STATISTICAL ANALYSIS PLAN

Indoximod (1-methyl-D-tryptophan, D-1MT)

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 Number: [redacted]

Date of Plan: 18 September 2019

Based on: Protocol Version 6 (06 February 2017)

CRF Version 1.8.1

SPONSOR:

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This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

Statistical Analysis Plan Approval

SAP:	NLG-2103 SAP
SAP Version:	Version 2.0
Sponsor Representative:	[redacted]
Approval Signature:	
Date Approved:	
Protocol Version:	Version 6 (06 February 2017)
CRF Version:	Version 1.8.1
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SAP Author Approval Signature:	
Date Approved:	

TABLE OF CONTENTS

LIST OF TABLES

1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Term
AE	adverse event
BID	twice daily
CR	complete response
CRF	case report form
CTCAE	common terminology criteria for adverse events
DCR	disease control rate
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EE	efficacy evaluable
EEBC	efficacy evaluable including biopsy cohort
FNA	fine needle aspiration
irRC	Immune related response criteria
ITT	intent to treat
IV	Intravenously
MTD	maximum tolerated dose
NCI	National Cancer Institute
OS	overall survival
ORR	overall response rate
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
RP2D	recommended phase 2 dose
RECIST	response evaluation criteria in solid tumors
RLT	regimen limiting toxicity
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease

TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WHO	World Health Organization

2. INTRODUCTION

This is a non-randomized open-label Phase 1/2 trial designed to evaluate the concomitant administration of indoximod plus immune checkpoint inhibitors for adult patients with advanced or metastatic melanoma. The phase 1 portion is intended 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. The phase 2 portion of the study evaluates 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.

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.

Therefore while phase 1 data will be summarized, the focus of this analysis plan will be on the phase 2 objectives of the study.

3. STUDY INFORMATION, OBJECTIVE(S) AND ENDPOINT(S)

3.1. Protocol and Case Report Form Version

This SAP is based on NLG-2103 Protocol Version 6 date 06 February 2017 and case report forms (CRFs) version 1.8.1.

3.2. Study Objectives

3.3. 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.

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 were similar to but more frequent and severe than those seen with nivolumab or pembrolizumab. The phase 1 dose escalation set an expected phase 2 dose and toxicity profile for immune checkpoint inhibitors in combination with indoximod. Therefore, this analysis plan will focus on the analysis of phase 2 portion of the study.

3.4. 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.

3.5. 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.

3.6. Study Endpoints

3.6.1. Primary

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 RECIST, irRC, and mWHO criteria.

3.6.2. Secondary

The secondary objectives are:

- disease control rate (DCR)
- duration of response (DOR)
- Progression-free Survival
- Overall Survival
- Other time to response events

3.6.3. Safety

The safety and tolerability of immune checkpoint inhibitors in addition to indoximod will be assessed with incidence of AEs, laboratory values, ECGs, vital signs, ECOG performance status and other safety assessments.

4. STUDY DESIGN

4.1. Phase 1

Choice of the phase 1 dose for indoximod: A single-agent phase 1 study of indoximod has already been conducted, as described in protocol 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 the 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 of the clinical protocol.

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 protocol 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 of the clinical protocol.

- 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.

4.2. Phase 2

No patients will be enrolled in the Phase 2 portion of the study 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.

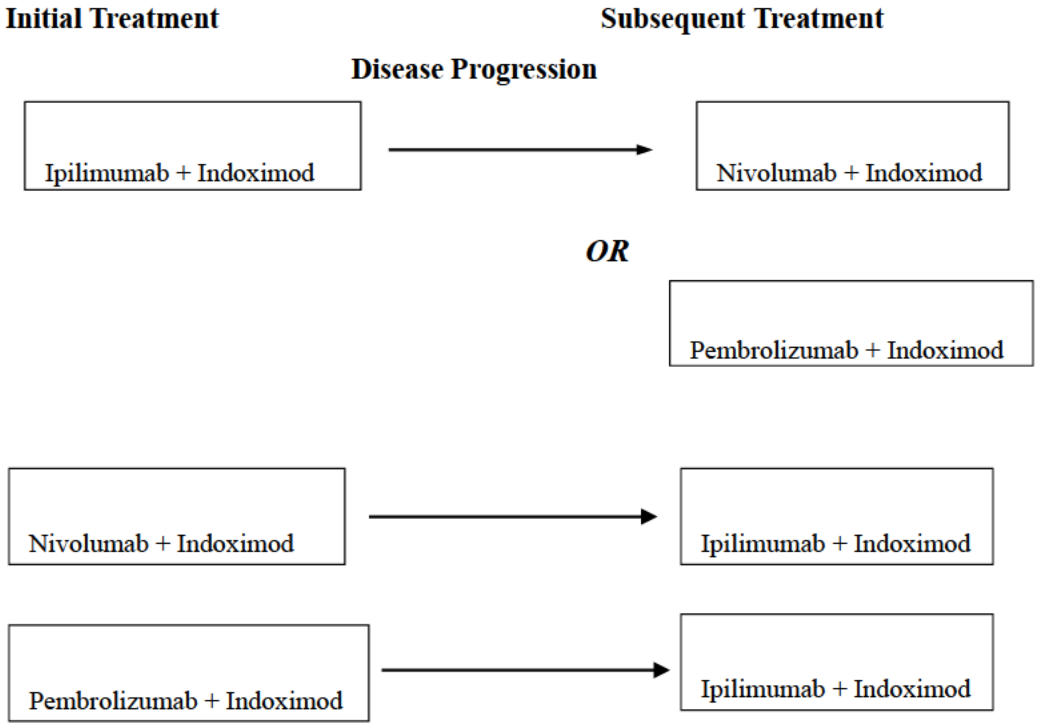
The intention in this study is to evaluate the benefit of adding indoximod to this regimen of immune checkpoint inhibition. Per design, the change from the initial checkpoint inhibitor to the second checkpoint inhibitor administered should only occur after definitive progression as defined by irRC or 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 the clinical protocol, Section 11, Study Calendar, for treatment regimen cycles.

Phase 2 Doses:

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



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

4.4. Sample Size Considerations

Phase 1 component: No formal sample-size estimation was performed and no formal statistical hypothesis testing will be performed during this phase. The selection of sample size was based on a standard 3 + 3 design that is commonly used in Phase 1 trials of anti-cancer investigational drugs. For the dose escalation portion of the study, the maximum sample size will be 18 patients if 6 patients are assigned at 3 dose levels.

Phase 2 component: The objective response rate for PD-1 inhibition with pembrolizumab after progression on ipilimumab is listed as approximately 25% in the pembrolizumab package insert. This was used as a reference point for the benefit provided by immune checkpoint inhibitors used in sequence. To detect an increase in 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.

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 40 patients would provide a reasonable precision for the estimation of pilot information.

The PASS 12 package was used for the Phase 2 component sample size estimation (NCSS, LLC. Kaysville, UT)[1].

4.5. Schedule of Assessments

Table 2 and Table 3 provides the schedules for study visit assessments and laboratory sampling for the safety and efficacy variables defined for this study.

Table 2: 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.

	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																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															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
Blood for Kyn/Trp Ratio		X			X			X			X			E				
Blood for Flow Cytometry		X			X			X										
Blood for future testing		X			X			X			X			X				
Archival tumor tissue		F																
Core Needle BX	G									G								

Table 3: 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.

	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
Blood for Kyn/Trp Ratio		X				X				X				E				
Blood for Flow Cytometry		X				X				X								
Blood for future testing		X				X				X				X				
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).
E: Kyn/Trp Ratio completed Day 1 of each checkpoint inhibitor + indoximod cycle and then just the first 2 indoximod only cycles.
F: Archival tumor tissue is obtained if possible.

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.

Table 4: Required observations following the completion of protocol therapy

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.

5. DATA HANDLING DEFINITIONS AND CONVENTIONS

5.1. Scheduled Study Evaluations and Study Periods

5.1.1. Study Drug

Study drug is defined as indoximod, ipilimumab, pembrolizumab or nivolumab unless specified otherwise. Standard of care checkpoint immunotherapy refers to ipilimumab, pembrolizumab or nivolumab.

5.1.2. Day 1

Day 1 is the date of first dose of treatment with study drug. Study drug is defined as any of the following: indoximod, ipilimumab, pembrolizumab or nivolumab.

5.1.3. Study Day

The study day at a visit or reporting date will be calculated by the visit or reporting date minus Day 1 date plus 1 (visit date - Day 1 date + 1). This study day will be subtracted by 1 if it is prior to Day 1, so that a study day of zero will never occur. A study day of -1 indicates 1 day before Day 1.

Additionally, cycle day will be determined as the day of the first dose of study drug within each cycle.

5.1.4. Baseline Value

Baseline is the last non-missing measurement obtained on or before the day of the first dose of study drug.

5.1.5. End of Treatment Value

End of treatment value is the last non-missing post-baseline value for each patient.

5.1.6. Cycle Length and Duration

For purposes of safety and efficacy: Cycle 1 Day 1 is defined as the day of the first dose of study drug. Subsequent cycles have Day 1 as the corresponding visit date associated with the corresponding cycle.

For purposes of exposure evaluation:

> For nivolumab and ipilimumab, Cycle 1 Day 1 is defined as the day of the first dose of study medication. The end of the first cycle of therapy is the earlier of: (1) 28 calendar days (inclusive) later; or (2) permanent discontinuation of Study drug. Subsequent cycles

are the periods starting 1 day after the end of the previous cycle and ending the earlier of: (1) 28 calendar days (inclusive) later; or (2) permanent discontinuation of study medication.

For pembrolizumab, Cycle 1 Day 1 is defined as the day of the first dose of study medication. The end of the first cycle of therapy is the earlier of: (1) 21 calendar days (inclusive) later; or (2) permanent discontinuation of Study drug. Subsequent cycles are the periods starting 1 day after the end of the previous cycle and ending the earlier of: (1) 21 calendar days (inclusive) later; or (2) permanent discontinuation of study medication.

5.2. Variable Definitions

5.2.1. Age

Patient age will be calculated as the integer part of the number of years from date of birth to the date of signing the informed consent form, using the following formula:

Age = integer part of (date of informed consent – date of birth + 1)/365.25.

5.2.2. Body Mass Index (BMI)

Body mass index (BMI) will be calculated as follows:

$$BMI\ (kg/m^2) = [weight\ (kg)] / [height\ (m)]^2$$

5.2.3. Body Surface Area (BSA)

Body surface area (BSA) will be calculated based on the Mosteller formula as follows:

$$BSA\ (m^2) = \{[weight\ (kg) \times height\ (cm)] / 3600\}^{1/2}$$

5.2.4. Concomitant Medication

Concomitant medication is defined as any non-study medication that is:

- Started before the date of first administration of study drug and is ongoing throughout the study or ends on/after the date of first study medication administration.
- Started on/after the date of first administration of study drug and is ongoing or ends during the course of study medication.

The start/stop dates recorded in the CRF will be used to identify when a concomitant medication was taken during the study. Unresolved missing start dates will be handled as follows for determination of concomitance only:

- If the date is completely missing, the medication will be considered concomitant.

- If only the day is missing, and the last day of the month is before the first dose date on Day 1, then the concomitant medication will be considered as starting before Day 1, and the incomplete date will be imputed as the last day of the month.

- If only the day is missing, and the first day of the month is after the first dose date on Day 1, then the concomitant medication will be considered as starting after Day 1, and the incomplete date will be imputed as the first day of the month.

- If only the day is missing, and the month is equal to the month of the first dose date on Day 1, then the incomplete date will be imputed as the first day of the month.

- If both the month and day are missing, and the last day of the year is before the first dose date on Day 1, then the concomitant medication will be considered as starting before Day 1, and the incomplete date will be imputed as if it is the last day of the year. Otherwise, the incomplete date will be imputed as if it is the first day of the year.

6. STATISTICAL METHODOLOGY

6.1. General Methodology

Unless otherwise noted, SAS software (SAS Institute Inc, Cary, NC; Version 9 or later) will be used for the generation of all tables, graphs, and statistical analyses. All summaries will be presented by initial checkpoint immunotherapy, unless otherwise stated. Descriptive summaries for continuous variables will include the number of observations, mean, standard deviation, standard error (as appropriate), median, minimum, and maximum. Descriptive summaries for categorical variables will include the number and percentage of patients in each category.

6.2. Analysis Populations

6.2.1. Safety Population

The safety population includes all patients receiving at least 1 dose of study drug in any phase of the study.

6.2.2. Intent-to-Treat Population

The intent-to–treat population will include all patients enrolled in either phase of the study. Patients with uveal melanoma will be summarized separately within the ITT population.

6.2.3. Efficacy Evaluable (EE) Population (without Uveal Melanoma)

The EE population consists of patients who received at least one dose of phase 2 study treatment and had at least 1 post-baseline response evaluation in the range of subject numbers (010 through 111). The EE population only includes patients where pembrolizumab is their initial checkpoint immunotherapy who do not have uveal melanoma and who are not in the biopsy cohort.

6.2.4. Efficacy Evaluable Including Biopsy Cohort (EEBC) Population (without Uveal Melanoma)

The EEBC population consists of patients who received at least one dose of phase 2 study treatment and had at least 1 post-baseline response evaluation in the range of subject numbers (010 through 132). The EEBC population only includes patients where pembrolizumab is their initial checkpoint immunotherapy who do not have uveal melanoma.

7. BASELINE, EXPOSURE, AND DISPOSITION VARIABLES AND ANALYSES

Unless otherwise stated, all analyses in this section will be performed on the safety population and presented by initial checkpoint immunotherapy. All tables based on the EEBC population will have a total column only, since, by definition, those patients initial checkpoint immunotherapy was pembrolizumab. All data that is summarized will be supported by a patient level data listing. Additional listings may be described in the relevant section.

7.1. Disposition of Patients

The number and percentage of patients as described below will be summarized for all patients by initial checkpoint immunotherapy:

- enrolled
- enrolled and not treated
- in the safety population
- who completed at least 1 cycle of treatment
- in the ITT population
- in the ITT with Uveal melanoma
- in the EE population
- in the EEBC population
- patients who were withdrawn from treatment (with a primary reason for treatment withdrawal)
- who were withdrawn from the study (with a primary reason for study withdrawal)

7.2. Demographics and Baseline Disease Characteristics

The following demographic and baseline characteristics will be summarized for the safety and EEBC populations: age, sex, race, ethnicity, weight (by gender), height, BMI, BSA, baseline ECOG performance status, and number (%) of patients with LDH above (upper limit of normal) ULN at baseline. Additionally, staging information of histological type, primary tumor (T) stage, regional lymph node (N) stage, distant metastasis (M) stage will be summarized. Current disease status will also be summarized including number of disease sites, location of sites, and current staging using descriptive statistics.

7.3. Protocol Deviations

Protocol deviations captured on the Protocol Deviation Log will be presented in the patient data listings.

7.4. Medical History

Medical history will be summarized by CTCAE grade within each body system.

7.5. Physical Exam

Baseline physical exam results will be summarized by body system and result category (normal, abnormal, clinically significant abnormal).

7.6. Concomitant Medication

For patients in the safety population, concomitant medications will be coded using the WHO Drug Dictionary and summarized by WHO drug class and WHO drug term. Results will be summarized as number and percentage of patients with concomitant medications by preferred term and WHO drug class.

7.7. Baseline Electrocardiogram (ECG)

Results from ECG at baseline will be summarized by ECG measurement (Normal, Abnormal, clinically significant abnormal). Cardiac rhythm type and overall assessment at baseline will be included in the summary.

7.8. Prior Systemic and Radiation Therapy

For patients in the safety population, prior systemic therapy will be summarized by therapy type, number of cycles, and best response. Prior radiation therapy type, duration and best response will also be summarized.

7.9. Exposure

For patients in the safety population, descriptive statistics will be provided for the number of cycles started, number of cycles completed, duration of treatment (days), average daily dose (mg) for each study medication, total dose (mg) for each study medication, and dose intensity (%) for each study medication.

- **Number of Cycles Started**: Number of cycles started will be the number of cycles with a nonzero dose of any study drug.

- **Number of Cycles Completed**: Number of cycles completed will be the number of cycles where 1 dose of ipilimumab or pembrolizumab or 2 doses of nivolumab were administered or 28 days of indoximod alone.

- **Duration of Treatment**: The number of study days between Day 1 and the last nonzero dosing record of study drug taken by the patient. If the last dosing record is non-zero and has a missing end date, then the last day of treatment is defined as the earliest of: (1) the end-of-treatment visit; (2) date of death; or, (3) the last on-study visit.

- **Total Dose**: The total dose administered across the duration of the study for each study medication as recorded on the CRF.

- **Average daily dose**: average daily dose is the total dose (mg)/duration of treatment (days)

- **Assigned Dose (use weight for each cycle):**

Ipilimumab=3 (mg) × weight (kg) (calculated for each cycle then summed to get a total)
Pembrolizumab= 2 (mg) × weight (kg) (calculated for each cycle then summed to get a total)
Nivolumab= 3 (mg) x weight (kg) OR 240 mg × 2 (calculated for each cycle then summed to get a total)

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

- **Relative Dose Intensity**:

Standard of care checkpoint immunotherapy dose intensity (%) = 100× [total dose (mg)]/[assigned dose (mg)×number of cycles]

7.10. Indoximod Compliance

For patients in the safety population, overall indoximod compliance (%) will be summarized using descriptive statistics. Compliance is calculated for each cycle for each patient as:

compliance (%) = 100 × [total dose taken(mg)]/[duration of treatment(days) × dose level (mg) × 2 (BID)]

8. EFFICACY

8.1. General Considerations

Missing observations will be handled for specific endpoints as detailed in the appropriate section of the statistical analysis plan. All time-to event efficacy analyses will be performed on the EEBC populations and ITT population. All other efficacy analysis will be performed on the EEBC population unless otherwise stated. All data that is summarized will be supported by a patient level data listing. Additional listings may described in the relevant section.

Efficacy tables will be presented by initial checkpoint immunotherapy, unless otherwise stated.

The ORR for PD-1 inhibition with pembrolizumab is listed as approximately 33% in the pembrolizumab package insert using 10 mg/kg. The exact binomial test (one-sided, alpha=.10) will be used to detect a change in ORR from 33% to 43% when combining pembrolizumab with indoximod.

8.2. Phase 1 Component Primary Endpoint

The primary endpoints of the Phase 1 component are to characterize the RLTs and to determine the RP2D of indoximod when administered with a standard of care chemotherapy backbone consisting of gemcitabine plus nab-paclitaxel.

An RLT is defined in Section 4.1.

Regimen limiting toxicities (RLTs) will be summarized by indoximod dose level for patients in phase 1 by RLT category. Analysis of Phase 1 component primary endpoints will be performed on the safety population for patients in Phase 1.

8.3. Phase 2 Primary Endpoint

The primary efficacy endpoint is best overall response rate (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.

8.4. Efficacy Hypotheses

Best Overall Response Rate (Primary Endpoint): Administration of indoximod in combination with standard of care checkpoint immunotherapy improves best ORR in patients with patients with unresectable stage III or stage IV melanoma, compared to historical immune checkpoint inhibitors response rate (33%).

8.5. Analysis of the Primary Efficacy Parameter

8.5.1. Evaluation of Best Overall Response using RECIST

The best overall response is the best response from the start of the initial treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria as defined in Table 5. If patients received a second checkpoint immunotherapy, RECIST response is only determined based off the initial treatment.

8.5.1.1. RECIST Evaluation of Target Lesions

To evaluate lesion data for RECIST[3], first, the sum of the longest diameters is obtained using target lesion measurements. For any target lesion identified as a lymph node (through manual review of data by sponsor) – the shortest axis will be used in the sum calculation. Once the sum of target lesions diameters is obtained, the below criteria are applied at each visit for target response evaluation.

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

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

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

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

8.5.1.2. RECIST Evaluation of Non-Target Lesions

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

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump

target lesion status. It must be representative of overall disease status change, not a single lesion increase.

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

8.5.1.3. Evaluation of Best Overall Response using RECIST

For patients who have measurable disease, overall response will be assessed using Table 5. For patients who do not have measurable disease, overall response can be assessed using Table 6. Response rate is defined as the percentage of patients with either complete or partial response while on study. Response rates will be presented for target and non-target lesions, by initial checkpoint immunotherapy and overall, p-values (one-sided) and 90% confidence intervals based on the normal approximation to the binomial will be presented for response rates.

Table 5: RECIST Evaluation Criteria for Overall Response: For Patients with Measurable Disease (i.e., Target Disease)

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

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

Table 6: RECIST Evaluation Criteria for Overall Response: For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

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

8.5.2. Evaluation of Best Overall 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 mWHO 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 time point 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.

8.5.2.1.1. 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 (eg, due to image quality).

8.5.2.1.2. 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)

8.5.2.1.3. Definition of Overall Response (OR) using mWHO:

All subjects will have the OVERALL RESPONSE classified based on time point 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 (eg, due to image quality, inability to assess all relevant lesions, etc.) will be reported as unknown (UNK). Response rate is defined as the percentage of patients with either complete or partial response while on study. Response rates will be presented for target and non-target lesions, by initial checkpoint immunotherapy and overall, 90% confidence intervals based on the normal approximation to the binomial will be presented for response rates.

8.5.3. Overall Response using Immune Related Response Criteria (irRC)

The overall response according to the irRC is derived from time-point response assessments and documented on the case report form (based on tumor burden) as follows:

irCR: complete disappearance of all lesions (whether measureable or not, and no new lesions) confirmed by a repeat, consecutive assessment no less than 4 weeks from the date first documented

irPR: decrease in tumor burden > 50% relative to baseline confirmed by a consecutive assessment at least 4 weeks after first documentation
irSD: not meeting criteria for irCR or irPR, in absence of irPD
irPD: increase in tumor burden > 25% relative to nadir (minimum recorded tumor burden) confirmed by a repeat, consecutive assessment no less than 4 weeks from the date first documented
irRC rate is defined as the percentage of patients with either irCR or irPR while on study.

Immune related response rates will be presented for target and non-target lesions, by initial checkpoint immunotherapy and overall, and 90% confidence intervals based on the normal approximation to the binomial will be presented for response rates. The normal approximation to the binomial will be used to test that the ORR (CR+PR) ≥43%.

8.6. Analysis of the Secondary Efficacy Parameters

All secondary parameters will be based on evaluation of RECIST criteria, unless otherwise stated.

8.6.1. Progression-Free Survival

PFS will be calculated from the date of enrollment to the time of CT scan documenting relapse or other unambiguous indicator of disease development), or date of death, whichever occurs first. Patients who have no documented relapse as defined by RECIST and are still alive prior to the database lock, or who dropout prior to study end, will be censored at the date of the last radiological evidence documenting absence of relapse. PFS will be summarized for the EEBC and ITT populations.

Kaplan-Meier methods will be used to estimate the survival time distribution and the median, 25th and 75th percentiles of survival (in weeks). Confidence intervals around median survival time will be calculated using the method of Brookmeyer and Crowley[2], which is the default method within SAS version 9.3. Figures for Kaplan-Meier estimates will also be presented.

8.6.2. Disease Control Rate (DCR)

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 RECIST 1.1 criteria. DCRs will be presented by initial checkpoint immunotherapy and overall, and 95% confidence intervals based on the normal approximation to the binomial will be presented for control rates.

Duration of CR/PR/SD will be measured from the time measurement criteria are met for CR, PR or SD (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

8.6.3. Overall Survival (OS)

For all patients, OS will be calculated from the start of treatment to the time of death. Patients who are still alive prior to the database lock, or who dropout prior to study end, will be censored at the day they were last known to be alive.

The same statistical methods used for estimating PFS rates will be used to estimate OS.

8.6.4. Other Time-to-Event Endpoints (RECIST)

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

The duration of overall complete response (CR) is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

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

The duration of overall partial response (PR) is measured from the time measurement criteria are first met for PR until the first date that progressive disease is objectively documented.

Time to response is measured from start of treatment to time of PR or CR, whichever occurs first. Time to progression is measured from the start of treatment to the time of CT scan documenting relapse or other unambiguous indicator of disease development.

Time to response, time to progression and time to treatment discontinuation will also be summarized. There will be no censoring for time to treatment discontinuation.

The same statistical methods used for estimating PFS rates will be used to estimate duration of overall response, duration of complete response, duration of partial response and duration of stable disease.

9. SAFETY AND TOLERABILITY

9.1. General Considerations

All safety analysis will be performed using the safety population and presented by study phase (and dose level in phase 1) and by initial checkpoint immunotherapy, unless otherwise specified. All data that is summarized will be supported by a patient level data listing. Additional listings may be described in the relevant section.

9.2. Adverse Events

9.2.1. Adverse Event Definitions

A treatment-emergent AE (TEAE) is any AE either reported for the first time or the worsening of a pre-existing event after first dose of study drug. Analysis of AEs (as discussed below) will be limited to TEAEs, but data listings will include all AEs regardless of their timing to study drug administration.

Adverse events will be tabulated by MedDRA preferred term and system organ class. Severity of AEs will be described and graded using the NCI CTCAE version 4.03. NCI CTCAE grading reference can be found at https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

The subset of AEs considered by the investigator to be related to any study drug will be considered to be treatment-related AEs if the investigator has classified the AE as having a possible, probable, or definite relationship to any of the treatments. If the investigator does not specify the relationship of the AE to study drug, the AE will be considered to be treatment-related to all study drugs with a missing classification.

Unresolved missing values for causality and severity will be handled according to the following rules:

- An unresolved missing causality will be considered treatment-related
- An unresolved missing severity will be identified as an unknown severity

For purposes of analysis, all AEs will be considered a TEAE unless the AE can unequivocally be defined as not treatment-emergent. Therefore, an unresolved missing onset date will be considered treatment-emergent, with the following exceptions:

- If the stop/resolution date is before the date of the first dose on Day 1, then the AE will be considered as not being treatment-emergent.
- If both the month and day are missing, and the last day of the year is before the date of the first dose on Day 1, then the AE will not be considered treatment-emergent.

- If only the day is missing, and the last day of the month is before the date of the first dose on Day 1, then the AE will not be considered treatment-emergent.

- If only the day is missing, and the first day of the month is after the date of the first dose on Day 1, then the AE will be considered treatment emergent.

9.2.2. Adverse Event Summaries

An overall summary of AEs by phase and initial checkpoint immunotherapy will include (phase 1 will be presented by indoximod dose level):

- Number (%) of patients reporting any TEAEs
- Number (%) of patients reporting any indoximod-related AEs
- Number (%) of patients reporting any pembrolizumab-related AEs
- Number (%) of patients reporting any ipilimumab-related AEs
- Number (%) of patients reporting any nivolumab-related AEs
- Number (%) of patients reporting any treatment regimen-related AEs
- Number (%) of patients reporting any SAEs
- Number (%) of patients reporting any Grade 3 or 4 AEs
- Number (%) of patients who discontinued treatment because of AEs
- Number (%) of patients who withdrew from study because of an AE
- Number (%) of patients who had a fatal AE (CTCAE Grade 5)

The following summaries will be produced by study phase (all tables for phase 1 will be reported by indoximod dose level):

- Number (%) of patients reporting TEAEs by system organ class and preferred term.
- Number (%) of patients reporting Serious TEAEs by system organ class and preferred term.
- Number (%) of patients reporting CTCAE Grade 3 or 4 TEAEs by system organ class and preferred term.
- Number (%) of patients reporting CTCAE Grade 3 or 4 indoximod-related TEAEs by system organ class and preferred term.
- Number (%) of patients reporting TEAEs by CTCAE Grade system organ class and preferred term.
- Number (%) of patients reporting Fatal AEs by system organ class and preferred term.
- Number (%) of patients reporting indoximod-related AEs by system organ class and preferred term.

- Number (%) of patients reporting Indoximod-related Serious AEs by system organ class and preferred term.
- Number (%) of patients reporting pembrolizumab-related AEs by system organ class and preferred term.
- Number (%) of patients reporting ipilimumab-related AEs by system organ class and preferred term.
- Number (%) of patients reporting nivolumab-related AEs by system organ class and preferred term.
- Number (%) of patients reporting treatment regimen-related AEs by system organ class and preferred term.
- Number (%) of patients reporting treatment-emergent AEs by preferred term in descending order of frequency.
- Number (%) of patients reporting treatment-regimen related treatment emergent AEs by preferred term in descending order of frequency.

The TEAEs occurring in ≥ 5% of the safety population are called frequently reported AEs and will be summarized by MedDRA preferred term for all TEAEs as well as indoximod related TEAEs. Treatment regimen-related AEs are AEs that are related to any of the study treatments: indoximod, pembrolizumab, ipilimumab or nivolumab.

Separate listings will be provided for patients with the following types of AEs: SAEs, Fatal AEs, Grade 3 or 4 AEs, Indoximod Related AEs, treatment regimen-related AEs, treatment regimen-related AEs Grade 3 or 4, and AEs leading to treatment discontinuation.

9.3. Clinical Laboratory Tests

9.3.1. Laboratory Value Definitions

Laboratory values will be converted to SI units prior to summarization using Appendix B. Additionally, WBC differentials will be calculated as both a cell count and a percentage of total WBC, and both will be summarized.

Chemistry, Hematology, Urinalysis and Other laboratory values and changes from baseline values will be summarized descriptively by visit. The incidence of clinically significant abnormal laboratory values and shift tables relative to baseline will also be presented. In the event of repeat values on a given study day, the last non-missing value based on the time of the sample will be used for tabulation.

9.4. Vital Signs

The actual value and change from baseline to each visit will be summarized for vital signs (systolic blood pressure, diastolic blood pressure, heart rate, respiration rate, and body temperature). Potentially clinically significant vital sign abnormalities are defined in Table 7.

The number and percent of patients with potentially clinically significant post-baseline vital sign values will be summarized over all post-baseline visits.

Separate listings for patients with potentially clinically significant values will be provided.

Table 7: Criteria for Potentially Clinically Significant (PCS) Vital Sign Abnormalities

	PCS – Low if:			PCS – High if:		
	Observed Value is:	**AND**	**Decrease from Baseline is:**	**Observed Value is:**	**AND**	**Increase from Baseline is:**
Systolic Blood Pressure	<90 mmHg		≥20 mmHg	>180 mmHg		≥20 mmHg
Diastolic Blood Pressure	<50 mmHg		≥10 mmHg	>105 mmHg		≥10 mmHg
Heart Rate	<50 bpm		≥15 bpm	>120 bpm		≥15 bpm

9.5. ECOG Performance Status

Assessment categories for ECOG performance status can be found in Appendix C. ECOG performance status will be summarized by visit. Additionally, shifts in ECOG from baseline to worst post-baseline and last assessment will be presented.

10. CHANGES TO PROTOCOL DEFINED ANALYSES

According to the protocol, the 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 and was assessed according to irRC, as well as separately by mWHO criteria. In addition to mWHO and irRC, the response will also be evaluated using RECIST 1.1 criteria for the primary analysis of this study, with mWHO and irRC as supportive assessments. RECIST criteria will be derived using tumor measurements as described in section 8.5.1.

Additionally, protocol section 14.8 states that "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." The decision was made to not present data for the ATP population.

In the protocol, section 14.3.1 states the following:

"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."

While this was the initial intent of the study, there were not enough patients who met this criteria (n=15) due to the change in clinical practice of physician's choosing pembrolizumab over ipilimumab as first line therapy in this patient population. Therefore, the statistical testing was changed to compare the ORR for pembrolizumab in ipilimumab-naïve patients with advanced melanoma, which is around 33% on 10 mg/kg every 3 weeks, according to the pembrolizumab package insert. See section 8.1 for changes.

11. REFERENCES

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12. PLANNED TABLES, LISTINGS, AND FIGURES

12.1. Tables

Table No	Title	Population
14.1.1	Patient Disposition by Study Phase and Initial Immune Checkpoint Therapy	All Patients
14.1.2.1	Summary of Demographics and Baseline Disease Characteristics by Study Phase and Initial Immune Checkpoint Therapy	Safety Population
14.1.2.2	Summary of Demographics and Baseline Disease Characteristics by Initial Immune Checkpoint Therapy	EEBC Population
14.1.3	Summary of Histology by Study Phase and Initial Immune Checkpoint Therapy	Safety Population
14.1.4	Summary of Medical History by Study Phase and Initial Immune Checkpoint Therapy	Safety Population
14.1.5	Summary of Baseline Physical Examination by Study Phase and Initial Immune Checkpoint Therapy	Safety Population
14.1.6	Summary of Concomitant Medications by Study Phase and Initial Immune Checkpoint Therapy	Safety Population
14.1.7	Summary of Electrocardiogram Results (ECG) at Baseline by Study Phase and Initial Immune Checkpoint Therapy	Safety Population
14.1.8	Summary of Prior Systemic Therapy by Study Phase and Initial Immune Checkpoint Therapy	Safety Population
14.1.9	Summary of Prior Radiation Therapy by Study Phase and Initial Immune Checkpoint Therapy	Safety Population
14.1.10.1	Summary of Exposure to Indoximod by Study Phase	Safety Population
14.1.10.2	Summary of Exposure to Pembrolizumab by Study Phase	Safety Population
14.1.10.3	Summary of Exposure to Ipilimumab by Study Phase	Safety Population
14.1.10.4	Summary of Exposure to Nivolumab by Study Phase	Safety Population
14.1.11	Summary of Regimen Limiting Toxicities Phase 1 Only	Safety Population
14.2.1.1	Best Overall Response Using RECIST Criteria	EEBC Population
14.2.1.2	Best Overall Response Using RECIST Criteria by Study Phase and Initial Immune Checkpoint Therapy	ITT Population
14.2.1.3	Best Overall Response Using mWHO Criteria	EEBC Population
14.2.1.4	Best Overall Response Using mWHO Criteria by Study Phase and Initial Immune Checkpoint Therapy	ITT Population
14.2.1.5	Best Overall Response Using irRC Criteria	EEBC Population
14.2.1.6	Best Overall Response Using irRC Criteria by Study Phase and Initial Immune Checkpoint Therapy	ITT Population
14.2.2.1	Summary of Progression-free Survival Using RECIST Criteria	EEBC Population
14.2.2.2	Summary of Progression-free Survival Using RECIST Criteria by Study Phase and Initial Immune Checkpoint Therapy	ITT Population
14.2.3.1	Summary of Disease Control Rate Using RECIST Criteria	EEBC Population
14.2.3.2	Summary of Disease Control Rate Using RECIST Criteria by Study Phase and Initial Immune Checkpoint Therapy	ITT Population
14.2.3.3	Summary of Duration of Disease Control Rate Criteria (CR/PR/SD) Using RECIST Criteria	EEBC Population
14.2.3.4	Summary of Duration of Disease Control Rate Criteria (CR/PR/SD) Using RECIST Criteria by Study Phase and Initial Immune Checkpoint Therapy	ITT Population
14.2.4.1	Summary of Overall Survival	EEBC Population
14.2.4.2	Summary of Overall Survival by Study Phase and Initial Immune Checkpoint Therapy	ITT Population
14.2.5.1	Summary of Duration of Overall Response Using RECIST Criteria	EEBC Population

Table No	Title	Population
14.2.5.2	Summary of Duration of Overall Response Using RECIST Criteria by Study Phase and Initial Immune Checkpoint Therapy	ITT Population
14.2.6.1	Summary of Duration of Complete Response Using RECIST Criteria	EEBC Population
14.2.6.2	Summary of Duration of Complete Response Using RECIST Criteria by Study Phase and Initial Immune Checkpoint Therapy	ITT Population
14.2.7.1	Summary of Duration of Stable Disease Using RECIST Criteria	EEBC Population
14.2.7.2	Summary of Duration of Stable Disease Using RECIST Criteria by Study Phase and Initial Immune Checkpoint Therapy	ITT Population
14.2.8.1	Summary of Duration of Partial Response Using RECIST Criteria	EEBC Population
14.2.8.2	Summary of Duration of Partial Response Using RECIST Criteria by Study Phase and Initial Immune Checkpoint Therapy	ITT Population
14.2.9	Summary of Time to Response Using RECIST Criteria by Study Phase and Initial Immune Checkpoint Therapy	ITT Population
14.2.10	Summary of Time to Progression Using RECIST Criteria by Study Phase and Initial Immune Checkpoint Therapy	ITT Population
14.2.11	Summary of Time to Treatment Discontinuation Using RECIST Criteria by Study Phase and Initial Immune Checkpoint Therapy	ITT Population
14.3.1	Overall Summary of Treatment-Emergent Adverse Events by Study Phase and Initial Immune Checkpoint Therapy	Safety Population
14.3.2.1	Summary of Treatment-Emergent Adverse Events By MedDRA System Organ Class, Preferred Term, Study Phase and Initial Immune Checkpoint Therapy	Safety Population
14.3.2.2	Summary of Serious Treatment-Emergent Adverse Events By MedDRA System Organ Class, Preferred Term, Study Phase and Initial Immune Checkpoint Therapy	Safety Population
14.3.2.3	Summary of CTCAE Grade 3 and 4 Treatment-Emergent Adverse Events By MedDRA System Organ Class, Preferred Term, Study Phase and Initial Immune Checkpoint Therapy	Safety Population
14.3.2.4	Summary of CTCAE Grade 3 and 4 Indoximod-Related Treatment-Emergent Adverse Events By MedDRA System Organ Class, Preferred Term, Study Phase and Initial Immune Checkpoint Therapy	Safety Population
14.3.2.5	Summary of Treatment-Emergent Adverse Events By MedDRA System Organ Class, Preferred Term, CTCAE Grade, Study Phase and Initial Immune Checkpoint Therapy	Safety Population
14.3.2.6	Summary of Fatal Adverse Events By MedDRA System Organ Class, Preferred Term, Study Phase and Initial Immune Checkpoint Therapy	Safety Population
14.3.2.7	Summary of Indoximod-Related Treatment-Emergent Adverse Events By MedDRA System Organ Class, Preferred Term, Study Phase and Initial Immune Checkpoint Therapy	Safety Population
14.3.2.8	Summary of Indoximod-Related Serious Treatment-Emergent Adverse Events By MedDRA System Organ Class, Preferred Term, Study Phase and Initial Immune Checkpoint Therapy	Safety Population
14.3.2.9	Summary of Pembrolizumab -Related Treatment-Emergent Adverse Events By MedDRA System Organ Class, Preferred Term, Study Phase and Initial Immune Checkpoint Therapy	Safety Population
14.3.2.10	Summary of Ipilimumab-Related Treatment-Emergent Adverse Events By MedDRA System Organ Class, Preferred Term, Study Phase and Initial Immune Checkpoint Therapy	Safety Population
14.3.2.11	Summary of Nivolumab -Related Treatment-Emergent Adverse Events By MedDRA System Organ Class, Preferred Term, Study Phase and Initial Immune Checkpoint Therapy	Safety Population

Table No	Title	Population
14.3.2.12	Summary of Treatment Emergent Adverse Events By MedDRA Preferred Term in Decreasing Order of Frequency, Study Phase and Initial Immune Checkpoint Therapy	Safety Population
14.3.2.13	Summary of Treatment Regimen-Related Adverse Events By MedDRA Preferred Term in Decreasing Order of Frequency, Study Phase and Initial Immune Checkpoint Therapy	Safety Population
14.3.2.14	Summary of Frequently Reported (>=5%) Treatment Emergent Adverse Events By MedDRA Preferred Term in Decreasing Order of Frequency by Study Phase and Initial Immune Checkpoint Therapy	Safety Population
14.3.2.15	Summary of Frequently Reported (>=5%) Indoximod-Related Treatment Emergent Adverse Events By MedDRA Preferred Term in Decreasing Order of Frequency by Study Phase and Initial Immune Checkpoint Therapy	Safety Population
14.3.3.1	Summary of Hematology Laboratory Values and Change from Baseline by Visit, Study Phase and Initial Immune Checkpoint Therapy	Safety Population
14.3.3.2	Shift Table of Hematology Values - To the Worst Abnormal Value by Study Phase and Initial Immune Checkpoint Therapy	Safety Population
14.3.3.3	Summary of Clinically Significant Abnormal Hematology Laboratory Values by Study Phase and Initial Immune Checkpoint Therapy	Safety Population
14.3.3.4	Summary of Chemistry Laboratory Values and Change from Baseline by Visit, Study Phase and Initial Immune Checkpoint Therapy	Safety Population
14.3.3.5	Shift Summary of Chemistry Values - To the Worst Abnormal Value by Study Phase and Initial Immune Checkpoint Therapy	Safety Population
14.3.3.6	Summary of Clinically Significant Abnormal Chemistry Laboratory Values by Study Phase and Initial Immune Checkpoint Therapy	Safety Population
14.3.3.7	Summary of Urinalysis Laboratory Results by Visit, Study Phase and Initial Immune Checkpoint Therapy	Safety Population
14.3.3.8	Summary of Other Laboratory Values and Change from Baseline by Visit, Study Phase and Initial Immune Checkpoint Therapy	Safety Population

Table No	Title	Population
14.3.4.1	Summary of Vital Sign Values and Change from Baseline by Visit, Study Phase and Initial Immune Checkpoint Therapy	Safety Population
14.3.4.2	Summary of Potentially Clinically Significant Vital Sign Abnormalities by Study Phase and Initial Immune Checkpoint Therapy	Safety Population
14.3.5.1	Summary of ECOG Status by Visit, Study Phase and Initial Immune Checkpoint Therapy	Safety Population
14.3.5.2	Shift Summary of ECOG Status from Baseline to Worst Post-Baseline Status by Study Phase and Initial Immune Checkpoint Therapy	Safety Population

12.2. Figures

Figure No	Title	Population
14.4.1	Kaplan-Meier Plot of Overall Survival	EEBC Population
14.4.2	Kaplan-Meier Plot of Progression-free (RECIST) Survival	EEBC Population
14.4.3	Kaplan-Meier Plot of Duration of DCR Criteria (CR/PR/SD)	EEBC Population
14.4.4	Kaplan-Meier Plot of Duration of Overall Response (RECIST)	EEBC Population
14.4.5	Kaplan-Meier Plot of Duration of Overall Complete Response (RECIST)	EEBC Population
14.4.6	Kaplan-Meier Plot of Duration of Stable Disease (RECIST)	EEBC Population

12.3. Listings

Listing No	Title
16.1.1	Patient Enrollment and Disposition Status
16.1.2	Patient Demographics
16.1.3	End of Treatments/Study
16.1.4	Medical History
16.1.5	Staging
16.1.6	Protocol Deviations/Violations
16.1.7	Physical Exam Findings at Baseline
16.1.8	ECOG Performance Status
16.1.9	Concomitant Medications
16.1.10	Concomitant Procedures
16.1.11	Prior Systemic Therapy
16.1.12	Prior Radiation therapy
16.1.13	Additional Imaging
16.2.1	Study Drug Compliance
16.2.2	Study Drug Exposure
16.2.3	Pembrolizumab, Ipilimumab and Nivolumab Administration
16.2.4	Indoximod Administration
16.3.1	Regimen Limiting Toxicities
16.3.2	RECIST Response
16.3.3	Index Lesions (mWHO and irRC)
16.3.4	New Measurable Lesions (irRC)
16.3.5	irRC Response
16.3.6	mWHO Response
16.3.7	Non-Index Lesions (mWHO)
16.3.8	Survival Status
16.3.9	Death Report Information
16.3.10	Overall Survival, Progression-Free and Other Survival Events and Assessments

Listing No	Title
16.4.1	Adverse Events
16.4.2	Serious Adverse Events
16.4.3	Fatal Adverse Events
16.4.4	Grade 3 or 4 Adverse Events
16.4.5	Grade 3 or 4 Indoximod-Related Adverse Events
16.4.6	Indoximod-Related Adverse Events
16.4.7	Pembrolizumab-Related Adverse Events
16.4.8	Ipilimumab-Related Adverse Events
16.4.9	Nivolumab-Related Adverse Events
16.4.10	Adverse Events Causing Treatment Discontinuation
16.5.1	Chemistry Laboratory Values
16.5.2	Abnormal Chemistry Laboratory Values
16.5.3	Hematology Laboratory Values
16.5.4	Abnormal Hematology Laboratory Values
16.5.5	Urinalysis Laboratory Values
16.5.6	Other Laboratory Values
16.5.7	Pregnancy Test Results
16.6.1	Vital Signs
16.6.2	Abnormal Vital Sign Values
16.7.1	12-Lead ECG Values and Interpretation
16.7.2	Abnormal 12-Lead ECG Values

APPENDIX A. CLINICAL LABORATORY TESTS

Serum Chemistry	Hematology	Urinalysis	Other
Alkaline phosphatase	WBC Count	Specific Gravity	C-reactive protein
ACTH	Neutrophil	Protein	CA 19-9
ALT/SGPT	Eosinophil	Glucose	LH
Albumin	Basophil	pH	FSH
Amylase	Monocyte	Ketones	Carcinoembryonic Antigen (CEA)
AST/SGOT	Lymphocyte	Bacteria	INR
Bicarbonate	Hemoglobin	RBC	PT
BUN	Hematocrit	WBC	PTT
Calcium	Platelet		
Chloride			
Creatinine			
Electrolytes			
Free T4			
Glucose			
Lipase			
LDH			
Magnesium			
Phosphate			
Potassium			
Sodium			
Direct Bilirubin			
Indirect Bilirubin			
Total Bilirubin			
Total Protein			
TSH			

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen

APPENDIX B. CLINICAL LABORATORY CONVERSION FACTORS*

Analyte	Conventional Units	Conversion (mult. by)	SI Units
CHEMISTRY			
Alkaline phosphatase	U/L	1	U/L
ALT	U/L	1	U/L
AST	U/L	1	U/L
Bicarbonate	mEq/L	1	mmol/L
BUN	mg/dL	0.3571	mmol/L
Calcium	mg/dL	0.25	mmol/L
Chloride	mEq/L	1	mmol/L
Creatinine	mg/dL	88.4	µmol/L
Glucose	mg/dL	0.055	mmol/L
Potassium	mEq/L	1	mmol/L
Sodium	mEq/L	1	mmol/L
Total Bilirubin	mg/dL	17.1	µmol/L
HEMATOLOGY			
WBC Count/differentials	$10^3/mm^3$	1	10^9/L
Hemoglobin	g/dL	10	g/L
Hemoglobin	Mmol/L	10.61	g/L
Platelet	$10^3/mm^3$	1	10^9/L

*An external document will be created to incorporate all labs and their conversion factors to SI Units, if necessary.

APPENDIX C. PERFORMANCE STATUS CRITERIA

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