity, and causality of each AE, the duration of the event, and any required treatment interventions will be tabulated. Physical examination results will be presented in the patient data listings. The DLT will be listed per dose level and treatment along with overall frequencies. The data from the expansion part (phase 2) will be used for this part of safety and tolerability assessment.

14.3.2 Endpoints for secondary objectives

Adverse event profile of immune checkpoint inhibitors and indoximod in patients with unresectable stage III or stage IV melanoma participating in phase 2 portion of the study will be listed, summarized, and classified by body system. The type, incidence, severity, and causality of each AE, the duration of the event, and any required treatment interventions will be tabulated. Physical examination results will be presented in the patient data listings. The data from the expansion part (phase 2) will be used for this part of safety and tolerability assessment.

Additional secondary endpoints of DCR and DOR, will be determined for each checkpoint combination individually per patient as well as for the overall treatment course. Rates along with 95% confidence intervals will be presented.

A separate PFS time will be determined for each commercially available checkpoint inhibitor used sequentially. The PFS durations along with 95% confidence intervals will be presented.

To evaluate the overall survival (OS) of patients with unresectable stage III or stage IV melanoma receiving immune checkpoint inhibitors and indoximod. OS, defined as the time between the first dose of study therapy and death (subjects who have not died will be censored at the most recent last-known-alive date), will also be analyzed. The OS rate along with its 95% confidence interval will be presented.

The number of patients to be enrolled in phase 1 (dose escalation) will depend upon the observed safety profile, which will drive the number of patients per dose level and the number of dose escalations. A minimum of 9 patients will be enrolled on the dose escalation part. There will be additional 96 patients for the phase 2 study to assess the preliminary efficacy of the combination treatment.

Phase 2 biopsy cohort: The endpoint of the biopsy cohort is to obtain pre- and post-treatment tumor biopsies that can be analyzed retrospectively upon completion of the trial to gain insight into the scientific basis for any observed treatment effect and possibly guide future trial design and patient selection. As this is an exploratory effort, no formal sample-size estimation can be performed. According to general guidelines regarding the sample size for pilot or translational studies, a sample size of up to 20 patients would provide a reasonable precision for the estimation of pilot information.

14.4 Treatment randomization and blinding

There is no randomization or blinding for this study.

14.5 Analysis Populations

The safety population will consist of all subjects receiving at least 1 dose of study medication. This includes both the Phase 2 cohort and the biopsy expansion cohort. All subjects who received at least one dose of study treatment and had at least 1 post-baseline response evaluation will be included in the efficacy analysis set. Following completion of the study, best response

will be determined for each subject in accordance with irRC and mWHO criteria guidelines and the objective response rate presented.

14.5.1 Patient Disposition

The number and percent of patients entering and completing the clinical study will be presented by dose and cohort and study portion.

14.5.2 Demographic Information and Baseline Characteristics

Demographic and baseline characteristic will be descriptively summarized by study phase and dose treatment.

14.6 Protocol deviation

Protocol deviations will be listed by patient.

14.7 Interim analysis

No formal interim analysis is planned for the study. As an open label trial, data may be periodically evaluated to monitor study progress. However, reports will be generated post the dose escalation part of the study and adverse events and toxicity reports will be monitored.

14.8 Handling of missing data

The data for the efficacy endpoint will be analyzed as Intention to treat (ITT) and according to protocol (ATP). Primary endpoint estimate and associated hypothesis testing will be provided for both ITT and ATP analyses. The OS rate as a secondary endpoint analysis will be provided for ITT and ATP.

15.0 REFERENCES

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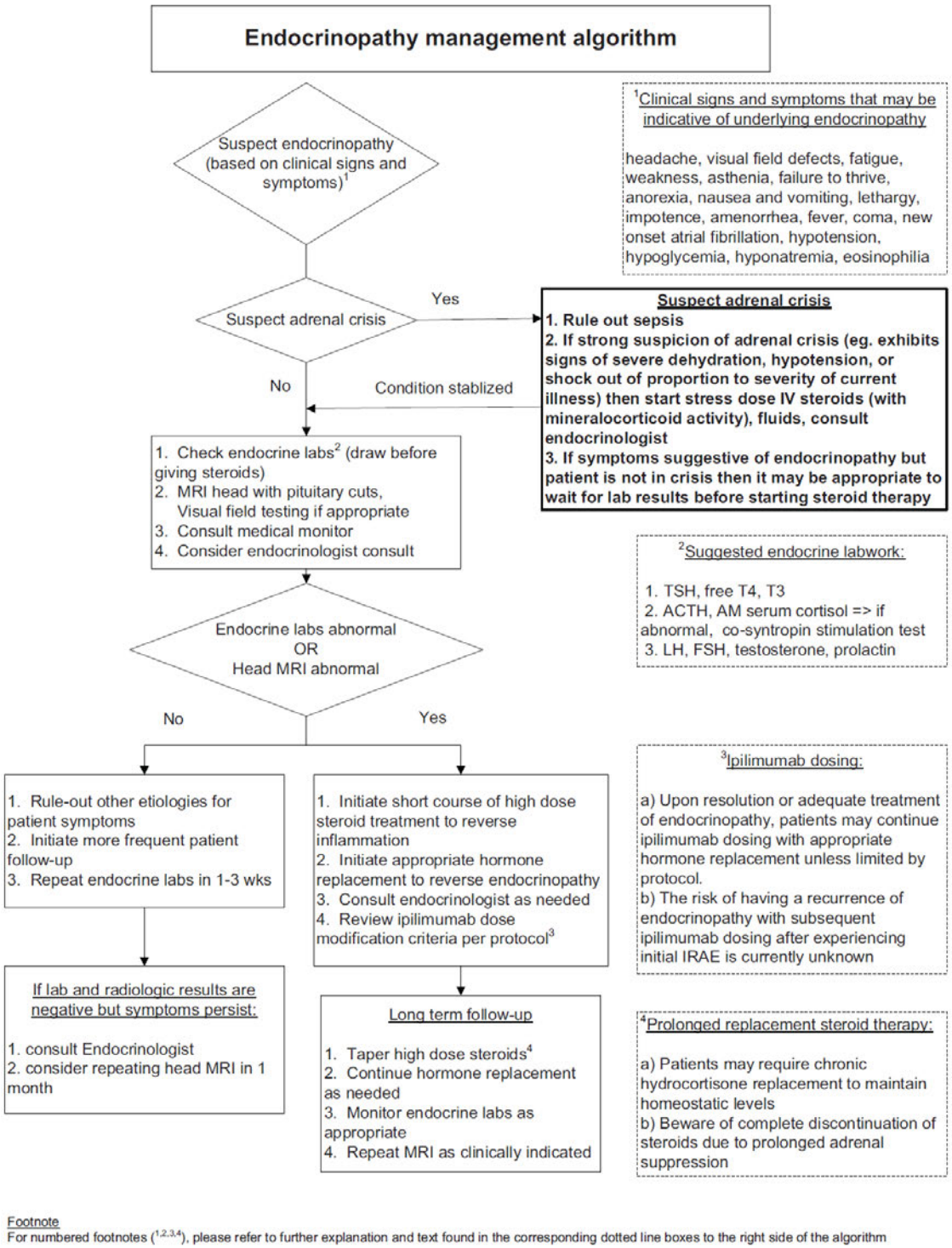
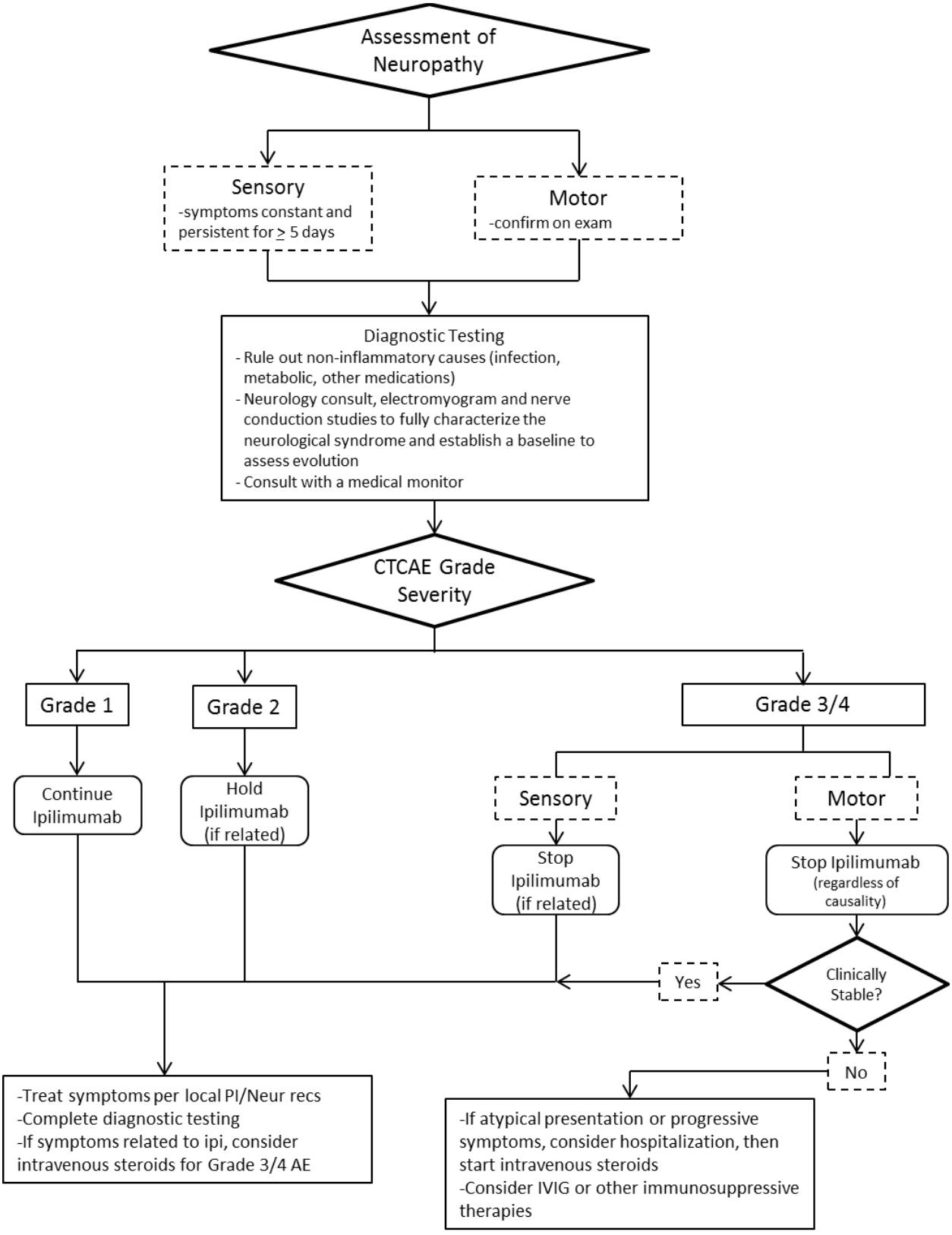
16.0 APPENDICES

16.1 APPENDIX A: Management of Adverse Events of Interest Algorithms

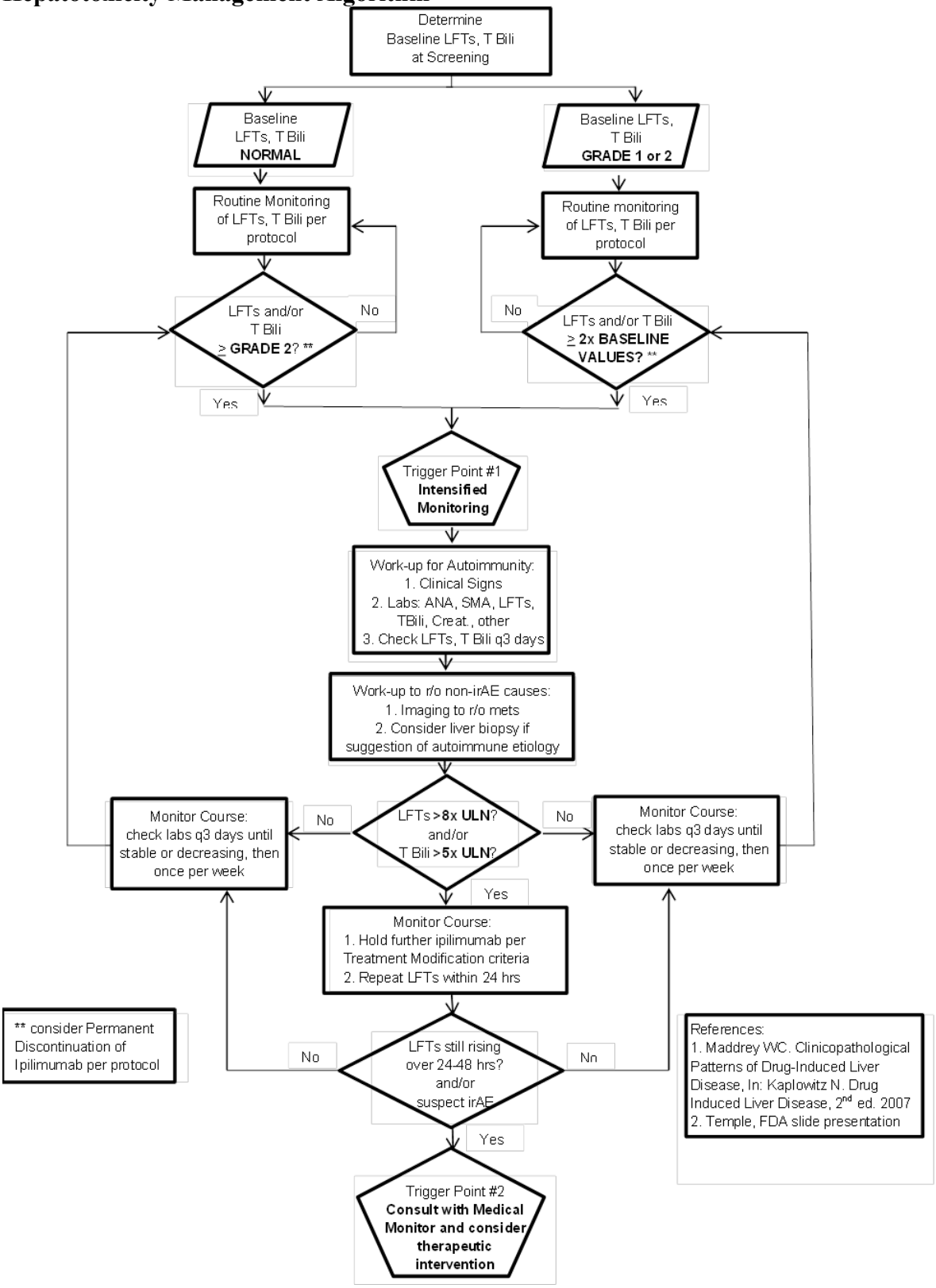


Footnote
For numbered footnotes ([1,2,3,4]), please refer to further explanation and text found in the corresponding dotted line boxes to the right side of the algorithm

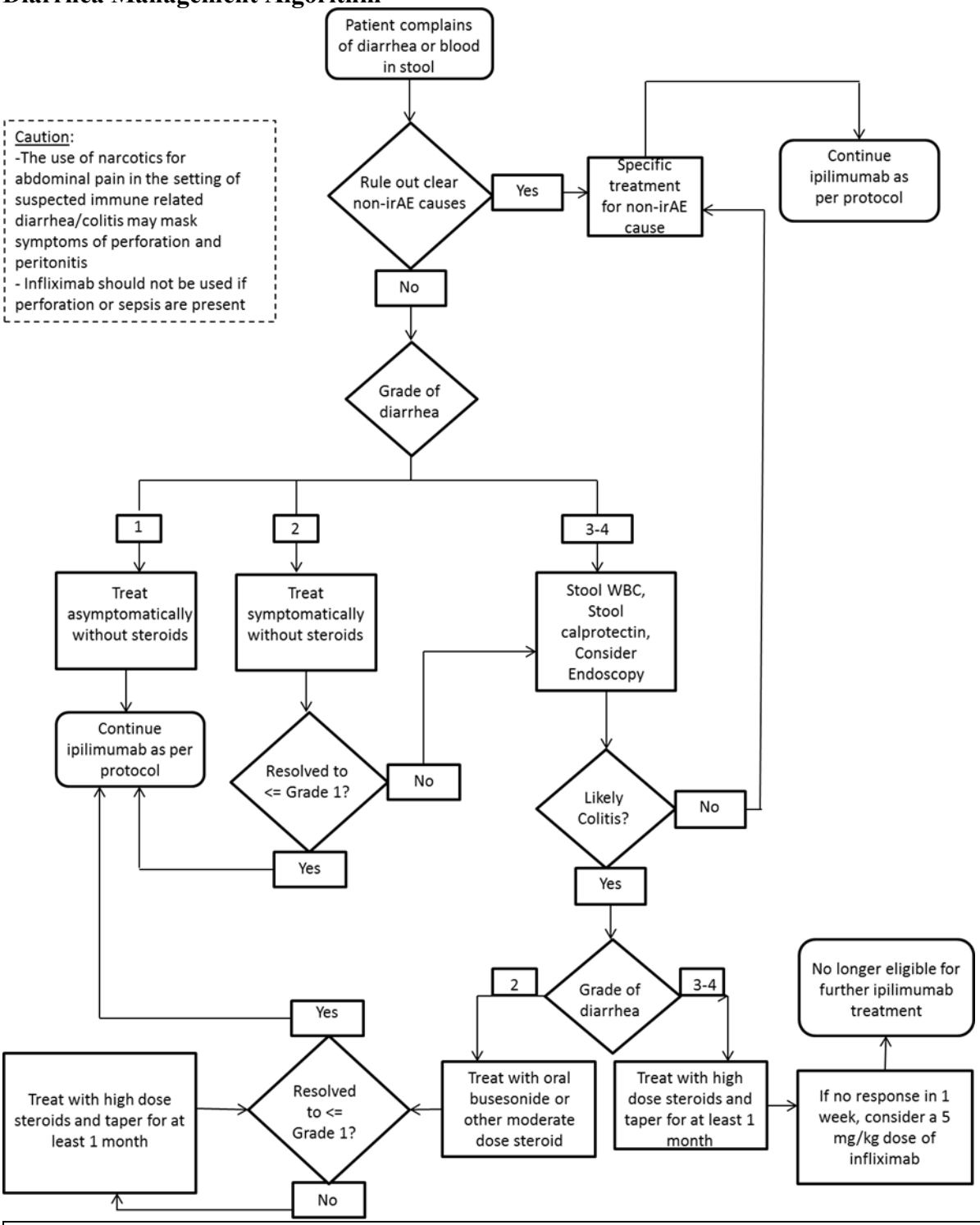
Neuropathy Toxicity Algorithm



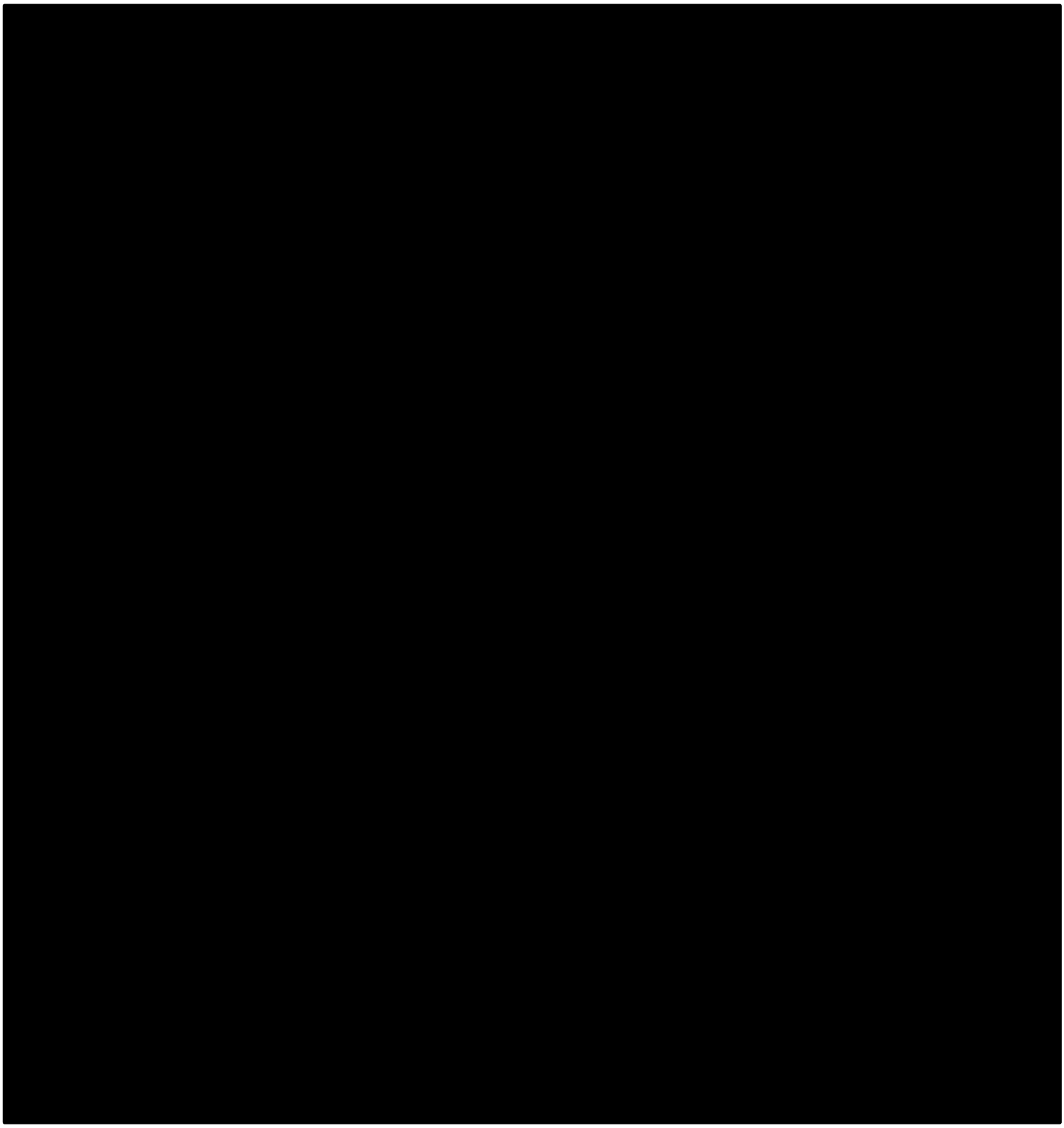
Hepatotoxicity Management Algorithm



Diarrhea Management Algorithm



Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Increase of < 4 stools per day over baseline; mild increase in ostomy output compared with baseline	Increase of 4-6 stools per day over baseline; IV fluids indicated < 24 hrs; moderate increase in ostomy output compared to baseline; not interfering with ADL	Increase of >7 stools per day over baseline; incontinence; IV fluids > 24hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with ADL	Life-threatening consequences (hemodynamic collapse)	Death



16.3 APPENDIX C: Informed Consent Template

RESEARCH PATIENT INFORMATION AND CONSENT FORM

TITLE:
A Phase 1/2 Study of the Concomitant Administration of Indoximod plus Immune Checkpoint Inhibitors for Adult Patients with Advanced or Metastatic Melanoma

Federal regulations require written informed consent from subjects before participation in a research study so that they can know the nature and risks of participation and decide to participate or not to participate in a free and informed manner. You are asked to read this consent form describing the research study and how you will participate in it if you consent to do so. Signing this consent form will indicate that you have been informed and that you give your consent.

Participation

You are being asked to consider participation in a research study. Your participation in this study is entirely voluntary. It is up to you to decide whether to take part or not. Even if you do decide to take part, you are free to partially or completely end your participation in the study.

Your eligibility to participate in this study will be decided based on the screening procedures described below and other eligibility criteria. Before you can take part in this study, it is important that you understand what this study involves. Please read this information carefully and ask any questions that you might have.

You are being asked to take part in this research study because you have been diagnosed with advanced (stage 3 or 4) melanoma.

Why is this research being done?

The purpose of this study is to determine the effects, good and/or bad, of immune checkpoint inhibitors (drugs called ipilimumab, nivolumab, or pembrolizumab) with the addition of indoximod (an experimental drug) to find out if the combination is possibly better than the checkpoint inhibitor alone.

About the study drugs:

Indoximod treatment is experimental at this time whereas the checkpoint inhibitors are intravenous drugs that are approved for commercial use as prescribed drugs by the US Food and Drug Administration (US FDA) for the treatment of metastatic melanoma.

The experimental drug indoximod is an oral medication that blocks an enzyme called IDO. Doctors think that tumors use IDO to escape attack by your body's immune system, so by blocking this IDO enzyme it may help your body attack the tumor cells more effectively. Indoximod given along with the checkpoint inhibitor may increase the effectiveness of the checkpoint inhibitor.

Should you take part in this study?
This form tells you about this research study. After reading through this form and having the research explained to you by someone conducting this research, you can decide if you want to take part in it.

- You may have questions this form does not answer. If you have questions, feel free to ask the study doctor or the person explaining the study, as you go along. You do not have to guess at things you do not understand. Ask the people doing the study to explain things in a way you can understand.
- Take your time to think about the information that has been provided to you.
- Have a friend or family member go over the form with you.
- Talk it over with your regular doctor

It is up to you. If you choose to be in the study, then you should sign the form. If you **do not** want to take part in this study, you should **not** sign the form.

Why are you being asked to take part?

We are asking you to take part in this research study because you have advanced melanoma.

How many people will participate in the study?

This study will have two parts, a dose-escalation phase (the first part of the study) and then later, a dose-expansion part (the second part of the study). In the first part of the study, up to 18 people will be asked to participate. In the second part, approximately 116 additional people will be asked to participate across multiple institutions. Approximately <<XX>> patients will be enrolled at <<CLINICAL SITE>>>.

What will happen during this study?
You will receive the study drug, indoximod, plus at least one checkpoint inhibitor during the course of the study. The checkpoint inhibitors allowed in this study include ipilimumab, nivolumab, and pembrolizumab. Each of these are described below. These are considered standard of care for your cancer and your physician will explain the difference to you and recommend the best inhibitor for you.

Ipilimumab
Ipilimumab (Yervoy™) is an antibody that acts against CTLA-4. An antibody is a common type of protein produced by your body that your immune system (a system that defends your body against potentially harmful particles) uses to find and destroy molecules not typically found in your body such as bacteria and viruses. Antibodies can also be produced in the laboratory for use in treating patients. There are now several approved antibodies for the therapy of cancer and other diseases.

CTLA-4 is a molecule that controls a part of your immune system by shutting it down. Researchers believe that one way cancers can escape the immune system could also be by shutting it down. An antibody against CTLA-4 can stop CTLA-4 from turning off the immune system, allowing the

immune reaction to continue. Your body's immune reaction may help your body to destroy cancer cells.

Nivolumab and Pembrolizumab

Nivolumab and Pembrolizumab are antibodies that block a protein called PD-1. Normally the immune system helps defend against cancer. Specialized immune cells called T cells attack threats to the body, like melanoma. Some melanoma cells send a signal to the PD-1 receptor on T cells. This signal makes T cells inactive and unable to attack melanoma, allowing the melanoma to grow. Nivolumab and Pembrolizumab block the PD-1 receptor on T cells, preventing the signal from melanoma from reaching the T cells, allowing them to do their job

If you agree to participate in this study, you will receive at least one of these immune checkpoint inhibitors and indoximod.

Screening

The screening period is held within 14 days before starting the study treatment to find out if you can be in the study. During this period, you will need to come to the clinic or study site for multiple tests. More than one screening visit may be required. If these tests show that you can be in the study and you choose to take part, then you will be entered in the study. The following screening examinations, tests, or procedures will be performed after you have given consent to participate in this study:

- Medical history, including information about you and your cancer, previous treatments for your cancer and other medications you are taking or have taken. Certain medications are not allowed to be taken during the study treatment.
- Complete physical exam including vital signs (heart rate, temperature, breathing rate, blood pressure, height and weight)
- An ECG to determine if your heart is healthy enough for treatment.
- Performance Status (questions about your ability to perform everyday activities)
- Your tumor size will be measured by CT scans or MRI.
- Standard blood tests, using up to 6 teaspoons of blood, to measure your liver and kidney function, white blood cells, red blood cells and platelets, your blood sugar and blood electrolytes and if you are female and able to become pregnant, to confirm you are not pregnant. You will not be allowed to enter the study of you are pregnant or lactating.
- Research blood tests will be taken to monitor how your body will be affected by the drug. These initial tests will serve as a guide to see how your body reacts after you have received the study drug throughout the study.
- Additionally, 3 teaspoons of blood will be drawn and stored for later testing of an enzyme that is released in tumors, called IDO enzyme (this is an immune suppressing enzyme released by the tumor and indoximod seems to block this enzyme). This is an optional test that may help us better understand who will respond to study treatment with indoximod. You will sign a separate consent for this testing.

A biopsy of your tumor is usually done as part of routine care to make the diagnosis of cancer prior to starting this course or most courses of treatment. If there is any extra preserved tissue from the biopsy remaining after it has been used to make a diagnosis, a small portion of the tissue will be

requested as part of this study to look for the presence of the IDO/TDO enzyme. A separate biopsy will not be done for research purposes alone. It is not required for participation in this study, and you do not have to agree to provide the tumor sample. If you say no, you can still participate in the main study. This testing will not benefit you directly or change how your disease is treated.

I agree to have left over tumor tissue provided for this study to test for IDO and TDO expression.

_____ YES _____NO _____Initials

DOSE-ESCALATION PHASE:
Subjects participating in this phase of the study will be enrolled to receive indoximod at a single dose level and successive subjects may receive higher doses in order to determine the highest dose that has acceptable side effects, is considered safe, and has the best potential to affect your cancer. Your dose will not increase and your schedule (how often you receive indoximod) will stay the same during your treatment period with indoximod.

Treatment Regimen for all Doses
If you continue to be eligible for study participation after screening, you will begin taking 6 capsules of indoximod (study drug) two times per day. Indoximod comes in 200 mg capsules. No food should be taken for at least 2 hours before and at least 1 hour after taking the morning and evening doses. Antacids should also not be taken for 2 hours before and 1 hour after taking the indoximod. You must swallow the capsules whole with a full 8 ounce glass of water and not chew them. It is very important that you follow these instructions listed above because they could change the safety and how well the study drug works.

Bottles containing indoximod capsules will be given to you periodically. It is very important that you take this medicine just as the doctor tells you. Do not miss any capsules. It is important to tell the study staff about any other medications you are taking during the study, including prescription drugs, over-the-counter medicines and vitamins. You will be asked to complete dosing diaries while you are taking the study medication and it will be distributed to you at the start of the study. You must bring your dosing diary and indoximod bottle(s) back to the clinic at regular intervals so the study staff can make sure you are taking your indoximod as you should. The study staff will review the dosing diary with you to ensure accuracy and assess compliance.

Your doctor and/or research team will describe your treatment schedule. Your treatment schedule will depend on the checkpoint inhibitor that you receive. If you receive ipilimumab you will receive it every 3 weeks for a total of 4 doses. If you receive nivolumab you will receive it every 2 weeks until your doctor decides it is not in your best interest to continue (disease gets worse or you have significant side effects). If you receive pembrolizumab you will receive it every 3 weeks until your doctor decides it is not in your best interest to continue (disease gets worse or you have significant side effects).

If you experience side effects or your disease progresses, your doctor may decide to switch you to another regimen or take you off the study.

The checkpoint inhibitors will be administered by intravenous (IV) infusion. This process involves inserting a needle into a vein in your arm. A pump will be used to ensure that the correct amount of medicine is given through the needle. Ipilimumab (3 mg/kg) is usually given over 90 minutes. Nivolumab (240 mg) is usually given over 60 minutes. Pembrolizumab (2 mg/kg) is usually given over 30 minutes.

If you have any side effects during the treatment period, you and your doctor will decide if you should continue in the study.

You will return to your doctor's office at regular intervals so that your disease can be monitored and routine blood tests and safety evaluations can be carried out. Please tell your study doctor or study staff if you have any unusual symptoms. You will be closely monitored for any side effects and you should report any changes in the way you feel to your study doctor. If you experience any side effects, your study doctor may instruct you to stop the study drug temporarily and restart at the same or lower dose after the side effect has resolved.

How long will you be asked to stay in the study?

It is unknown exactly how long you would stay on the study. The checkpoint inhibitor and indoximod treatment would continue until your disease stops responding to the treatment or you can no longer tolerate the study therapy. You are also free to stop participating at any time you decide to do so.

What other choices do you have if you do not participate?

If you decide you do not want to take part in this study that is okay. If you decide not to participate in this research, you have other choices. These choices include other clinical trials, conventional chemotherapy agents, or best supportive care to ease any symptoms you have without treating the underlying cancer.

When will you be taken off study?

You may be removed from the study for any of the following reasons:

- If your disease progresses
- If you do not adhere to the protocol treatment plan
- If you request to withdraw from the study or refuse further therapy
- Unacceptable side effects. You may be removed from the study for any complication of treatment that the investigator feels is life threatening.
- If you do not meet eligibility criteria

Will you be paid for taking part in this study?

We will not pay you for the time you volunteer while being in this study.

What will it cost you to take part in this study?

You and/or your insurance company will be financially responsible for your hospital inpatient, outpatient and follow-up visits that would normally or routinely occur in the management of your disease. Inpatient and outpatient visits could include charges for treatments, medications, physician visits, laboratory tests and procedures. You and/or your insurance company will be responsible for paying for the charges, which are considered routine, since you would have received these services even if you were not participating in this study

You will be responsible for any costs not covered by your insurance company, including deductibles, co-payments and all out-of-pocket expenses.

You and/or your insurance company will not be responsible for paying for testing and procedures that are specifically required for this research study and are not considered being part of the routine management of your disease, if these procedures are performed at <<<CLINICAL SITE>>>. Additionally, you and/or your insurance company will not be responsible for special blood tests to measure the drug levels.

NewLink Genetics will supply indoximod at no charge while you take part in this study.

Even though it probably won't happen, it is possible that the manufacturer may not continue to provide the indoximod to <<<CLINICAL SITE>>> for some reason. If this would occur, other possible options are:

- You might be able to get the indoximod from the manufacturer or your pharmacy, but you or your insurance company may have to pay for it.
- If there is no indoximod available at all, no one will be able to get more and the study would close.

If a problem with getting indoximod occurs, you study doctor will talk to you about these options.

What are the potential benefits if you take part in this study?

We do not know if you will get any health benefits by taking part in this study. We do not know if the experimental treatment will help you. That is why we are doing this study. We hope that what we may learn can benefit others in the future.

What are the risks if you take part in this study?

INDOXIMOD
The following may be related risks and side effects of the indoximod therapy that have been observed in patients that have received it:

Most Common: Likely to happen to 20% or more of patients

- Fatigue or feeling tired

Common: Likely to happen to 10 to 19% of patients

- Nausea
- Diarrhea
- Anorexia or loss of appetite

Less Common**:** Likely to happen to 5 - 10% of patients

- Anemia
- Vomiting
- Constipation
- Headache
- Hair loss
- Rash
- Low lymphocytes in blood

Rare: Likely to happen to less than 5% of patients

- Low white blood cells
- Decrease neutrophils
- Low platelets
- Colitis (inflammation of colon)
- Asthenia (muscle weakness)
- Hepatitis (inflammation of liver)
- Infection
- Increase in liver enzymes in the blood, including bilirubin, AST, ALT, and ALP
- Low sodium level in blood
- Dehydration
- High blood sugar level in blood
- Low blood sugar level in blood
- Low blood levels of calcium, magnesium, potassium and albumin
- Low phosphate level in blood
- Peripheral sensory neuropathy
- Dizziness
- Shortness of breath
- Abdominal pain
- Itching skin
- Blurred vision
- Altered taste
- Weight loss
- Fever associated with low white blood cells (febrile neutropenia)
- Tinnitus (ringing in ears), hearing loss
- Mouth sores
- Lung infection
- Multi-organ failure
- High potassium level in blood

- High creatinine level in blood
- Respiratory failure
- Arthritis
- Insomnia (sleeplessness)
- Low blood pressure (hypotension)
- Redness, pain, numbness, and possible peeling of the skin of the hands and feet
- Pneumonitis (inflammation of the lining in the lungs)
- Ascites (accumulation of fluid in the abdomen)
- Increase in white blood cells
- Parkinsonism (tremor, rigidity, instability, slowness of movement, masked face, voice changes)
- Kidney failure
- Influenza like illness
- Pneumonia
- Hypoxia (low levels of oxygen reaching body tissues)
- Prolonged partial thromboplastin time (may increase risk of bleeding)

Autoimmune Events

Autoimmunity is a term that describes when your immune system begins to attack normal cells in your body. Two patients out of 48 in a completed indoximod study developed an autoimmune reaction in their pituitary gland called hypophysitis. Both of these patients received prior experimental immune therapies which may have increased the risk of this occurring, but there is a distinct possibility that this may occur with indoximod alone. One of the two hypophysitis patients were on low dose steroids and thyroid hormone as long as they were alive, and one of the patients was able to stop the steroids but remained on thyroid hormone for the rest of her life. To date, none of the patients who did not receive prior immune therapies have developed this side effect. The pituitary gland is considered the "master gland" which coordinates the function of your other glands such as your thyroid, adrenals, and gonads (ovaries/testicles). If it does not function properly (pituitary insufficiency) you may experience symptoms of

- weakness
- fatigue
- loss of libido (lack of interest in sex)
- You may need to take hormone replacement therapy to treat these or other symptoms.

Another hormone called ACTH (a hormone secreted by the pituitary gland), excites the adrenal gland (a gland situated above the kidneys) to make steroids, particularly cortisol. If there is a decline in ACTH (ACTH deficiency) you may experience

- weight loss
- lack of appetite (anorexia)
- weakness
- nausea
- vomiting
- low blood pressure (hypotension).

Stopping the study drug and using steroids to calm the immune system are effective in many cases of autoimmune disease, but there is a risk of chronic autoimmune disease requiring treatment for longer periods of time. We will monitor you closely for any signs of autoimmune conditions and treat you for them if necessary. Prior experience with other immunotherapy agents seems to indicate those who do develop these autoimmune events may have a higher likelihood of their cancers responding to treatment, but it is not known if this is the case with indoximod.

IPILIMUMAB (Yervoy®)

During the study you may receive an anti-cancer drug called ipilimumab. This drug is approved by the FDA. This drug is given directly into the vein and will be given for about 90 minutes. This drug, like many other anti-cancer drugs, has side effects which include:

While receiving treatment with ipilimumab, you may be at risk of side effects that occur during or shortly after the infusion (within 24 hours). Other side effects related to ipilimumab can occur later after the infusion has finished. In very rare cases, some ipilimumab-related side effects may occur many months after the last dose of ipilimumab.

Some of these side effects occur through effects of your immune system (explained). You should tell your study doctor immediately if you think you are developing any unusual side effects even if they are not listed here.

You should not take any other medications, including non-prescription treatments such as aspirin, without the approval of your study doctor. Based on the clinical studies that have been conducted with ipilimumab the following adverse drug reactions are known:

Side Effects considered to be Related to Ipilimumab:

Ipilimumab has been most frequently studied in patients with advanced melanoma. Other studies have been conducted in patients with prostate cancer and lung cancer.

Advanced melanoma:

The most common treatment related side effects, occurring in patients with advanced melanoma on the 3 mg/kg dose level are listed below.

Common (greater than 30%)
- Diarrhea
- Fatigue

Less Common (10 – 29%)
- Itchy skin
- Skin rash
- Dermatitis (inflammation of the skin)

Rare but serious (less than 10%):

- Enterocolitis (inflammation of the intestines)- causing diarrhea, abdominal pain, mucus or blood in stool, with or without fever)
- Hepatotoxicity (elevated liver enzymes, liver failure)
- Neuropathy (nerve problem that causes pain, numbness, tingling, swelling, or muscle weakness)
- Endocrinopathy (hypopituitarism, adrenal insufficiency)
- Nephritis (kidney inflammation)
- Pneumonitis (inflammation of the lungs)
- Meningitis (inflammation of the membrane surrounding the spinal cord and brain)
- Pericarditis (inflammation of the sac around the heart)
- Uveitis (inflammation of the iris of the eye)
- Iritis (eye inflammation)
- Hemolytic anemia (destruction of red blood cells)

Serious Side Effects:

Any of the side effects listed above can become serious. Serious side effects can be fatal or threaten your life, require you to be hospitalized, permanently disable you, or make you weak and unable to function at your current level. They may also put your health at risk or require surgery or intervention by your study doctor.

Rapid destruction of cancer cells can result in a very serious and sometimes life-threatening condition that results from abnormal blood levels. This elevation in certain blood levels (for example, uric acid, phosphorous, potassium) can cause the kidneys to shut down, the heart to function irregularly (for example, an irregular heartbeat), shortness of breath, and loss of consciousness. This condition, medically called tumor lysis syndrome, has been rarely reported (in less than 1% of patients) with ipilimumab treatment.

Death resulting from side effects considered related to ipilimumab occurred in about 1% of patients treated with ipilimumab. Severe infections including sepsis have also been reported in ipilimumab-treated patients, some of which had resulted in death.

Immune-Related Adverse Events (IRAEs) Considered to be Related to Ipilimumab:

Ipilimumab can cause side effects due to effects of your immune system attacking your normal cells. These are called immune-related adverse events or IRAEs. These IRAEs have usually been controlled by stopping ipilimumab treatment temporarily or permanently and if needed, with medications, including steroids (medications that are used to decrease inflammation). If you develop an immune-related event, the symptoms may take several months to improve.

Side effects related to the immune system fall into several categories described below:

Stomach/Intestine: The most common stomach/intestinal IRAE is diarrhea (30%). Severe stomach/intestine side effects have been reported in about 6-12% of patients receiving ipilimumab. Patients either had diarrhea alone or in combination with inflammation of the intestine associated with pain. Diarrhea due to treatment with ipilimumab ranges from mild to very severe with

bleeding and, in very few cases, can be life threatening. Some cases of diarrhea have started out as mild and then become severe.

About 1% of patients have had diarrhea or stomach/intestinal complications that required surgical removal of part of their intestine or resulted in death. Most of the other cases of diarrhea have been successfully treated by either stopping ipilimumab treatment and/or by giving an anti-diarrhea medicine or steroids. Rarely (in less than 1% of patients), ipilimumab treatment may cause constipation or ulcers of the large intestines.

Tell your study doctor if you develop any diarrhea, constipation, any change in your bowel movements, have blood in your stool, or have abdominal pain. Your study doctor may want to perform tests to better understand why you have these symptoms. These tests will allow your study doctor to look at your intestine for damage and figure out if you need additional treatment. You may also have to go to the hospital for additional tests and treatments.

Skin disorders: The most common skin related IRAE is rash. Most skin-related IRAEs have been mild and approximately 3% of cases have been severe. Some patients have had itching alone or together with the rash. Vitiligo, a condition where the skin loses pigment and turns white, has occurred in less than 5% of patients. This condition is likely to be irreversible and permanent.

In very rare cases (in less than 1% of patients), blistering and peeling of the top layer of skin resembling that of a severe burn has occurred. This condition is called toxic epidermal necrolysis and it can be life threatening and fatal.

Eye: In rare cases (in less than 1% of patients), ipilimumab has caused inflammation in the various parts of the eye or with pigment (color) changes in the retina (a thin layer of tissue that lines the inside back wall of the eye). There have been no known cases of permanent eye damage but these conditions could interfere with your eyesight or even cause blindness if untreated.

If these conditions occur they may require treatment to reduce inflammation. In rare cases (in less than 1% of patients), double vision occurred as a result of muscle weakness. You should immediately tell your doctor if you think there is a change in your eyesight, develop double vision or if you develop eye pain while you are on this study.

Endocrine glands: Approximately 3 - 6% of patients taking ipilimumab have developed problems with particular glands (a gland is a group of cells or an organ that secretes a substance) such as the pituitary gland, the thyroid or the adrenal gland. Severe problems with particular glands were reported in approximately 3% of patients. Symptoms that may be associated with problems of the pituitary or adrenal glands include fatigue, confusion, weight loss, impotence (inability to perform sexually), and headache. Most of those symptoms were controlled using hormone therapy and steroids.

Liver: Approximately 8 - 37% of patients have developed problems with the liver as a result of ipilimumab treatment. Inflammation of the liver due to ipilimumab can range from mild or moderate (around 1%) to severe (around 7%) and in a very few cases, it can be life threatening. Acute liver failure resulting in death has occurred in less than 1% of patients. However, most

severe cases have been successfully treated by stopping ipilimumab treatment and by administering anti-inflammatory medications such as steroids. Your study doctor will regularly monitor your liver function by drawing blood.

You should contact your study doctor if you experience symptoms that may be associated with problems of the liver that include fatigue, weakness, vomiting, nausea, yellow discoloration of the eye or the skin or abdominal pain. More frequent blood draws and a liver biopsy may be required if you develop serious liver abnormalities.

Neurologic disorders: In very rare cases (in less than 1% of patients), immune-related motor neuropathy (inflammation of the nerves that control muscles) such as Guillain-Barré Syndrome may occur, which could be life-threatening if not treated appropriately. You should tell your study doctor if you experience weakness of your limbs with or without numbness or tingling. Hearing loss was also seen in less than 1% of patients.

Other rare IRAEs: Rarely, patients have developed problems in more than one organ system at a time such as liver, kidney, heart, muscles, blood vessels, and lung while taking ipilimumab. Acute failure of such organs resulting in death considered related to ipilimumab has occurred in about 1% of patients.

Meningitis (inflammation of the membrane surrounding the spinal cord and brain) has developed in less than 1% of patients treated with ipilimumab. This can cause headache, nausea and vomiting, stiff neck, and sensitivity of your eyes to light.

Nephritis (inflammation of the kidneys) has developed in less than 1% of patients treated with ipilimumab. The cases of meningitis and nephritis usually can be managed with treatment.

In addition, immune-related reactions of any other organs, such as the pancreas, thyroid, brain and joints, could also occur. This could cause pain and swelling. Joint pain has been reported by less than 1% of patients receiving ipilimumab. In rare cases (less than 1%), varying degrees of weakness of the voluntary muscles of the body have been reported and it is called myasthenia gravis.

Side Effects Considered to be Related to Nivolumab (Opdivo®)

The most common treatment related side effects, occurring in patients with advanced melanoma on the 3 mg/kg dose level are listed below.

Most Common (greater than 10%)

- Itchy skin
- Skin rash
- Cough
- Upper respiratory tract infection
- Peripheral edema
- Increased liver function tests in blood
- Decreased sodium levels in blood

- Increased potassium level in blood

Rare but may be serious (less than 10%):

- Iridocyclitis (inflammation of colored ring of eye)
- Ventricular arrhythmia (irregular heart rhythm)
- Infusion related reactions
- Increased pancreatic enzymes in blood (amylase, lipase)
- Dizziness
- Peripheral and sensory neuropathy (inflammation of the nerves)
- Exfoliate dermatitis (widespread scaling of the skin)
- Erythema multiforme (skin lesions due to reaction)
- Vitiligo (loss of skin color in blotches)
- Psoriasis (thick, white, silvery, or red patches of skin)
- Abdominal pain
- Immune-Mediated Pneumonitis (inflammation of lungs)
- Immune-Mediated Colitis (inflammation of colon)
- Immune-Mediated Hepatitis (inflammation of liver)
- Immune-Mediated Hypophysitis (inflammation of the pituitary gland)
- Immune-Mediated Nephritis (inflammation of kidneys)
- Immune-Mediated Hyperthyroidism or Hypothyroidism (thyroid gland produces too much or too little of the hormone thyroxine)

Side Effects Considered to be Related to Pembrolizumab (Keytruda®)

The most common treatment related side effects, occurring in patients with advanced melanoma on the 2 mg/kg dose level are listed below.

Common (30% or greater)

- Fatigue
- Nausea
- Cough
- Itching skin
- Increased blood sugar
- Decreased sodium level in blood
- Decreased albumin level in blood
- Anemia

Less Common (10 – 29%)

- Peripheral edema
- Chills
- Fever
- Constipation
- Diarrhea

- Vomiting
- Abdominal pain
- Shortness of breath
- Rash
- Vitiligo (loss of skin color in blotches)
- Decreased appetite
- Joint pain
- Pain in extremity
- Muscle pain
- Back pain
- Headache
- Dizziness
- Insomnia (difficulty sleeping)
- Upper respiratory tract infection

Rare but may be serious (less than 10%):

- Blood infection
- Immune-Mediated Pneumonitis (inflammation of lungs)
- Immune-Mediated Colitis (inflammation of colon)
- Immune-Mediated Hepatitis (inflammation of liver)
- Immune-Mediated Hypophysitis (inflammation of the pituitary gland)
- Immune-Mediated Nephritis (inflammation of kidneys)
- Immune-Mediated Hyperthyroidism or Hypothyroidism (thyroid gland produces too much or too little of the hormone thyroxine)
- Immune-Mediated Guillain-Barré Syndrome (inflammation of the nerves that may cause pain, weakness or tingling in the hands and feet, and may spread to the legs, arms and upper body leading to severe muscle weakness)
- Stevens-Johnson Syndrome. Stevens-Johnson syndrome is a rare, serious disorder of the skin and mucous membranes. It often begins with flu-like symptoms (fever, fatigue, cough), facial and tongue swelling, hives and skin pain, followed by a painful red or purplish rash that spreads and blisters. Stevens-Johnson syndrome is a medical emergency that usually requires hospitalization and rarely fatal.

Side Effects That May Occur During Infusion of Ipilimumab, Nivolumab, or Pembrolizumab:

During the infusion of the checkpoint inhibitor you may experience an infusion reaction. Symptoms of infusion reaction are: fever, hypotension (low blood pressure), chills, flushing, nausea and/or vomiting.

You may experience none, one, some or all of these symptoms. If an infusion reaction occurs, the infusion will be slowed or stopped until the symptoms have been treated (usually with fluids given into your vein or other common medications). These symptoms can also occur hours after the completion of the infusion.

Is there any risk to your unborn children if you take part in this study?

For Women:
If you are pregnant, you may not participate in this study, because there may be risks to you and your unborn baby. Breastfeeding (nursing) mothers will not be included in this study, since it is not known whether the drugs in this study will be passed on to the baby in the mother's milk. If you are currently breastfeeding and wish to continue, your study doctor may recommend another treatment.

If you are a female of childbearing potential (able to become pregnant), you will be given a pregnancy test at no cost to you before beginning any study treatment.

Tell one of the study doctors right away if:
- You are pregnant
- You get pregnant
- You are breastfeeding

If you are a man:
We do not know what the experimental drug will do to your sperm. Should you get a woman pregnant, there could be harm to the unborn baby. You and your partner should use at least one effective birth control method (two are preferable when possible) if you are having sexual intercourse with a woman of childbearing potential.

For men and women:
Whether you are a man or a woman, there may be risks to your unborn children. If you take part in this study, you must use at least one effective birth control method (two are preferable when possible) as discussed with your study doctor. Examples of birth control methods include:
- Oral birth control pills
- Birth control patch
- Implanted (injectable contraceptive hormones or mechanical products such as intrauterine device)
- Barrier methods (diaphragm, condoms, spermicidal)
- Tubal ligation or vasectomy
- Abstinence

Certain birth control methods may not be a good choice for you (for example some patients with breast cancer should not use birth control methods that contain hormones). You should discuss the method of birth control which is best for you to use both during study treatment and for a period of time after treatment. Also, if you are a sexually active premenopausal woman or man the study staff will review your birth control use at each study visit. Use of contraception or abstinence should continue for a minimum of 1 month after completion of the study.

Please place your **initials** in the appropriate box below:

☐ I am surgically sterile (hysterectomy, tubal ligation or vasectomy) or have gone through menopause (no period for 24 consecutive months).

☐ I understand and agree to use contraception during treatment and for the time recommended by my doctor after treatment is over.

Whether you are a woman or a man, you should tell your doctor immediately if you become pregnant or if your partner becomes pregnant. The long-term effects of the study treatment on fertility are unknown. This means that it is unknown if treatment with these medication will affect your ability to have children in the future.

What if you get sick or hurt while you are in the study?

If you become ill or are hurt while you are in the study, get the medical care that you need right away.

Research-Related Injury

Your safety is the major concern of every member of the research team. If you experience physical injury or illness as a result of participating in this research study, the sponsor will reimburse you for reasonable and necessary medical expenses when the injury is found to be the result of the study drug used as indicated in the research plan and is not the result of negligence or misconduct of any agent or employee of <<clinical site>>. Financial compensation for lost wages or other non-medical costs will not be provided. Agreeing to participate in this study and signing this document does not waive your rights in the event of negligence on the part of the Hospital or research staff.

Further information about research-related injuries is available by contacting the <<clinical site>> Institutional Review Board at (XXX) XXX-XXXX.

Further information concerning policies in this regard, or information about the conduct of this study or rights of research subjects, may be obtained from the principal investigator.

<u>Confidentiality, Collection and Use of Study Data</u>

Your study doctor will collect information about you, on your health, on your race and on your ethnic origin. This collected information about you is called “data” or “study data” in this document.

For the purposes of your participation in this study and the protection of your identity, your study doctor will assign you a unique code, such as a series of numbers and/or letters. The study doctor

will record the study data collected from you in a report form that uses your assigned code, not your name. This is to protect your study data by making it anonymous for most study purposes.

The data that is recorded with your assigned code rather than your name is called "key-coded data". The key-coded data will be entered into the study's computer database. Your study doctor will keep a confidential list linking your name to your code and only authorized persons will have access to this list. The ways in which key-coded data may be used and shared is described below.

Some study data will identify you (such as medical records), and the ways in which this data may be used and shared is described below. Your key-coded data may be shared with and used by the following:

- The study doctor and study staff
- The study sponsor, its current or future research partners, collaborators, assignees, licensees or designees and their affiliates, agents, and employees
- Other individuals and organizations that analyze or use your information in connection with these research activities, including laboratories and study sites (in the event you transfer to another study site)
- Domestic or foreign health authorities; such as the Food and Drug Administration (FDA)
- Other persons required by law

Your key-coded data will be used in connection with this study and may also be:

- Used for other current or future research involving the same drug(s), the same or related health conditions, or for other relevant health research;
- Transferred to individuals or companies located outside of the country or region in which you reside. However, all access to the key coded data will be controlled in accordance with applicable laws and regulations.
- This may include written agreements that require that the data be kept confidential and secure and be used only for the purposes permitted by this consent form or applicable laws and regulations;
- Used in publications about this study but it will remain coded. Your identity will not be revealed in any compilation, study report or publication at any time.

Use and Sharing of Study Data that Identifies You

The use and sharing by your study doctor of study data that identifies you, such as your original medical records, are explained in a separate HIPAA Authorization. By signing that form, you show that you give permission for the uses and sharing of this data as described in that document. You do not have to sign that form, but if you do not, you will not be allowed to participate in this study. To withdraw your HIPAA Authorization you will need to do so in writing as described in that document. There is a risk that your information will be given to others without your permission.

What if new information becomes available?

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

What happens if you decide not to take part in this study?

You should only take part in this study if you want to volunteer. You should not feel that there is any pressure to take part in the study. If you feel any pressure to take part in the research study please talk to your study doctor or the research staff.

You can decide after signing this informed consent document that you no longer want to take part in this study. We will keep you informed of any new developments that might affect your willingness to continue to participate in the study. However, you can decide you want to stop taking part in the study for any reason at any time. If you decide you want to stop taking part in the study, tell the study staff as soon as you can. Any information that has been collected before you withdraw your authorization from the study will continue to be used for research purposes.

- We will tell you how to stop safely. We will tell you if there are any dangers if you stop suddenly.

Are there any reasons we might take you out of the study later on?

Even if you want to stay in the study, there may be reasons we will need to take you out of it. You may be taken out of this study if:

- We find out it is not safe for you to stay in the study. For example, your health may worsen or we may find that the experimental drug might harm you.
- You are not taking your medication properly or are not coming for your study visits as scheduled.
- The doctor feels it is not in your best interest to continue.
- If the sponsor or investigator stops the study or your participation for any reason.

You can get answers to your questions, concerns, or complaints.

You have rights as a research subject. These rights have been explained in this consent form that you have been given. If you have any questions concerning your rights, talk to the investigator or call the Institutional Review Board (IRB), telephone (xxx) xxx-xxxx.

If you have any problems or questions about this study, or about your rights as a research subject, or about any research-related injury, contact the main study doctor, *Principal Investigator, M.D.* at (xxx) xxx-xxxx.

Clinical Trial Information in Public Database
A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Statement of Participation in Research and Authorization for the Collection, Use and Disclosure of Health Information

It is up to you to decide whether you want to take part in this study. If you want to take part, please read the statements below and sign the form if the statements are true. A representative of the <<CLINICAL SITE>>> must answer your questions completely before providing this form to you. You or your personal representative should read this form and understand it before signing it.

I freely give my consent to take part in this study and authorize that my health information as agreed above, be collected/disclosed in this study. I understand that by signing this form I am agreeing to take part in research. I have received a copy of this form to take with me.

Signature of Person Taking Part in Study Date

Printed Name of Person Taking Part in Study

Statement of Person Obtaining Informed Consent / Research Authorization
I have carefully explained the study and consent to the person as signed above. I have taken part in the consent process prior to the patient's signature and discussed in detail the study aims, methods, anticipated benefits, potential hazards or discomforts, and treatment alternatives. I have answered all questions the patient and/or family have asked. No Study procedures were initiated prior to consent.

Signature of Person Obtaining Informed Consent / Research Authorization Date

Printed Name of Person Obtaining Informed Consent / Research Authorization

Statement of Investigator
I certify that I am signing this form within seven days of the patient's signature and prior to randomization and/or treatment, but after the patient's signature has been obtained.

Signature of Study Investigator **Date**

Addendum to the Consent
Consent to take and store additional blood samples

We are asking you to allow us to take and store additional samples of your blood. This is an optional test that may help us better understand who will respond to treatment with indoximod.

This means we will take an additional 18 mL (about 3½ teaspoons) of blood to be stored for subsequent (later) analysis related to the IDO enzyme. The IDO enzyme is an immune suppressing enzyme released by the tumor and indoximod seems to block this enzyme.

These samples may be stored at NewLink Genetics Corporation within a climate controlled, restricted access area requiring key cards for entry. These samples will be used for future research to help us better understand who may respond to treatment with indoximod.

These samples will only have subject identifiers consisting of your initials followed by your study subject number (XX-111). No one except your physician or clinical research team will be able to connect your coded health information to you.

You can decide if you want us to store and use your samples for this future analysis of the IDO enzyme.

You do not have to agree to these optional samples of blood in order to take part in the study that has been previously explained to you.

Please initial your choice below:

____ I give my consent to provide an additional 18 mL of blood for that purpose on the first day of each treatment cycle.

____ I do not give my consent to provide an additional 18 mL of blood for that purpose.

Even if you sign this consent, you have the right to withdraw your samples at any time. To do so, please submit a written request to Dr. XXXXXXX at:

Attn: Principal Investigator, MD
Institution Name
Address
City, State Zip

_____
Printed Name of Person Explaining Consent

_____ _____
Signature of Person Explaining Consent Date

Tumor Biopsy Expansion Study Addendum

Why are you being asked to take part?

You have been asked to participate in the Expansion Study because you have a tumor lesion that can be readily accessed through the skin by performing a core needle biopsy. Core needle biopsy uses a long hollow needle to remove samples of tumor tissue.

How many people will participate in the expansion study?

Twenty (20) patients will be asked to participate across multiple institutions. Approximately <<XX>> patients will be enrolled at <<CLINICAL SITE>>>.

What will happen during the expansion study?

Study treatment in the Phase 2 expansion will follow the same treatment plan for Phase 2 already described in this consent form except for the addition of obtaining two tumor biopsies.
Your doctor will perform a core needle biopsy one time before you start study treatment and then again after the third (3^{rd}) cycle of pembrolizumab, right before your 4^{th} cycle.

The core needle biopsies are required for participation in the expansion study and are being obtained to evaluate the possible effects of the treatment on your cancer and immune system.

How is a core needle biopsy done?

Most needle biopsy procedures don't require any preparation on your part. However, you may be asked to stop taking blood-thinning medications, such as warfarin (Coumadin) or aspirin, in the days before your biopsy. Depending on what part of your body will be biopsied, your doctor may ask you not to eat or drink before the procedure.

In certain cases, you may receive intravenous (IV) sedatives or general anesthetics before your needle biopsy. If this is the case, your doctor may ask that you fast (don't eat) the day before your procedure. Tell your doctor about any medications you're taking, as you may need to stop taking certain medications before undergoing anesthesia.

Your health care team will position you in a way that makes it easy for the doctor to access the area where the needle will be inserted. You may be asked to lie flat on a table.

In certain cases, you may undergo imaging procedures, such as a CT scan or ultrasound. These allow your doctor to see the target area and plan the best way to proceed. Imaging procedures are sometimes done before your needle biopsy and sometimes performed during the biopsy. What type of imaging you'll undergo, if any, will depend on what part of your body is being biopsied.

Your health care team will clean the area of your body where the needle will be inserted. An anesthetic may be injected into the skin around the area to numb it. In some cases, you'll receive an IV sedative or other medication to relax you during the procedure.

During the needle biopsy, the doctor guides a needle through your skin and into the area of the tumor. A sample of tumor cells is collected and the needle is withdrawn. This process may be repeated several times until enough cells are collected.

What are the risks of the Core Needle Biopsies?

Core needle biopsy carries a small risk of bleeding and infection at the site where the needle was inserted. Some mild pain can be expected after needle biopsy, though it is usually controlled with over-the-counter pain relievers or prescription medications.

Tell your doctor if you experience:
- Fever
- Pain at the biopsy site that worsens or isn't helped by medications
- Swelling at the biopsy site
- Drainage from the biopsy site
- Bleeding that doesn't stop with pressure or a bandage

Who will pay for the Core Needle Biopsies?

The sponsor of this study, NewLink Genetics Corporation, will pay for these procedures as long as they are being completed for research purposes only and not conducted for diagnostic or standard of care purposes. You and/or your insurance company will be responsible for paying for the procedures if they were conducted as a normal occurrence for the management of your disease.

The nature and purpose of this expansion study has been explained to me and I understand that if I choose to participate in this study, there will be an insertion of a needle into my body so that tissue can be removed. The risks of injury, infection, bleeding and other complications, despite precautions, have been explained to me.

I freely give my consent to take part in this study. I understand that by signing this form I am agreeing to take part in research. **I have received a copy of this form to take with me.**

Signature of Person Taking Part in Study Date

Printed Name of Person Taking Part in Study

Signature of Person Explaining Consent Addendum Date

Printed Name of Person Explaining Consent Addendum