PROTOCOL NUMBER:	**NLG2107**
TITLE:	**A Phase 2/3 (Adaptive Design) Study of the Concomitant Administration of Indoximod or Placebo plus Pembrolizumab or Nivolumab in Adult Patients with Unresectable Stage III or Stage IV Malignant Melanoma**
STUDY PHASE:	**2/3**
INVESTIGATIONAL PRODUCT:	**INDOXIMOD**
IND #	[redacted]
CLINICALTRIALS.GOV#	**NCT03301636**
SPONSOR:	NewLink Genetics Corporation 2503 South Loop Drive, Suite 5100 Ames, IA 50010
STUDY DIRECTOR:	Eugene Kennedy, MD Chief Medical Officer NewLink Genetics Corporation
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PROTOCOL REVISION:	**Version 4.0 Global**
VERSION DATE:	**27-AUG-2018**

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(see confidentiality statement page 3)

This Version 4.0 of the protocol number NLG2107 has been prepared and reviewed by the Sponsor for distribution to designated clinical sites, associated Institutional Review Boards (IRB)/Ethic Committees, designated contractors, regulatory agencies, and with permission by the Sponsor. This version of the protocol shall supersede all previous draft versions of the specified protocol.

[redacted] 29 Aug 2018

Eugene Kennedy, MD, FACP
Chief Medical Officer

Date

Medical Monitor Name and Contact Information

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INVESTIGATOR ACKNOWLEDGEMENT

I have received and read the Investigator's Brochure for indoximod and this protocol NLG2107, including all appendices, and agree to make all reasonable efforts to adhere to the protocol. I agree to conduct the study in compliance with all applicable US FDA regulations (including 21 CFR Parts 312, 50 and 54), ICH Good Clinical Practice (GCP), and any locally applicable regulations. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

I agree that, prior to the commencement of this study, I must obtain all required Institutional approvals including Independent Ethics Committee/ Institutional Review Board associated with the clinical facility where the study will be conducted for this protocol and the informed consent document.

I will provide all study personnel under my supervision with copies of this protocol, the indoximod Investigator's Brochure, and access to all study-related information provided by the Sponsor and designated CRA. I will discuss this study-related information with my staff to ensure that they are fully informed about the investigational product and the protocol.

I agree to provide all Subjects with a signed and dated copy of the informed consent document, as required by FDA regulations and ICH GCP. I further agree to report to NewLink Genetics any adverse events in accordance with the terms of this protocol, as per the applicable regulations from US FDA regulation 21 CFR 312.64 where applicable.

Principal Investigator Printed Name	Site Number
Principal Investigator Signature	Date

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment Version 4.0	*27-AUG-2018*
Amendment Version 3.0 Global	*30-MAR-2018*
Amendment Version 2.0 Global (2.1 UK Specific)	*28-DEC-2017*
Amendment Version 2.0	*07-NOV-2017*
Amendment Version 1.1	*18-SEP-2017*
Original Protocol (Version 1.0)	*21-AUG-2017*

Amendment V4.0, 27-AUG-2018

Overall Rationale for the Amendment:

1. To modify the protocol to reflect only the phase 2 dose escalation portion of the study is proceeding. The double-blind phase 3 portion will no longer be implemented.
2. To allow the transition of current subjects on the Phase 2 dose level 1 (600mg) indoximod dose cohort to transition from the indoximod HCl F1 tablets over to the indoximod HCl F2 tablets.
3. To make minor edits and administrative changes

Summary of Revisions

1. Cover page and running head: Updated protocol version # and date
2. Minor administrative edits throughout
3. Added the statement "With protocol Version 4: The phase 3 study will not proceed." to all applicable sections:
    a. Sections 1.1 and 1.2, 1.3.3, 1.3.4, and 1.3.5
    b. Section 2.1
    c. Section 3
    d. Sections 4.1, 4.2.2, 4.3, and 4.4.2
    e. Section 6, 6.1.1, 6.3.1, 6.3.2, 6.3.3, and 6.11
    f. Section 7.2.7, 7.2.8, and 7.7.2
    g. Section 8.1, 8.2.1, 8.4.1, 8.5.1, and 8.5.2.2
4. In Section 2.1 Study Rationale, added "The sponsor has decided not to pursue the Phase 3 portion of the trial given the recent announcement of the negative Phase 3 trial results observed in melanoma patients with another IDO inhibitor currently in development. At this time, further development of indoximod in melanoma is pending additional data from smaller scale trials."
5. In Section 6.1.1, clarified that with protocol Version 4, subjects on the Phase 2 dose level 1 (600mg) will be transitioned over to the indoximod HCl F2 tablets after re-consent.
6. In Section 6.7, added information regarding NewLink Genetics' expanded access program.

Table of Contents

1. Protocol Summary

1.1. Synopsis

A Phase 2/3 (Adaptive Design) Study of the Concomitant Administration of Indoximod or Placebo plus Pembrolizumab or Nivolumab in Adult Patients with Unresectable Stage III or Stage IV Malignant Melanoma

Clinical Trial Protocol NLG2107

Objectives and Endpoints

Primary Objectives:

Phase 2 — To establish the Phase 3 dose of indoximod in combination with immune checkpoint inhibitor pembrolizumab or nivolumab in adult patients with unresectable stage III or stage IV malignant melanoma – an open label evaluation of [redacted] safety and tolerability of the combined treatment.

Phase 3 — **With protocol Version 4: The phase 3 study will not proceed.**

Secondary Objectives:

Phase 3 — **With protocol Version 4: The phase 3 study will not proceed.**

Overall Design:

Phase 2 — Phase 2, open-label, dose-escalation study to establish the Phase 3 dose of indoximod given in combination with pembrolizumab or nivolumab – study assessing the [redacted] safety and tolerability of indoximod plus pembrolizumab or nivolumab (combination therapy) in adult patients with unresectable stage III or stage IV malignant melanoma

Phase 3 — **With protocol Version 4: The phase 3 study will not proceed.**

Primary Endpoints: The co-primary endpoints are:

Progression-free survival (PFS) time which is defined as time from date of randomization until the earliest date of disease progression per RECIST 1.1, or death from any cause, whichever comes first. Patients who have neither progressed nor died will be censored at the last tumor assessment date for the endpoint PFS and will be assessed per RECIST 1.1.

OS is defined as the time from the date of randomization until death from any cause. Any patient not known to have died at the

time of analysis will be censored based on the last recorded date on which the patient was known to be alive.

Secondary Endpoints:

Objective response rate: The first tumor assessment test will be conducted at 9 weeks (+/- 1 week) followed by assessments every 9 weeks (+/- 1 week) for duration of study participation. Defined as the proportion of subjects who have best response as complete response or partial response based on RECIST 1.1.

Safety and tolerability:
As assessed by percentage of subjects with adverse events, through up to 30 days after end of treatment and

As assessed by percentage of subjects with changes in laboratory parameters, through up to 30 days after end of treatment.

Number of Participants:

Phase 2	12-18 subjects (depending on dose escalation) – 3 to 6 per dose level
Phase 3	600 subjects (**With protocol Version 4: The phase 3 study will not proceed**.**)**

Treatment and Study Duration:

The maximum treatment duration for individual patients will be 24 months of treatment.

The duration of the overall study is projected to be 34 months (from first patient first visit to last patient last visit).

1.2. Study Schema

Phase 2

Table below summarizes dose levels of indoximod and pembrolizumab or nivolumab for the Phase 2 study. The Phase 2 study will be completed in the United States and therefore the fixed doses of pembrolizumab and nivolumab will be used as provided below.

Dose Level	Indoximod (oral)	Pembrolizumab Dose (IV)	Nivolumab Dose (IV)
1	600 mg Q12 hours	200 mg IV Q3 weeks	240 mg IV Q2 weeks
2	1200 mg Q12 hours	200 mg IV Q3 weeks	240 mg IV Q2 weeks
3	1800 mg Q12 hours	200 mg IV Q3 weeks	240 mg IV Q2 weeks

Dosing regimen: Dosing cycles will be 21 days in length during combination immunotherapy (indoximod plus pembrolizumab) and will be 14 days in length during combination immunotherapy (indoximod plus nivolumab). Pembrolizumab will be dosed on the 1st day of each 21-day cycle. Nivolumab will be dosed on the 1st day of each 14-day cycle. Indoximod will be given as a single dose on Cycle 1 Day 1 and then blood for [redacted] testing will be collected at designated timepoints for the next 3 days. Indoximod will then be dosed twice daily on all days of each cycle.

Phase 3 - With protocol Version 4: The phase 3 study will not proceed.

Once a dose for indoximod in combination with pembrolizumab/nivolumab is established in Phase 2, an additional 600 patients will be enrolled in a two-arm, randomized, double-blind, placebo-controlled, fixed-dose Phase 3 study. Treatment will be initiated using standard of care (SOC) immune checkpoint inhibition consisting of pembrolizumab or nivolumab in combination with indoximod or placebo.

Three possible treatment schedules are available depending on the checkpoint inhibitor and frequency of administration that is chosen by the study physician.

Schedule	Checkpoint Inhibitor*	Indoximod/Placebo
A	Pembrolizumab IV every 3 weeks	Given orally every 12 hours
B	Nivolumab IV every 2 weeks	Given orally every 12 hours
C	Nivolumab IV every 4 weeks	Given orally every 12 hours

*Dose to be as per package insert/approved label in country of treatment

RANDOMIZATION SCHEMA - With protocol Version 4: The phase 3 study will not proceed.

Randomization stratified by:

- Choice of checkpoint inhibitor (pembrolizumab vs nivolumab)
- Prior BRAF inhibitor treatment
- Stage at randomization (Stage III/M1a/M1b vs M1c/M1d)

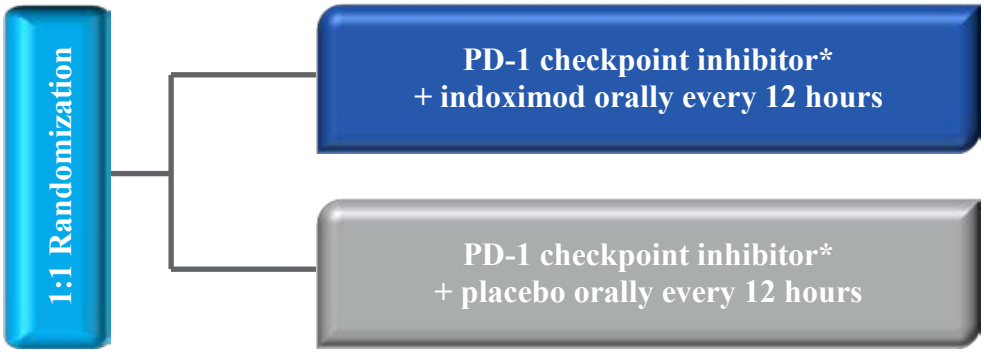
Criteria for M1 status:

M1a – Metastases to skin, subcutaneous, or distant lymph nodes (M1a, M1a(0), and M1a(1))

M1b – Metastases to lung (M1b, M1b(0), and M1b(1))

M1c – Metastases to all other visceral sites (non-central nervous system) sites (M1c, M1c(0), and M1c(1))

M1d – Distant metastasis to central nervous system (M1d, M1d(0), and M1d(1))



*Standard-of-care dosing of pembrolizumab or nivolumab per country

Note: On study treatment must be initiated within 5 days after randomization.

1.3. Schedule of Activities (SoA)

1.3.1. Phase 2 Schedule A: Pembrolizumab Q3 weeks plus Indoximod Q12 hours 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			End of Tx Visit
		D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	
		Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	
Pembrolizumab		A			A			A			A			
Indoximod		B			B			B			B			
Informed consent	X													
Demographics	X													
Medical history	X													
Concomitant meds	X	X	X	X	X			X			X			X
Physical exam	X	X	X	X	X			X			X			X
Vital signs	X	X	X	X	X			X			X			X
Height	X													
Weight	X	X			X			X			X			X
ECOG PS	X	X	X	X	X			X			X			X
CBC w/diff, plts	X	X	X	X	X			X			X			X
Serum chemistry	D	D	X	X	D			D			D			D
INR, PT/PTT	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												X
ECG	E	E			E									E
[redacted]	[redacted]													
[redacted]		[redacted]			[redacted]						[redacted]			
AE evaluation	X	X ---------- X												X
Radiologic Tumor measurements	X	**Radiologic evaluations should be performed every 9 weeks (+/- 1 week) and whenever disease progression is suspected** (H)												
Pregnancy Tests	I	I			I			I			I			I
Archival tumor tissue	J													

Phase 2 Schedule A Notes:

A: **Pembrolizumab** 200mg IV Q3 weeks

B: **Indoximod: Dose TBD** mg PO Q12 hours administered daily throughout study, dispensed on day 1 of each cycle. Cycles are 21 days each when given in combination with pembrolizumab.

D: Albumin, alkaline phosphatase, total bilirubin, BUN, calcium, magnesium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium. Liver function tests (AST, ALT, T Bili) must be performed within 3 days prior to each pembrolizumab administration. The results of these tests must be reviewed by the investigator (or designee) prior to dosing.

E: Triplicate ECGs (3 reads approximately 2-4 minutes apart) per [redacted] collection schedule per Section 7.7

F: If not previously completed, must be completed prior to enrollment.

[redacted]

H: CT/MRI of brain, chest, and abdomen required at baseline. CT/MRI of chest and abdomen required at each tumor assessment. Additional anatomic regions required when there is known or clinical suspicion of disease. 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.

I: Pregnancy test (women of childbearing potential) must be completed within 72 hours prior to first study treatment and every 3 weeks (day 1 of each cycle) during treatment.

[redacted]

Required Observations following the completion/discontinuation 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**
Med History	X	X	X	X	X	X	X	X
Physical Exam (VS, Wt, ECOG PS)	X	X	X	X	X	X	X	X
CBC w/diff/ Chemistry	Per standard of care schedule							
Disease Imaging	Q9 weeks (+/- 1 week) until disease progression. Per standard of care schedule after progression							
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 Meds	Capture all concomitant medication for 30 days after last dose of treatment.							

1.3.2. Phase 2 Schedule B: Nivolumab Q2 weeks plus Indoximod Q12 hours 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		Cycle 5		Cycle 6 and Subsequent		End of Tx Visit
		D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	
		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		A		A		A		A		A		A		
Indoximod		B				B				B		B		
Informed consent	X													
Demographics	X													
Medical history	X													
Concomitant meds	X	X	X	X	X	X		X		X		X		X
Physical exam	X	X	X	X	X	X		X		X		X		X
Vital signs	X	X	X	X	X	X		X		X		X		X
Height	X													
Weight	X	X				X				X		X		X
ECOG PS	X	X	X	X	X	X		X		X		X		X
CBC w/diff, plts	X	X	X	X	X	X		X		X		X		X
Serum chemistry	D	D	D	D	D	D		D		D		D		D
INR, PT/PTT	X													X
Amylase, lipase	X	X		X		X		X		X		X		
LH, FSH	X	X		X		X		X		X		X		
Free T4,TSH, ACTH	X	X		X		X		X		X		X		
Urinalysis	X	Completed if clinically indicated												X
ECG	E	E		E										E
[redacted]	[redacted]													
[redacted]		[redacted]		[redacted]				[redacted]				[redacted]		
AE evaluation	X	X----------X												X
Radiologic Tumor measurements	X	**Radiologic evaluations should be performed every 9 weeks (+/- 1 week) and whenever disease progression is suspected. (H)**												
Pregnancy test	I	I				I				I		I		I
[redacted]	[redacted]													

Phase 2 Schedule B Notes:

A: **Nivolumab** 240 mg IV Q2 weeks

B: **Indoximod:** **Dose TBD** mg PO Q12 hours administered daily throughout study, dispensed at each cycle day 1. Cycles are 14 days each when given in combination with nivolumab.

D: Albumin, alkaline phosphatase, total bilirubin, BUN, calcium, magnesium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium. Liver function tests (AST, ALT, T Bili) must be performed within 3 days prior to each nivolumab administration. The results of these tests must be reviewed by the investigator (or designee) prior to dosing.

E: Triplicate ECGs (3 reads approximately 2-4 minutes apart) per [redacted] schedule per Section 7.7

F: If not previously completed, must be completed prior to enrollment.

[redacted]

H: CT/MRI of brain, chest, and abdomen required at baseline. CT/MRI of chest and abdomen required at each tumor assessment. Additional anatomic regions required when there is known or clinical suspicion of disease. 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.

I: Pregnancy test (women of childbearing potential) must be completed within 72 hours prior to first study treatment and every 4 weeks (day 1 of every other cycle) during treatment.

[redacted]

Required Observations following the completion/discontinuation 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**
Med History	X	X	X	X	X	X	X	X
Physical Exam (VS, Wt, ECOG PS)	X	X	X	X	X	X	X	X
CBCw/diff/Chemistry	Per standard of care schedule							
Disease Imaging	Q9 weeks (+/- 1 week) until disease progression. Per standard of care schedule after progression.							
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 Meds	Capture all concomitant medication for 30 days after last dose of treatment.							

1.3.3. Phase 3 Schedule A: Pembrolizumab Q3 weeks plus Indoximod/Placebo Q12 hours until toxicity/ progression. - With protocol Version 4: The phase 3 study will not proceed.

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.

		Cycle 1			Cycle 2			Cycle 3			Cycle 4 and Subsequent Cycles			End of Tx Visit
	Pre-Study	D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	
Evaluations		Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	
Pembrolizumab		A			A			A			A			
Indoximod/Placebo		B			B			B			B			
Informed consent	X													
Demographics	X													
Medical history	X													
Concomitant meds	X	X			X			X			X			X
Physical exam	X	X			X			X			X			X
Vital signs	X	X			X			X			X			X
Height	X													
Weight	X	X			X			X			X			X
ECOG PS	X	X			X			X			X			X
[redacted]	[redacted]	[redacted]			[redacted]			[redacted]			[redacted]			[redacted]
CBC w/diff, plts	X	X			X			X			X			X
Serum chemistry	D	D			D			D			D			D
INR, PT/PTT	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												X
ECG	E	E			E			E			E			E
[redacted]	[redacted]													
[redacted]		[redacted]			[redacted]			[redacted]			[redacted]			
AE evaluation	X	X---------- X												X
Radiologic Tumor measurements	X	**Radiologic evaluations should be performed every 9 weeks (+/- 1 week) and whenever disease progression is suspected** (H)												
Pregnancy Tests	I	I			I			I			I			I
[redacted]	[redacted]													

Phase 3 Schedule A Notes:

A: **Pembrolizumab** IV Q3 weeks (dosing per package insert/approved label/ marketing authorization in country where treatment is being provided)

B: **Indoximod/Placebo:** **Dose TBD** mg PO Q12 hours administered daily throughout study, dispensed on day 1 of each cycle. Cycles are 21 days each when given in combination with pembrolizumab.

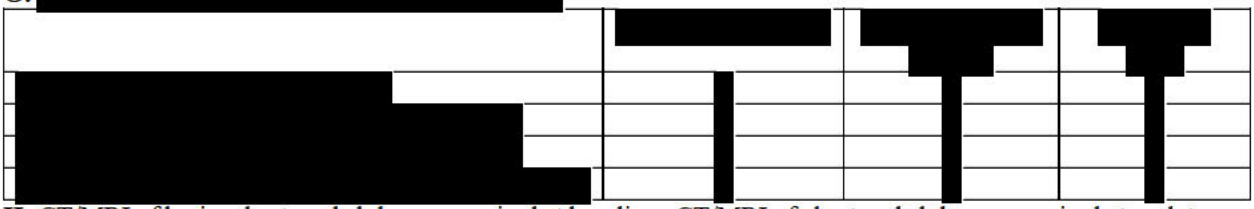
C: [redacted]

D: Albumin, alkaline phosphatase, total bilirubin, BUN, calcium, magnesium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium. Liver function tests (AST, ALT, T Bili) must be performed within 3 days prior to each pembrolizumab administration. The results of these tests must be reviewed by the investigator (or designee) prior to dosing.

E: Triplicate ECGs (3 reads approximately 2-4 minutes apart) per [redacted] (Note G below)

F: If not previously completed, must be completed prior to enrollment.

G: [redacted]



H: CT/MRI of brain, chest, and abdomen required at baseline. CT/MRI of chest and abdomen required at each tumor assessment. Additional anatomic regions required when there is known or clinical suspicion of disease. 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.

I: Pregnancy test (women of childbearing potential) must be completed within 72 hours prior to first study treatment and every 3 weeks (day 1 of each cycle) during treatment.

J: [redacted]

Required Observations following the completion/discontinuation 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**
Med History	X	X	X	X	X	X	X	X
Physical Exam (VS, Wt, ECOG PS)	X	X	X	X	X	X	X	X
CBCw/diff/Chemistry	Per standard of care schedule							
Disease Imaging	Q9 weeks (+/- 1 week) until disease progression. Per standard of care schedule after progression							
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 Meds	Capture all concomitant medication for 30 days after last dose of treatment.							

1.3.4. Phase 3 Schedule B: Nivolumab Q2 weeks plus Indoximod/Placebo Q12 hours until toxicity/ progression. - With protocol Version 4: The phase 3 study will not proceed.

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		Cycle 5		Cycle 6 and Subsequent		End of Tx Visit
		D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	
		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		A		A		A		A		A		A		
Indoximod/Placebo		B		B		B		B		B		B		
Informed consent	X													
Demographics	X													
Medical history	X													
Concomitant meds	X	X		X		X		X		X		X		X
Physical exam	X	X		X		X		X		X		X		X
Vital signs	X	X		X		X		X		X		X		X
Height	X													
Weight	X	X				X				X		X		X
ECOG PS	X	X		X		X		X		X		X		X
[redacted]	[redacted]	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]
CBC w/diff, plts	X	X		X		X		X		X		X		X
Serum chemistry	D	D		D		D		D		D		D		D
INR, PT/PTT	X													X
Amylase, lipase	X	X		X		X		X		X		X		
LH, FSH	X	X		X		X		X		X		X		
Free T4,TSH, ACTH	X	X		X		X		X		X		X		
Urinalysis	X	Completed if clinically indicated												X
ECG	E	E		E		E		E		E		E		E
[redacted]	[redacted]													
[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		
AE evaluation	X	X----------X												X
Radiologic Tumor measurements	X	**Radiologic evaluations should be performed every 9 weeks (+/- 1 week) and whenever disease progression is suspected. (H)**												
Pregnancy test	I	I				I				I		I		I
[redacted]	[redacted]													

Phase 3 Schedule B Notes:

A: **Nivolumab** IV Q2 weeks (dosing per package insert/approved label/marketing authorization in country where treatment is being provided)

B: **Indoximod/Placebo: Dose TBD** mg PO Q12 hours administered daily throughout study, dispensed at each cycle day 1. Cycles are 14 days each when given in combination with nivolumab Q2 weeks.

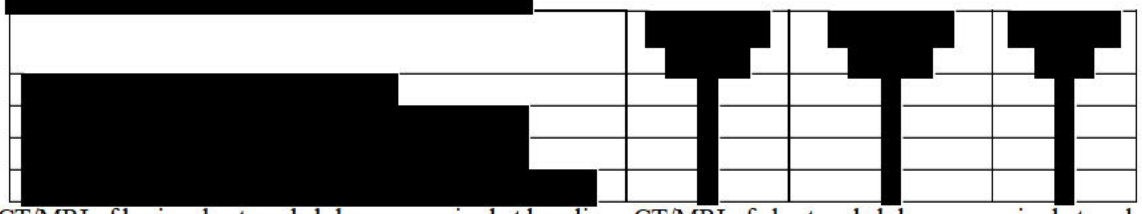
C: [redacted] to be completed in Phase 3

D: Albumin, alkaline phosphatase, total bilirubin, BUN, calcium, magnesium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium. Liver function tests (AST, ALT, T Bili) must be performed within 3 days prior to each nivolumab administration. The results of these tests must be reviewed by the investigator (or designee) prior to dosing.

E: Triplicate ECGs (3 reads approximately 2-4 minutes apart) per [redacted] schedule (Note G below)

F: If not previously completed, must be completed prior to enrollment.

G: [redacted]



H: CT/MRI of brain, chest, and abdomen required at baseline. CT/MRI of chest and abdomen required at each tumor assessment. Additional anatomic regions required when there is known or clinical suspicion of disease. 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.

I: Pregnancy test (women of childbearing potential) must be completed within 72 hours prior to first study treatment and every 4 weeks (day 1 of every other cycle) during treatment.

J: [redacted]

Required Observations following the completion/discontinuation 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**
Med History	X	X	X	X	X	X	X	X
Physical Exam (VS, Wt, ECOG PS)	X	X	X	X	X	X	X	X
CBCw/diff/Chemistry	Per standard of care schedule							
Disease Imaging	Q9 weeks (+/- 1 week) until disease progression. Per standard of care schedule after progression.							
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 Meds	Capture all concomitant medication for 30 days after last dose of treatment.							

1.3.5. Phase 3 Schedule C: Nivolumab Q4 weeks plus Indoximod/Placebo Q12 hours until toxicity/ progression. - With protocol Version 4: The phase 3 study will not proceed.

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 all subsequent cycles				End of Tx Visit
		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		A				A				A				
Indoximod/Placebo		B				B				B				
Informed consent	X													
Demographics	X													
Medical history	X													
Concomitant meds	X	X				X				X				X
Physical exam	X	X				X				X				X
Vital signs	X	X				X				X				X
Height	X													
Weight	X	X				X				X				X
ECOG PS	X	X				X				X				X
[redacted]	[redacted]	[redacted]				[redacted]				[redacted]				[redacted]
CBC w/diff, plts	X	X				X				X				X
Serum chemistry	D	D				D				D				D
INR, PT/PTT	X													X
Amylase, lipase	X	X				X				X				
LH, FSH	X	X				X				X				
Free T4,TSH, ACTH	X	X				X				X				
Urinalysis	X	Completed if clinically indicated												X
ECG	E	E				E				E				E
[redacted]	[redacted]													
[redacted]		[redacted]				[redacted]				[redacted]				
AE evaluation	X	X----------X												X
Radiologic Tumor measurements	X	**Radiologic evaluations should be performed every 9 weeks (+/- 1 week) and whenever disease progression is suspected. (H)**												
Pregnancy test	I	I				I				I				I
[redacted]	[redacted]													

Phase 3 Schedule C Notes:

A: **Nivolumab** IV Q4 weeks (dosing per package insert/approved label/marketing authorization in country where treatment is being provided)

B: **Indoximod/Placebo: Dose TBD** mg PO Q12 hours administered daily throughout study, dispensed at each cycle day 1. Cycles are 28 days each when given in combination with nivolumab Q4 weeks.

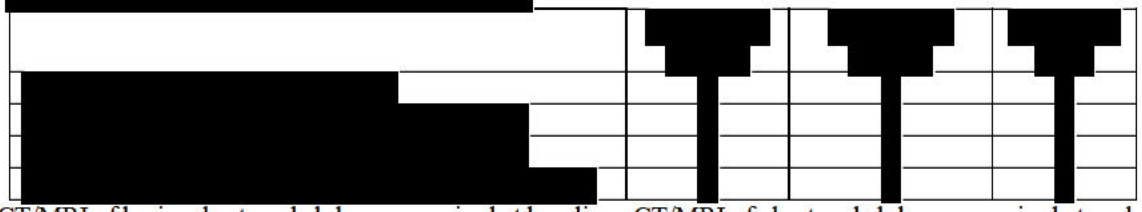
C: [redacted] be completed in Phase 3

D: Albumin, alkaline phosphatase, total bilirubin, BUN, calcium, magnesium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium. Liver function tests (AST, ALT, T Bili) must be performed within 3 days prior to each pembrolizumab administration. The results of these tests must be reviewed by the investigator (or designee) prior to dosing.

E: Triplicate ECGs (3 reads approximately 2-4 minutes apart) per [redacted] schedule (Note G below)

F: If not previously completed, must be completed prior to enrollment.

G: [redacted]



H: CT/MRI of brain, chest, and abdomen required at baseline. CT/MRI of chest and abdomen required at each tumor assessment. Additional anatomic regions required when there is known or clinical suspicion of disease. 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.

I: Pregnancy test (women of childbearing potential) must be completed within 72 hours prior to first study treatment and every 4 weeks (day 1 of every cycle) during treatment.

J: [redacted].

Required Observations following the completion/discontinuation 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**
Med History	X	X	X	X	X	X	X	X
Physical Exam (VS, Wt, ECOG PS)	X	X	X	X	X	X	X	X
CBCw/diff/Chemistry	Per standard of care schedule							
Disease Imaging	Q9 weeks (+/- 1 week) until disease progression. Per standard of care schedule after progression.							
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 Meds	Capture all concomitant medication for 30 days after last dose of treatment.							

2. Introduction

Indoximod is an investigational drug candidate for the treatment of cancer. The intended clinical application of indoximod is in combination with other cancer therapies that involve stimulation of an immune response to the tumor, such as cancer immunotherapy, chemotherapy or radiotherapy. Indoximod is currently being tested in human cancer clinical trials in combination with multiple cancer therapies.

2.1. Study Rationale

The goal of the current study is to enhance and prolong the immune response in combination with immune checkpoint inhibition by administering a sustained period of indoximod treatment concurrent with and after standard-dose immune checkpoint inhibition.

[redacted]

With protocol Version 4: The phase 3 study will not proceed. The sponsor has decided not to pursue the Phase 3 portion of the trial given the recent announcement of the negative Phase 3 trial results observed in melanoma patients with another IDO inhibitor currently in development. At this time, further development of indoximod in melanoma is pending additional data from smaller scale trials.

2.2. Background

Melanoma is the most aggressive form of skin cancer. Invasive melanoma accounts for only about 1% of all skin cancer cases, but the vast majority of skin cancer deaths. An estimated 87,110 new cases of melanoma will be diagnosed in the United States (US) in 2017. In the US, melanoma is the fifth leading cancer in men and the sixth in women. In 2017, an estimated 9,730 deaths from melanoma will occur (American Cancer Society, 2017). 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.

In Europe, melanoma is the sixth and seventh most common malignancy in men and women, respectively [8]. The median age at diagnosis is 59 years. The incidence of melanoma varies between different European countries but the estimated incidence was about 39.6 cases /100,000 men and 42.5 cases /100,000 women in 2012. In Europe in 2012, the mortality rate was approximately 8.8 cases/100,000 in males and 6.9 cases/100.000 in females [8]. The outcome of melanoma depends on the stage at presentation [2].

Most patients (84%) with melanoma initially present with stage I or II (localized) disease; 8% have stage III (regional) disease; and 4% have stage IV disease (distant metastases) [28]. Of the patients who present with localized melanoma, however, up to 12% will eventually develop distant metastases [14, 18, 42]. The survival rate for patients with stage IV melanoma is low; from 2001 to 2007, 85% of patients with distant metastases were not expected to survive 5 years [28]. The median survival of patients with stage IV disease is less than 1 year [48, 1].

Current treatments for metastatic melanoma include systemic therapy, surgery and radiotherapy. Spontaneous regression of melanoma has been reported with an incidence of less than 1%. Complete resection of isolated metastases to one anatomic site (lung, gastrointestinal tract, bone or brain) may occasionally achieve long term survival. Systemic treatment may consist of chemotherapy, and/or immunotherapy. Palliative radiotherapy is indicated for symptomatic relief of metastases to brain, bones and viscera.

2.2.1. Systemic Therapy for Metastatic Malignant Melanoma

Current standard of care – overview.
Current standard of care for metastatic and unresectable melanoma per the NCCN guidelines [29] is to select the appropriate first line systemic therapy based on the individual characteristics of each patient.

First line options are:
Immunotherapy: Anti–programmed death 1 (anti-PD-1) antibodies guidelines [29]**:**

- Pembrolizumab (Keytruda®)
- Nivolumab (Opdivo®)

Targeted therapy if BRAF V600 positive mutation: preferred if clinically needed for early response
Combination therapy BRAF/MEK inhibition provided by either:

- Dabrafenib/ trametinib
- Vemurafenib/cobimetinib

Combination therapy with nivolumab (anti-PD1) combined with ipilimumab (CTLA-4) therapy produces a better objective response rate (ORR) and median progression-free survival time (PFS), than either monotherapy but with significantly higher risk of severe toxicity [38]. Whilst this

combination therapy may be considered a first-line option due to the potential superior efficacy of either monotherapy, current NCCN guidelines recommend this regime only after progression of disease following first line PD-1 and/or BRAF/MEK inhibitor therapy in patients with performance status as measured by the ECOG scale of 0-2. [29].

PD-1 monotherapy and in combination with CTLA-4 therapy has been subject to UK National Institute for Health and care excellence (NICE) technology review and both the monotherapy and combination are endorsed as options for first line therapy. [30, 31, 33].

2.2.2. PD-1 Checkpoint Inhibition for Melanoma

Clinical evidence for PD-1 inhibitors.
There are currently two anti–programmed death 1 (PD-1) antibodies approved by the Food and Drug Administration (FDA) for the treatment of metastatic melanoma:

- Pembrolizumab (Keytruda®) [36]
- Nivolumab (Opdivo®) [37]

Keytruda is indicated for the treatment of patients with unresectable or metastatic melanoma [36]. Opdivo is indicated for: BRAF V600 wild-type unresectable or metastatic melanoma, as a single agent and BRAF V600 mutation-positive unresectable or metastatic melanoma, as a single agent. This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials [37].

Both agents also hold a marketing authorization from the European Medicines Agency (EMA) and are indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults. [45, 46].

Nivolumab (Opdivo®) in combination with ipilimumab (Yervoy®), a therapy with anti CTLA-4 activity is also approved by both the FDA and EMA for treatment of adult patients with advanced (unresectable or metastatic) melanoma [37, 46].

2.2.3. [redacted]

[redacted]

[redacted]

[redacted]

2.2.4. [redacted]

[redacted]

[redacted]

2.3. Benefit/Risk Assessment

Advanced melanomas has 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 likelihood that this experimental treatment will provide clinical benefits 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.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of indoximod may be found in the Investigator's Brochure.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
Phase 2: To establish the Phase 3 dose of indoximod in combination with immune checkpoint inhibition pembrolizumab or nivolumab in adult patients with unresectable stage III or stage IV malignant melanoma-an open label evaluation of [redacted] safety and tolerability of the combined treatment **With protocol Version 4: The phase 3 study will not proceed.** Phase 3: To evaluate progression-free-survival (PFS) and/or overall survival (OS) in adult patients with unresectable stage III or stage IV malignant melanoma receiving either indoximod plus pembrolizumab or nivolumab or placebo plus pembrolizumab or nivolumab	Phase 2: The recommended Phase 3 dose will be based on dose escalation method provided in Section 4.2.1 and the adverse events will be listed along with identification of the regimen-limiting toxicities (RLT) of indoximod plus pembrolizumab/nivolumab in combination therapy. **With protocol Version 4: The phase 3 study will not proceed.** Phase 3: The co-primary efficacy endpoints are 1. Progression-free survival (PFS) time which is defined as time from date of randomization until the earliest date of disease progression per RECIST 1.1, or death from any cause, whichever comes first. Patients who have neither progressed nor died will be censored at the last tumor assessment date for the endpoint PFS and will be assessed per RECIST 1.1. Assessment and response will be determined by blinded independent central review using RECIST 1.1. 2. OS is defined as the time from the date of randomization until death from any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.
Secondary	
With protocol Version 4: The phase 3 study will not proceed. Phase 3: 1. To evaluate the objective response rate (ORR) in adult patients with unresectable stage III or stage IV malignant melanoma receiving either indoximod plus pembrolizumab or nivolumab or placebo plus pembrolizumab or nivolumab	**With protocol Version 4: The phase 3 study will not proceed.** 1. The following secondary efficacy endpoint will be analyzed: • Objective response rate (ORR): The first tumor assessment test will be conducted at 9 weeks (+/- 1 week) followed by assessments every 9 weeks (+/- 1 week) for duration of study participation. Defined as patients who have a best response as complete or partial response based on RECIST 1.1

2. To evaluate the safety, tolerability and adverse experience profile of a combination of indoximod and pembrolizumab or nivolumab versus placebo plus pembrolizumab or nivolumab	2. As assessed by percentage of subjects with adverse events, and by percentage of subjects with changes in laboratory parameters, through up to 30 days after end of treatment.
Key Exploratory Objectives	
Phase 2: [redacted] **With protocol Version 4: The phase 3 study will not proceed.** Phase 3: [redacted] To explore correlations between measures of indoximod exposure and response (efficacy and safety).	Phase 2: [redacted] **With protocol Version 4: The phase 3 study will not proceed.** Phase 3: [redacted]

4. Study Design

4.1. Overall Design

This protocol has an adaptive trial design with two distinct phases: a Phase 2 dose escalation of indoximod in combination with pembrolizumab or nivolumab (at the FDA approved flat dose) to establish the recommended dose to progress into the Phase 3 portion of the study. The Phase 2 portion is an open label design and will also evaluate the [redacted] safety and tolerability of the combined treatment and dose of indoximod with pembrolizumab or nivolumab in adult patients with unresectable stage III or IV malignant melanoma.

The dose escalation portion of the trial includes clearly defined stopping rules if any unexpected toxicity is observed. Once the recommended dose is established in the dose-escalation phase, the study will then be expanded into the Phase 3 randomized-controlled Phase 3 pivotal trial. This adaptive approach will allow NewLink to proceed in an expeditious manner to the Phase 3 portion by allowing those sites that participated in the dose escalation phase to participate in the pivotal study.

[redacted]

The Phase 2 portion of the study will be followed by a two-arm, fixed-dose, placebo-controlled, randomized Phase 3 study to evaluate the efficacy, safety and tolerability of indoximod plus pembrolizumab or nivolumab versus placebo plus pembrolizumab or nivolumab in adult patients with unresectable stage III or stage IV malignant melanoma. **With protocol Version 4: The phase 3 study will not proceed.**

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Sections 6.1 and 7.4. Appropriate dose modifications are described in Section 6.6. No investigational or commercial cancer directed agents or therapies other than those described within this protocol 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 radiographically approximately every 9 weeks after initiation of treatment for duration of study participation. Post-treatment scans will be compared to the baseline scan and responses will be assessed using response criteria RECIST 1.1. [4].

4.2. Scientific Rationale for Study Design

[redacted]

[redacted]

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.

4.2.1. Phase 2 Portion

The Phase 2 portion is designed to assess the preliminary safety [redacted] indoximod in combination with a fixed dose of pembrolizumab or nivolumab, the potential regimen limiting toxicities (RLT) of the combination, and to establish the Phase 3 dose of combination indoximod and immune checkpoint inhibition pembrolizumab or nivolumab.

The goal of the Phase 2 trial is to find the maximum dose of indoximod that does not induce a regimen-limiting toxicity (RLT) in more than 1/6 of patients treated concurrently with pembrolizumab or nivolumab, and the dose below RLT that achieves maximum exposure levels. Three doses of indoximod (600, 1200, and 1800 mg) will be tested. The standard regimen with immune checkpoint inhibition is now one of the backbone regimens into which new agents will be integrated for patients with melanoma. To establish the safety and the Phase 3 dose of the new agent indoximod in combination with pembrolizumab or nivolumab, it is necessary to determine the attribution of all toxicities. However, when pembrolizumab or nivolumab are administered as standard regimen, they are 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.

The study will monitor patients for the known acute toxicity of pembrolizumab or nivolumab while the dose of indoximod is escalated while looking to detect any new unexpected toxicities or apparent changes in the expected frequencies of known pembrolizumab or nivolumab toxicities. In the pivotal Phase 3 study of pembrolizumab, severe, life-threatening immune-mediated adverse reactions have been reported in up to 10% of the patients. Based on that study, permanent discontinuation of pembrolizumab or nivolumab is recommended in those 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 pembrolizumab and nivolumab package insert. If one of these toxicities occurs during either the Phase 2 or Phase 3 components of this study, pembrolizumab/nivolumab and indoximod will be permanently discontinued.

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 **possibly** related to treatment irrespective of outcome:

- Any Grade 3 or higher (≥ Grade 3) non-hematologic AE that is not clearly related to the disease or unrelated intercurrent illness. Fatigue, nausea or vomiting are not RLTs unless it precludes administration of the immunotherapy checkpoint standard of care backbone therapy (pembrolizumab or nivolumab). Grade 3 elevation in bilirubin, AST, ALT, alkaline phosphatase or creatinine will be considered RLT only if resolution to ≤ Grade 2 requires more than 21 days. Permanent discontinuation of treatment for elevation in bilirubin, AST, ALT, alkaline phosphatase or creatinine is required if parameters for permanent discontinuation are met per Prescribing Information for pembrolizumab or nivolumab.
- Hematological toxicities to include:
  - Grade 4 thrombocytopenia or neutropenia lasting more than 5 days
  - Grade 3 or 4 thrombocytopenia with clinical significant bleeding (i.e., requires hospitalization, transfusion of blood products, or other urgent intervention)
  - Grade 3 febrile neutropenia lasting more than 5 days
  - Grade 4 anemia not explained by underlying disease or some other concomitant disorder
- A Grade 3 or greater immune-related severe adverse event that meets the accepted criteria for permanent discontinuation of pembrolizumab/nivolumab, as specified under the stopping- rules in Section 6.6, is considered a RLT.
- Any other adverse event possibly related to treatment causing a delay of more than 21 days.

Note, however, that less severe immune-related toxicity (Grade 2 or greater but not meeting the criteria for permanent discontinuation of pembrolizumab/nivolumab), 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. However, if, after this management, the event does **not** improve to Grade 1 or better, then nivolumab/pembrolizumab and indoximod will be discontinued permanently, and the event considered as a RLT.

Otherwise qualifying toxicities that can clearly be attributable to causes other than study treatment, such as disease progression or unrelated intercurrent illness, should be excluded 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 28 days of combination immunotherapy.

AEs not known and expected from pembrolizumab/nivolumab and not seen in previous 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 combination immunotherapy (indoximod plus pembrolizumab) or 14 days in length during combination immunotherapy (indoximod plus nivolumab). Pembrolizumab will be dosed on the 1st day of each 21-day cycle. Nivolumab will be dosed on the 1st day of each 14-day cycle. Indoximod will be dosed twice daily on all days of each cycle.

[redacted]

Indoximod and pembrolizumab or nivolumab will be dosed concurrently until unacceptable toxicity as described in Section 6.6 or disease progression occurs. If unacceptable pembrolizumab/nivolumab related toxicity occurs, pembrolizumab/nivolumab and indoximod are stopped (per Section 6.6).

Treatment with indoximod is given at the initial dose level until toxicity or disease progression unless a recommendation is made by the DSMC to change the dose level.

4.2.1.1. Dose escalation

The starting dose will be dose level 1 as provided in the first table in Section 1.2, and the dose escalation process will be the following:

The period for determination of regimen-limiting toxicities will be the initial 28 days of treatment. For the purposes of dose escalation decisions, a RLT occurring with the initial 28 days of treatment will be considered. Subjects who complete less than 80% of the prescribed doses during the RLT window due to a RLT will count as a RLT for the purposes of dose escalation. Subjects who complete less than 80% of the prescribed doses during the RLT window for reasons other than a RLT (unrelated AE or non-compliance) will be included in the overall safety evaluation of the trial but will not count towards dose escalation and will be replaced.

The dose escalation will follow a linear increase sequence as defined below to define a maximum tolerated dose (MTD):

- Up to 6 patients will be dosed at dose level 1 (600 mg Q12 hr) for at least 28 days (through cycle 1)
- if none of the first three patients or only 1 or less of the 6 patients in the dose level 1 (600 mg PO every 12 hours) experiences a RLT, the dose escalation continues to the dose level 2 (1200 mg PO every 12 hours).
- Up to 6 patients will then be treated at dose level 2.
- if none of the three patients or only 1 or less of the 6 patients in the dose level 2 (1200 mg PO every 12 hours) experiences a RLT, the dose escalation continues to the dose level 3 (1800 mg PO every 12 hours).
- Up to 6 patients will then be treated at dose level 3.

- if none of the three patients or 1 or less of the 6 patients in the dose level 3 (1800 mg PO every 12 hours) experiences a RLT, dose level 3 will be declared the recommended Phase 3 dose (RP3D), [redacted].
- If two or more patients at a particular dose level experience RLTs and the next lower dose has had only 3 patients enrolled, dosing will be de-escalated to the next lower dose and 3 additional patients will be enrolled so that at least 6 patients have been treated with the dose intended as the RP3D dose.
- In summary, the dose escalation continues until at least two patients among a cohort of six patients experience RLT (i.e., ≥ 33% of patients with a RLT at that dose level). The MTD informing the recommended dose for the phase 3 from a safety point of view is defined as the dose level just below this toxic dose level.

If increase in mean drug exposure after a single dose ($AUC_{(0\text{-}inf)}$) or after multiple Q12 hour doses ($AUC_{0\text{-}12}$) from one dose cohort to another is less than 50% of the expected dose-proportional increase, then enrollment into the next higher dose cohort may be cancelled subject to Sponsor decision following input from the DSMC. In that case, if the last dose cohort tested included only 3 patients and a decision is made to cancel enrollment into the next dose cohort based [redacted], 3 more patients will be added to the last dose cohort to test for MTD.

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 3, then no further dose-escalation will be allowed, based on the information [redacted] currently available on indoximod.

Delayed Toxicities: It is possible that some adverse events that would qualify as RLTs during the initial evaluation period may not emerge until many months on therapy with indoximod (hence, after escalation has already occurred to the next dose step). Any such late adverse event that may still be considered an RLT, the DSMC, study investigators, treating physician, and Sponsor will consult to determine if the adverse event qualifies as an RLT. If it does, it 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).

4.2.1.2. Restarting Pembrolizumab or Nivolumab and Indoximod During Dose Escalation

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 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 pembrolizumab or nivolumab (as defined in Section 6.6) and which resolves (to Grade 1 or better) with corticosteroids, may be re-started on pembrolizumab or nivolumab and indoximod (same dose) if they meet all of the restarting criteria described in Section 6.6.

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

4.2.2. Phase 3 Portion - With protocol Version 4: The phase 3 study will not proceed.

Patients will not be enrolled in the Phase 3 portion until all patients in the dose-escalation component have completed the RLT determining portion of the Phase 2 aspect of the trial, and the recommended Phase 3 dose determined. The independent DSMC 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-established Phase 3 dose, then the Phase 3 portion will begin. Once this has occurred, a letter with the results of this teleconference discussion will be sent out providing the established Phase 3 dose and stating enrollment into Phase 3 can proceed.

Once a dose for indoximod in combination with pembrolizumab or nivolumab is established in Phase 2, an additional 600 patients will be enrolled in a two-arm, randomized double-blind, placebo-controlled, fixed-dose Phase 3 study.

The established dose of indoximod (or placebo) will be administered concomitantly with pembrolizumab or nivolumab. If pembrolizumab/nivolumab must be stopped due to unacceptable pembrolizumab- or nivolumab-related toxicity, then indoximod will also be stopped. See Section 6.6 for details. In the case of disease progression or unacceptable toxicity, patients discontinued from the study treatment will be followed-up for survival.

The intention in this study is to evaluate the benefit of adding indoximod to the regimen of immune checkpoint inhibition. If a subject experiences an immune checkpoint inhibitor-related adverse event that requires withdrawal of the checkpoint inhibitor, the subject should also discontinue indoximod.

4.3. Justification for Dose

The starting dose of indoximod used in the Phase 2 dose escalation aspect of the protocol is based upon the safety data generated in greater than 700 study subjects to date. Indoximod has been dose escalated to doses as high as 2000 mg Q12 hr. The largest quantity of safety data has been generated at a dose of 1200 mg Q12 hr. No DLT/RLTs have been experienced with indoximod to date. Preclinical models in non-human primates indicate that the new formulation of indoximod can result in 30-50% increase in drug exposure levels. The starting dose of 600 mg was chosen as the dose that would provide an initial exposure range within a safety margin previously explored by the 1200 mg Q12 hr capsule formulation even if the current tablet formulation increased exposure in humans by as much as 100% compared to the previous capsule formulation. The dose will then be escalated according to standard 3+3 escalation rules. The Phase 3 dose will be set based upon data generated in Phase 2, along with review of safety [redacted] data from supporting studies including investigations in AML and healthy volunteers. - **With protocol Version 4: The phase 3 study will not proceed.**

4.4. End of Study Definition

4.4.1. End of Treatment/Off Study

End of Treatment: Subjects who discontinue treatment for any reason (progressive disease or other) and continue on follow-up and/or survival checks. Subjects that withdraw consent for treatment can still be followed for progressive disease and/or survival. The reason for discontinuation of treatment must be documented. For subjects who withdraw consent, every attempt will be made to determine the reason. Subjects that discontinue for reasons other than progressive disease should continue tumor assessments.

All subjects must have an End of Treatment Evaluation regardless of the reason for treatment discontinuation. At the time of the End of Treatment Evaluation Visit, the procedures outlined in Section 7.2.9 should be performed.

Off Study: Subjects will be considered off study at the time of death or withdrawal of full consent or the study ends. These subjects will not participate in follow-up or survival checks.

4.4.2. End of Study

With protocol Version 4: The phase 3 study will not proceed.

The end of study is defined as the date of the last visit of the last participant in the Phase 2 portion of the study.

5. Study Population

Male or female adult patients with unresectable stage III or IV advanced melanoma who meet all eligibility criteria. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be 18 years and older (adults and seniors) at the time of signing the informed consent.

Type of Participant and Disease Characteristics

1. Have histologically- or cytologically-confirmed unresectable stage III or stage IV melanoma, as per AJCC (8th Edition) staging system not amenable to local therapy
2. Subject must have at least one radiologically measurable lesion as per RECIST 1.1 (Appendix 7: RECIST 1.1 Guideline of the protocol) defined as a lesion that is 10mm in longest diameter or lymph node that is 15mm in short axis imaged by computed tomography (CT) scan or magnetic resonance imaging (MRI).
3. Have been untreated for advanced or metastatic disease except as follows.
   a) BRAF V600 mutant melanoma may have received standard of care targeted therapy (e.g. BRAF/MEK inhibitor, alone or in combination) and be eligible for this study Note: Targeted therapy is not required for eligibility.
   b) Prior adjuvant or neoadjuvant melanoma therapy is permitted if it was completed at least 4 weeks before randomization and all related adverse events have either returned to baseline or stabilized for non-immune therapy based regimens.
   c) Prior adjuvant therapy containing immunotherapy such as interferon or anti-CTLA-4 therapy will only be permitted if relapse did not occur during treatment or within 6 months of treatment discontinuation.
   d) Prior anti-PD-1, anti-PD-L1, or IDO1 inhibitors are excluded.
4. Have documentation of V600-activating BRAF mutation status or consent to BRAF V600 mutation testing during the screening period.
5. [redacted]
6. ECOG performance status 0 or 1
7. Patient has adequate bone marrow and organ function as defined by the following laboratory values:
   - Absolute Neutrophil Count (ANC) $\geq$ 1,500 cells/µL (1.5 x10^9/L), without growth factor support
   - Platelets $\geq$ 100,000 cells/µL (100 x10^9 cells/L), without growth factor support
   - Hemoglobin $\geq$ 9.0 g/dL (90g/L)
   - INR $\leq$ 2 x ULN
8. Any hyperkalemia, hypokalemia, hypermagnesemia, hypomagnesemia, hypercalcemia, hypocalcemia must be $\leq$ Grade 1 per CTCAE Version 4.03

9. Serum Creatinine ≤ 1.5 x ULN, or creatinine clearance (Ccr) ≥ 60 mL/min based on the Cockcroft-Gault equation.
10. Total 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)
11. Alanine Aminotransferase (ALT) or Aspartate Aminotransferase (AST) ≤ 3 x ULN, (in subjects with liver metastases, ≤ 5 x ULN)
12. Serum Albumin ≥ 3 g/dL
13. Patients must have normal pituitary function as determined by investigator clinical judgment.
14. HIV positive patients who are stable on antiretroviral medication (ART). Patients stable on ART are defined as those who have received ART for at least 1 year with no adverse drug reactions requiring regular monitoring, no current illnesses or pregnancy, a good understanding of lifelong adherence, and evidence of treatment success. Treatment success is defined as two consecutive undetectable viral load measures or, in the absence of viral load monitoring, rising CD4 counts or CD4 counts above 200 cells/mm^3 and an objective adherence measure.
15. Patients with known brain metastases will only be eligible after definitive treatment of brain metastases with SBRT or surgery provided that the brain lesions are stable (without evidence of progression by imaging for at least 4 weeks before the first dose of study treatment), subject is neurologically stable and has had no persistent side effects / complications from the treatment, have no evidence of new or enlarging brain metastases confirmed by repeat imaging, and have not required steroids for at least 14 days before study treatment.
16. If female of childbearing potential, must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. If female of childbearing potential, must be willing to use an adequate method of contraception as outlined in Appendix 4, for the course of the study through minimum of 4 months (for those who receive pembrolizumab) and a minimum of 5 months (for those who receive nivolumab) after the last dose of study medication. Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.
17. If male of childbearing potential, must agree to use an adequate method of contraception as outlined in Appendix 4, and not to donate sperm starting with the first dose of study therapy through minimum of 4 months (for those who receive pembrolizumab) and a minimum of 5 months (for those who receive nivolumab) after the last dose of study therapy. Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.
18. Ability to ingest oral medications
19. Ability to understand and the willingness to sign a written informed consent document.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Has Ocular Melanoma
2. Has received prior systemic treatment for unresectable or metastatic melanoma (except BRAF directed therapy as noted in inclusion criteria #3).
3. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or IDO1 inhibitor or any other antibody or drug specifically targeting checkpoint pathways other than anti-CTLA-4 which is permitted in the adjuvant setting.
4. Has received prior adjuvant therapy, monoclonal antibody or an investigational agent or device within 4 weeks or 5 half-lives (whichever is longer) before study Day 1 or not recovered (Grade 1 or at baseline) from AEs due to previously administered agents. Exception to this rule would be use of bisphosphonates, which is not excluded.
5. Has received prior radiotherapy within 2 weeks of therapy. Subjects must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (2 weeks of RT) to non-CNS disease.
6. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days before the first dose of study treatment.
7. Has known active, uncontrolled brain or CNS metastases and/or carcinomatous meningitis.
8. History or presence of an abnormal electrocardiogram (ECG) that, in the investigator's opinion, is clinically meaningful. Screening QTc interval > 480 msec is excluded (corrected by Fredericia or Bazett formula). In the event that a single QTc is > 480 msecs, the subject may enroll if the average QTc for the 3 ECGs is < 480 msecs.
9. Has clinically significant cardiac disease, including unstable angina, acute myocardial infarction within 6 months from first dose of study drug administration, New York Heart Association Class III or IV congestion heart failure (see Appendix 6), and arrhythmia requiring therapy. Medically controlled arrhythmia would be permitted.
10. Has history of allergic reactions attributed to compounds of similar chemical or biologic composition to pembrolizumab, nivolumab or tryptophan-containing substances.
11. Is pregnant or breast-feeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through minimum of 4 months (for those who receive pembrolizumab) and a minimum of 5 months (for those who receive nivolumab) after the last dose of study treatment.
12. Patients who have active, chronic, or on active treatment for Hep B or Hep C are excluded.
13. 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).
14. Patients with laboratory evidence of pancreatitis are excluded.
15. Has presence of a gastrointestinal condition that may affect drug absorption.
16. Patients with an active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid

replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

17. Chronic use of immune-suppressive drugs (i.e., systemic corticosteroids used in the management of cancer or non-cancer related illnesses, e.g., COPD in dosing exceeding 10 mg daily of prednisone equivalent). Inhaled steroids are allowed.
18. 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).
19. Patients taking L- tryptophan or 5-hydroxy-tryptophan supplements.
20. Patients with untreated or uncontrolled HIV
21. Patients who have received a live, attenuated vaccine 30 days prior to enrollment/randomization.
22. Patients receiving monoamine oxidase inhibitors (MAOIs) or drug which has significant MAOI activity (meperidine, linezolid, methylene blue) within the 21 days prior to enrollment/randomization.
23. Patients who have ever had Serotonin Syndrome (SS) after receiving 1 or more serotonergic drugs.
24. Patients who have chronic inflammatory systemic diseases (CIDs) such as rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

No food should be taken for at least 2 hours before and at least 1 hour after administration of the morning and evening doses of indoximod. The medication should be taken twice daily (Q12 hours) in a continuous fashion. Patients should be told to swallow the tablets whole without breaking, splitting, or chewing. Tablets should be taken with a full glass of water. Antacids are also not allowed to be taken for at least 1 hour before and 1 hour after administration of indoximod. No specific pre-medications are required. No supplements containing L- tryptophan or 5-hydroxy-tryptophan should be taken. [redacted]

5.3.2. Photosensitivity

As no formal studies of phototoxicity of indoximod have been completed to date, investigators must advise patients to take measures, such as use of sunscreen and wearing of hats, sunglasses and long-sleeve garments, to minimise exposure to UV light for the duration of the study and for one week after the last dosage.

5.4. Screen Failures

The screening period starts with the signing of the informed consent. During the screening period, inclusion/exclusion criteria for the study participation will be checked / tested. Subjects who meet all inclusion criteria and do not meet any exclusion criterion will be eligible to be

enrolled/randomized. Those who are not eligible for enrollment/randomization or dosing will be considered as screening failures. Data for screen failure reason, eligibility criteria, and demography will be captured in the eCRF.

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6. Study Intervention

Phase 2

The Table below summarizes dose levels of indoximod and pembrolizumab or nivolumab for the Phase 2 study. The Phase 2 study will be conducted only in the United States and therefore will follow the below dose levels.

Dose Level	Indoximod (oral)	Pembrolizumab Dose (IV)	Nivolumab Dose (IV)
1	600 mg Q12 hours	200 mg IV Q3 weeks	240 mg IV Q2 weeks
2	1200 mg Q12 hours	200 mg IV Q3 weeks	240 mg IV Q2 weeks
3	1800 mg Q12 hours	200 mg IV Q3 weeks	240 mg IV Q2 weeks

Dosing regimen: Dosing cycles will be 21 days in length during combination immunotherapy involving pembrolizumab and will be 14 days in length during combination immunotherapy involving nivolumab. Pembrolizumab will be dosed on the 1st day of each 21-day cycle. Nivolumab will be dosed on the 1st day of each 14-day cycle. Indoximod will be dosed twice daily on all days of each cycle.

[redacted]

Phase 3 - With protocol Version 4: The phase 3 study will not proceed.

Once a dose for indoximod in combination with pembrolizumab/nivolumab is established in Phase 2, 600 patients will be enrolled in a two-arm, randomized double-blind, placebo-controlled, fixed-dose Phase 3 study. Treatment will be initiated using standard of care (SOC) immune checkpoint inhibition consisting of pembrolizumab or nivolumab in combination with indoximod or placebo.

The established dose of indoximod will be administered concomitantly with pembrolizumab or nivolumab. If pembrolizumab or nivolumab has to be stopped due to unacceptable pembrolizumab/nivolumab-related toxicity, indoximod is to be discontinued also. In the case of disease progression or unacceptable toxicity, patients discontinued from the study treatment will be followed-up for survival.

Allowed Phase 3 Schedules:

Schedule A: Pembrolizumab IV Q3 weeks + Indoximod/Placebo PO Q12 hours

Schedule B: Nivolumab IV Q2 weeks + Indoximod/Placebo PO Q12 hours

Schedule C: Nivolumab IV Q4 weeks + Indoximod/Placebo PO Q12 hours

Note: Dosing of pembrolizumab and nivolumab will be per approved label in the country the patient is treated in. For example, in the U.S., pembrolizumab will be administered at 200 mg per dose and nivolumab will be administered at 240 mg per dose (per package inserts). For rest of world (ROW), pembrolizumab will be administered at 2 mg/kg and nivolumab will be administered at 3 mg/kg per dose unless the appropriate health authorities approve an alternate dosing regimen. In that case, the approved dosing regimen will be followed.

6.1. Study Intervention(s) Administered

Indoximod	Oral	600-1800 mg	Q12 hours
Nivolumab	Intravenous	240 mg, 480 mg, or 3 mg/kg (as per package insert/approved label in country of treatment)	Q2 or Q4 weeks
Pembrolizumab	Intravenous	200 mg or 2 mg/kg (as per package insert/approved label in country of treatment)	Q3 weeks

6.1.1. Indoximod

Chemical Name: (R)-2-amino-3-(1-methyl-1H-indol-3-yl) propanoic acid hydrochloride;
1-methyl-D-tryptophan hydrochloride

Other Names: indoximod, Indoximod Hydrochloride (HCl); 1-methyl-D-tryptophan HCl; D-1MT HCl

Classification: Immunomodulatory

Molecular Formula: $C_{12}H_{15}ClN_2O_2$ M.W.: 254.71 g/mol

Approximate Solubility: Highly soluble in water and simulated gastric fluids (SGFs).

Mode of Action: Inhibition of IDO pathway activity.

How Supplied: Indoximod is supplied by NewLink Genetics as Indoximod HCl (F1) 600 mg tablets (used for Phase 2 dose level 1) or Indoximod HCl (F2) 600 mg tablets (used for Phase 2 dose levels 2 and 3 and Phase 3). **With protocol Version 4, subjects on Phase 2 dose level 1 will be transitioned over to the indoximod HCl F2 tablets after re-consent. The phase 3 portion of this study will not proceed.**

The Indoximod HCl (F1) tablets contain indoximod HCl drug substance and the inactive ingredients microcrystalline cellulose,

sodium croscarmellose, magnesium stearate, hydroxypropyl methylcellulose (HPMC), colloidal silicon dioxide, and the film coating Opadry® 02A280001 white, which contains HPMC and titanium dioxide.

The Indoximod HCl (F2) tablets contain indoximod HCl drug substance and the inactive ingredients microcrystalline cellulose, sodium croscarmellose, magnesium stearate, hydroxypropyl methylcellulose (HPMC), colloidal silicon dioxide, and the film coating Opadry® II 85F18422 White, which contains polyvinyl alcohol, titanium dioxide, polyethylene glycol/macrogol, and talc.

The 600 mg film-coated tablets are white to off white hard tablets debossed with "IDX" on one side and bisected by a score on the other side.

Storage: Stored at controlled room temperature (59 - 77°F / 15 - 25°C)

Stability: Shelf-life surveillance of the intact bottles is on-going.

Route of Administration: Oral

6.1.2. Indoximod Administration

The indoximod tablets are 600 mg each. The number of tablets will be determined by the dose and 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 (Q12 hours) in a continuous fashion. Patients should be told to swallow whole tablets without breaking, splitting or chewing with a full glass of water. Antacids are also not allowed to be taken for at least 1 hour before and 1 hour after administration of the indoximod. No specific pre-medications are required.

6.1.3. Nivolumab (Opdivo®)

Please refer to the current Prescribing Information and/or Summary of Product Characteristics for nivolumab (Opdivo) for details on mechanism of action, [redacted] risks, and management of adverse events. Links are provided for reference.

https://packageinserts.bms.com/pi/pi_opdivo.pdf

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003985/WC500189765.pdf

6.1.4. Pembrolizumab (Keytruda®)

Please refer to the current Prescribing Information and/or Summary of Product Characteristics for pembrolizumab (Keytruda) for details on mechanism of action, [redacted] risks, and management of adverse events. Links are provided for reference.

https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003820/WC500190990.pdf

6.1.5. Immune Checkpoint Inhibitor (Pembrolizumab/Nivolumab) Administration

The study is designed to evaluate the addition of indoximod, to standard of care checkpoint immunotherapy, pembrolizumab or nivolumab. The administration of these agents (pembrolizumab/nivolumab) 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 per protocol.
- 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.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in

accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation, and final disposition records).
4. Details for the preparation, handling, storage, and accountability are provided in the NLG2107 Pharmacy Manual. Further guidance and information for the final disposition of unused study interventions are also provided in the NLG2107 Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Randomization with use of IVRS/IWRS - With protocol Version 4: The phase 3 study will not proceed.

The Phase 3 portion of the study will randomize 600 patients with a 1:1 ratio into two arms: indoximod plus pembrolizumab/nivolumab and placebo plus pembrolizumab/nivolumab. The randomization will be stratified by the choice of checkpoint inhibitor (physician's choice of pembrolizumab or nivolumab), M1 stage at time of randomization (StageIII/M1a/b vs M1c/d), and prior BRAF inhibitor treatment of the malignant melanoma.

All participants will be centrally assigned to randomized study intervention using an Interactive Voice/Web Response System (IVRS/IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log in information & directions for the IWRS will be provided to each site.

Study intervention will be dispensed at the study visits summarized in SoA.

6.3.2. Breaking the Blind (IVRS/IWRS) - With protocol Version 4: The phase 3 study will not proceed.

The IVRS/IWRS will be programmed with blind-breaking instructions. All effort must be made to maintain the double-blind. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's treatment assignment unless this could delay emergency treatment of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

6.3.3. Unintentional / Accidental Unblinding - With protocol Version 4: The phase 3 study will not proceed.

The term unintentional or accidental unblinding refers to occurrences in which personnel from the CRO, Investigator Sites, or the Sponsor are unblinded to treatment allocation when they should remain blinded. The incident was not planned and was not due to involvement in a planned

unblinding event or an emergency unblinding scenario. Accidental unblinding typically occurs when a study plan or process was not followed or the handling of unblinded information (or investigational product) deviates from defined standards resulting in a breakdown of the firewall between the blinded and unblinded team members.

In the case of an accidental unblinding at the site level, sites must contact their CRA (clinical monitor). The CRA will escalate to the Project Leader and Sponsor so that an investigation can occur. The site will be requested to complete documentation providing the date and reason for unblinding and the names and titles of the unblinded personnel. Documentation of the occurrence will be kept in the subject's source documents and the Investigator Site Files.

6.4. Study Intervention Compliance

Subjects must be compliant with study treatment. Non-compliance is defined as missing treatments or study visits for non-medical reasons or complying with indoximod/placebo administration below an 85% threshold on two sequential study visits.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy. In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient is permitted, except as specifically prohibited.

6.5.1. Live Vaccines

The administration of any live, attenuated vaccines are prohibited during the study and for three months after the last dose of study therapy.

6.5.2. CYP inhibitors/inducers

The administration of strong inhibitors/inducers of CYP3A4 including clarithromycin, telithromycin, nefazodone, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir, phenytoin, rifampin, phenobarbital; inhibitors/inducers of CYP2D6 including bupropion, fluoxetine, paroxetine, quinidine, rifampin; and inhibitors/inducers of CYP2C9 including amiodarone, rifampin, phenobarbital is prohibited in this study.

6.5.3. Anticancer Therapy

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. These cases should be discussed with the Medical Monitor.

Subjects are allowed to receive palliative radiotherapy and/or the use of bisphosphonates for painful bone lesions.

6.5.4. Steroid Therapy

Systemic corticosteroid use will not be permitted on this study with the exception of treating immune-mediated AEs or adrenal insufficiency. Systemic corticosteroid use for exacerbation of chronic conditions (such as asthma, COPD, rash) is allowed as long as dosing does not exceed 10 mg daily of prednisone equivalent.

6.5.5. Monoamine oxidase inhibitors and Serotonin Syndrome (SS)

As IDO inhibitors affect tryptophan metabolism, which could lead to an accumulation of serotonin, monoamine oxidase inhibitors are prohibited during study treatment. Investigators and patients should be made aware of this risk and the symptoms of serotonin syndrome.

Signs and symptoms include:
- Agitation or restlessness
- Confusion
- Rapid heart rate and high blood pressure
- Dilated pupils
- Loss of muscle coordination or twitching muscles
- Muscle rigidity
- Heavy sweating
- Diarrhea
- Headache
- Shivering
- Goose bumps

Severe serotonin syndrome can be life-threatening. Signs and symptoms include:
- High fever
- Seizures
- Irregular heartbeat
- Unconsciousness

6.6. Dose Modification

Dosing delays and/or modification of the following agents should be performed consistent with standard of care practice by the treating physician within the guidelines provided in the respective package inserts/Prescribing Information and/or Summary of Product Characteristics.

6.6.1. Pembrolizumab Dosing Modifications

Please refer to the current Prescribing Information and/or Summary of Product Characteristics for pembrolizumab (Keytruda) for details on management of adverse events and dosing modifications. Links are provided for reference.

https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003820/WC500190990.pdf

Note: If pembrolizumab is held and/or permanently discontinued, indoximod is also held and/or permanently discontinued.

6.6.2. Nivolumab Dosing Modifications

Please refer to the current Prescribing Information and/or Summary of Product Characteristics for nivolumab (Opdivo) for details on management of adverse events and dosing modifications. Links are provided for reference.

https://packageinserts.bms.com/pi/pi_opdivo.pdf

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003985/WC500189765.pdf

Note: If nivolumab is held and/or permanently discontinued, indoximod is also held and/or permanently discontinued.

6.6.3. 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.

6.6.4. Management of Adverse Events of Interest (Immune Related Adverse Events)

The most common toxicities that occur with indoximod are fatigue, nausea, vomiting and headache. These can be managed with general supportive care. When severe (Grade 3 or greater) or persistent, indoximod should be held until symptoms resolve to Grade 1 or resolve.

Indoximod can result in the same immune-mediated adverse reactions as the checkpoint inhibitors, nivolumab and pembrolizumab. At this time, attribution of these events is difficult to determine until more data are available. The underlying principle of determining toxicity in this treatment combination is determination if new, unique, toxicities arise or if the well described toxicities associated with PD-1 checkpoint inhibition occur at a meaningfully increased rate. When these toxicities occur, the management guidelines described in the respective package inserts/Prescribing Information and/or Summary of Product Characteristics (SmPCs) for nivolumab/pembrolizumab should be followed.

In general, assessment and management of any immune-mediated adverse events should follow the following algorithm unless specifically stated otherwise in the Prescribing Information and/or Summary of Product Characteristics (SmPCs).

Grade	Assessment and Management
Grade 1	Asymptomatic; Diagnostic changes only; Continue nivo/pembro and indoximod
Grade 2	Mild to moderate symptoms; Grade 2 diagnostic abnormalities. Hold nivo/pembro and indoximod treatment. Provide supportive care. IV Steroid Dose: Methylprednisolone 0.5-1.0 mg/kg/day or equivalent until stable **If improving:** Transition to oral steroid at start of taper. Dose suggested: 60 mg prednisone daily x 2 weeks Taper over 4 weeks or more to reduce recurrence of symptoms. May consider re-initiation of nivo/pembro and indoximod **If progressing:** Treat as Grade 3-4 Hospitalization if indicated. Multidisciplinary evaluation of toxicity
Grade 3/4	Discontinue nivo/pembro and indoximod (not in case of hypothyroidism) Hospitalization if indicated Increase dose of Methylprednisolone 2.0-4.0 mg/kg/day or equivalent until stable
Refractory to steroid treatment	If no improvement or progression, additional immunosuppressant treatment may be needed • Infliximab 5 mg/kg (except if contraindicated) • Mycophenolate mofetil 1 gram twice daily • Cyclosporine or intravenous immunoglobulin (IVIG)

6.6.5. 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 (~8 hrs), and discontinuation of indoximod results in a prompt reduction in drug levels. Indoximod is a reversible inhibitor of the IDO pathway. In multiple indoximod Phase 1 and 2 trials, patients did not show cumulative toxicity over many months of therapy.

The rules for holding and restarting indoximod will follow the same rules described for the checkpoint inhibitors pembrolizumab/nivolumab as described in the applicable package insert/Prescribing Information and/or Summary of Product Characteristics (SmPCs).

Follow the below recommendations for indoximod in addition to the recommendations outlined for the checkpoint inhibitor. Indoximod is only to be restarted in conjunction with the checkpoint inhibitor (pembrolizumab/nivolumab):

- When the AE is resolved to ≤ 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.
- Patients must re-start indoximod within 12 weeks of their last dose or go off treatment.
- 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).

In general, indoximod was very well tolerated in previous Phase 1 and 2 trials and seldom required any dose reductions. If a dose reduction is deemed necessary due to persistent grade 3-4 nausea due to the number or size of the tablets, one dose reduction by 600 mg per dose (1800mg BID to 1200mg BID as example) 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.

6.7. Intervention after the End of the Study

The Sponsor will offer post-trial access to indoximod free of charge to eligible patients in accordance with the NewLink Genetics Expanded Access Policy, as outlined on the NewLink website, http://www.newlinkgenetics.com/about-us/expanded-access/.

6.8. Discontinuation of Study Intervention

Eligible subjects who are enrolled into the study may be discontinued from study treatment and followed up per protocol if any of the following occur:

- Confirmed radiographic or clinical progression of disease. However, patients may continue treatment beyond progression if they are deriving clinical benefit, are clinically stable, and meet the following criteria:
  - Absence of clinically significant signs and symptoms indicating disease progression.
  - No decline in ECOG performance status.
  - Absence of rapid progression of disease.
  - Absence of progressive tumor critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

  While patients will be classified for statistical analysis as "progressed" upon first radiologic confirmation of tumor, such patients could continue study drug treatment. Patients who are allowed to continue study treatment beyond progression must be re-consented as they may be forgoing approved treatments for their disease.

- Any adverse event requiring permanent discontinuation of treatment as per the Prescribing Information and/or Summary of Product Characteristics.
- Intercurrent illness that prevents further administration of treatment
- Withdrawal of consent
- Lack of compliance or excessive deviations with study schedule in agreement with the Medical Monitor
- 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 study drug administration below an 85% threshold on two sequential study visits.
- Lost to follow-up (after repeated attempts for >30 days have been made to contact the subject including letters sent by registered mail to the subject and designated alternate contact)
- Subject becomes pregnant or starts breast-feeding
- Sponsor discontinuation of study
- Investigator's decision (in consultation with the Medical Monitor and subject for general or specific changes in the subject's medical condition and/or intercurrent illness that may render the subject unacceptable for further treatment. The reason for removal must be documented in the case report form [eCRF]).

***NOTE**: Subjects discontinued from study treatment will be followed-up per protocol (e.g., EOT visit, continue tumor evaluation by RECIST 1.1 if they discontinue from treatment for reasons other than progression) unless subject withdraws consent from all follow-up.

Patients who discontinue study treatment will be followed for survival status until they are lost to follow up or death whichever occurs first.

6.9. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- A participant may withdraw from receiving treatment but continue to participate in follow-up activities.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request in writing, destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

6.10. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

6.11. Discontinuation of Entire Study

This study may be discontinued for any of the following reasons:

- The study is completed per protocol.
- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Determination of futility
- The Sponsor may terminate the study electively or if required by regulatory decision.

One interim safety analysis is planned after approximately 60 subjects have been treated in the Phase 3 portion of the study. The results of this analysis may lead to termination of the study. Any time during the study, the data safety monitoring committee (DSMC) may recommend (and the Sponsor agrees) to discontinue the study. Please see Section 8.5.2 for details regarding the interim safety analysis and DSMC. - **With protocol Version 4: The phase 3 study will not proceed.**

If the study is terminated prematurely, the sponsor will notify the investigators, IRB and Ethics Committees, and regulatory authorities of the decision and the reason for terminating the study.

7. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

7.1. Screening and baseline examination

Informed consent must be signed before any screening procedures. 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, baseline characteristics, and assessments will be collected within 28 days prior to initiating therapy unless otherwise specified:

- General demography
- Medical history/current medical conditions (including prior and concomitant medications)
- Physical examination, weight and height
- Vital signs including sitting blood pressure/pulse and heart rate, respiratory rate and temperature
- ECOG performance status
- CBC w/diff, platelets - to be done within 7 days prior to initiating therapy.
- Serum chemistry (sodium, potassium, magnesium, calcium, chloride, glucose, blood urea nitrogen (BUN), creatinine, total protein, alkaline phosphatase, albumin, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), phosphorus) – 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 inhibitor administration per package insert.
- INR, PT, PTT
- Amylase, lipase
- LH, FSH
- Free T4, TSH, ACTH
- Urinalysis
- ECG (in triplicate)
- AE evaluation
- Radiologic Tumor measurements (CT/MRI of brain, chest, abdomen)
- Pregnancy test (urine or serum) – to be done within 72 hours prior to first treatment for all women with child-bearing potential

7.2. Treatment period

Patients will be asked to visit the clinic every two to four weeks depending on the checkpoint inhibitor and schedule they will receive. Treatment will continue until any off treatment criteria as outlined in Sections 6.6 and 6.8 are met.

The schedule of on-treatment assessments/activities (SoA) can be found in Section 1.3.

7.2.1. Physical Examination

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 neurological examination).

7.2.2. Vital signs

Body temperature, sitting pulse rate, respiratory rate and sitting blood pressure will be measured.

7.2.3. Height and weight

Height in centimeters will be measured at baseline and body weight to the nearest 0.1 kilogram will be measured.

7.2.4. Performance status

The performance status will be assessed according to:
- ECOG (Oken et al. 1982) performance status scale.

7.2.5. Laboratory evaluations

7.2.5.1. Hematology

Hematology tests are to be performed by the local laboratory according to the Visit Schedule outlined in Section 1.3. 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.

7.2.5.2. Clinical Chemistry

Clinical chemistry tests are to be performed by the local laboratory according to the Visit Schedule outlined in Section 1.3. The Clinical chemistry panel includes sodium, potassium, magnesium, calcium, chloride, glucose, blood urea nitrogen (BUN), creatinine, total protein, alkaline phosphatase, albumin, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), phosphorus.

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.

7.2.5.3. Endocrine

Free T4, thyroid-stimulating hormone (TSH), and adrenocorticotropic hormone (ACTH) levels are to be performed by the local laboratory according to the Visit Schedule outlined in Section 1.3.

7.2.5.4. Pituitary

Luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels are to be performed by the local laboratory according to the Visit Schedule outlined in Section 1.3.

7.2.5.5. Coagulation

Coagulation testing will be measured with international normalized ratio (INR), pro-thrombin time (PT) and Partial Thromboplastin Time (PTT) by the local laboratory according to the Visit Schedule outlined in Section 1.3.

7.2.5.6. Pancreas Function

Amylase and lipase levels are to be performed by the local laboratory according to the Visit Schedule outlined in Section 1.3.

7.2.5.7. Urinalysis

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

7.2.6. Pregnancy and assessments of fertility

All women of childbearing potential must undergo a pregnancy test at screening to confirm eligibility in the trial as well as at EOT. Additional pregnancy testing (urine or serum) to be performed in appropriate patients on approximately a monthly basis. Patients undergoing treatment with pembrolizumab will be tested every three weeks to keep alignment with clinic visits scheduled for treatment. Patients undergoing treatment with nivolumab will be tested every four weeks. 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.

7.2.7. [redacted]

[redacted].

[redacted] **- With protocol Version 4: The phase 3 study will not proceed.**

7.2.8. Electrocardiogram (ECG)

A standard 12 lead ECG will be performed according to the [redacted] schedule provided in Section 7.7 for all patients in Phase 2 and Phase 3. **With protocol Version 4: The phase 3 study will not proceed.**

At all scheduled timepoints, ECGs will be performed in triplicate. The triplicate ECGs will be taken approximately 2-4 minutes apart.

All ECGs recorded for each time point will be transmitted electronically to a central laboratory and must be centrally reviewed by an independent reviewer. Any original ECG not transmitted electronically to the central laboratory will be forwarded for central review.

Detailed instructions regarding the ECG collection will be provided to the investigators in a separate manual prior to the start of the study. Baseline ECGs must be performed within 30 minutes prior to [redacted].

An ECG may be repeated at the discretion of the investigator at any time during the study and as clinically indicated. Each ECG tracing must be labeled with the study number, patient initials (where regulations permit), patient number, date, and kept in the source documents at the study site.

7.2.9. End of treatment and premature withdrawal visit

- Complete 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.
- INR, PT, PTT
- Urinalysis.
- ECG (in triplicate)
- Pregnancy test (for women of child-bearing potential)
- Concomitant medications and adverse events assessed at end of treatment.

7.2.10. Follow-Up after End of Treatment

After the End of Treatment Visit, a follow-up visit will be conducted after 3 months to assess safety and tolerability and will include the following:

- Update medical history including current cancer therapy receiving every 3 months.
- Physical examination including ECOG performance status, 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 every 9 weeks until progression. Imaging per SOC practices after progression.
- Review of cancer-related treatments and adverse event assessments.

Patients will be followed for survival. Follow-up visits will continue for 2 years as per Section 1.2 (and as stated above). For those surviving longer than 2 years, follow-up can 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 or the study ends. Further therapy will be at the discretion of the treating physician.

7.3. Efficacy Assessments

Tumor response and progression will be determined by blinded independent central review using RECIST 1.1 criteria (see Appendix 7). An Imaging Manual will be provided to the clinical sites for details on submission of imaging data.

7.3.1. Tumor Assessments

At baseline, CT/MRI of brain, chest, and abdomen will be performed to assess disease status. Scans of additional locations may be necessary depending on known or suspected disease sites.

The first tumor assessment test after baseline will be conducted at 9 weeks (+/- 1 week) followed by assessments every 9 weeks (+/- 1 week) for duration of study participation. 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.

The tumor assessment (TA) performed during screening will be used as a baseline for efficacy assessments.

- CT/MRI of the brain is required during screening to determine eligibility. If no brain lesions at time of randomization, then subsequent brain scans are not required unless clinically indicated.
- 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.

To be considered measurable lesions, tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan and MRI (CT scan/MRI slice thickness no greater than 5 mm; see RECIST 1.1 Guidelines, Appendix II on imaging guidance).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm. It is not recommended to double the slice thickness/interval for measurable lymph nodes). At baseline and in follow-up, only the short axis will be measured and followed.

Sections should be contiguous, similarly sized and consistent from visit-to-visit. 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.

Subjects who are discontinued from study treatment for reasons other than disease progression will continue to have tumor evaluation by RECIST 1.1 until another anti-cancer treatment is started, progression of disease, death, loss to follow up or withdrawal of consent, whichever comes first.

7.3.2. Response Measurements

RECIST 1.1 criteria

To assess tumor response by RECIST 1.1, provided as Appendix 7: RECIST 1.1 Guideline, all tumors present at the Baseline Determination are documented. Lesions are classified into measurable and non-measurable, as defined by RECIST 1.1. From the measurable lesions, no more than 5 target lesions should be identified, and no more than 2 target lesions per organ. The sum of diameters for target lesions (longest diameters for non-nodal lesions and short-axis diameters for lymph nodes) is recorded and followed across future visits. All malignant lesions not selected as target lesions are documented and followed qualitatively as non-target lesions. At each follow-up visit, target and non-target lesion response is assessed as follows:

- Evaluation of Target lesions – criteria to be used to determine objective tumor response for target lesions
    - Complete Response (CR): disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
    - Partial Response (PR): at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
    - Progressive Disease (PD): at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Note: the appearance of one or more new lesions is also considered progression
    - Stable Disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum diameters while on study.
    - Not Evaluable (NE): no imaging or measurement is performed at a particular time point, or only a subset of lesion measurements are made at an assessment.
- 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 (short axis <10 mm).
    - 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): Unequivocal progression of existing non-target lesions. Note: appearance of one or more new lesions is also considered progression

At each visit, scans are also assessed for the presence of new lesions.

Overall response is determined by the combination of target lesion response, non-target lesion response, and the status of new lesions, as shown in the following table:

Target lesion	Non-target lesion	New lesion	Overall response
CR	CR	No	CR
CR	PR, non-CR/non-PD, or NE	No	PR
PR	Any except PD	No	PR
SD	Any except PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
NE	Any except PD	No	NE

The tumor response for this study is the best overall response obtained between the Baseline Determination scan obtained within no more than four weeks prior to randomization visit and the final visit. Unexpected changes in assessment observed after the final visit are characterized as delayed responses.

RECIST 1.1 response measurements are expected to be evaluated at each tumor assessment time point. The assessment must be documented in the subjects' source record.

7.4. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

In this protocol, the study drug indoximod is being combined with immune checkpoint immunotherapies, pembrolizumab or nivolumab, which have an established safety profile. The most frequently reported toxicities for each of these agents per the respective packaging inserts are provided below.

Pembrolizumab: Most common adverse reactions (reported in ≥ 20% of patients) are fatigue, pruritus, diarrhea, decreased appetite, rash, pyrexia, cough, dyspnea, musculoskeletal pain, constipation, and nausea.

Nivolumab: Most common adverse reactions (≥ 20%) in patients are:

- Nivolumab as a single agent: fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, pyrexia
- Nivolumab with ipilimumab: fatigue, rash, diarrhea, nausea, pyrexia, vomiting, and dyspnea

Indoximod: Most common adverse reactions (≥ 20%) in patients are fatigue and nausea. Diarrhea, anorexia, and vomiting are also common in 10-19% of patients.

All subjects will be assessed regularly for the occurrence of AEs from the time of first dose until 30 days after the last dose, initiation of new systemic anticancer therapy, or death, whichever comes first.

Subjects are to be questioned regarding any AEs or SAEs at every scheduled and non-scheduled visit. Subjects will be asked to volunteer information through open-ended questioning. AEs will

also be identified by physical examination and review of laboratory results. The Investigator or designee will record all pertinent information on the appropriate AE reporting page of the subject's eCRF whether or not they are considered causally related to the study interventions.

The Investigator should attempt to establish a diagnosis of the AE based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE verbatim term rather than individual signs/symptoms.

For every AE, the Investigator must document the following:

- Diagnosis or description of event
- Onset date
- Assessment of the severity
- Assessment of the causal relationship separately for pembrolizumab/nivolumab, indoximod
- Assessment of seriousness of the event (i.e. whether it is an SAE)
- Method of treatment taken for the AE
- Action taken related to each study drug (pembrolizumab, nivolumab, indoximod) include the following: dose interruption, dose delay, dose reduction, or study drug discontinuation
- Outcome of event and end date; all SAEs must be followed until resolution, subject death or until the SAE is deemed stable or irreversible
- Phase 2 during RLT window (first 28 days of treatment): any event which meets the criteria as a RLT will be noted as such on the eCRF.

7.5. Adverse Events and Serious Adverse Events

7.5.1. AE Definition

An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

For this clinical study, AEs will be captured with the start of treatment (treatment-emergent adverse events) and not at the time of informed consent.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- [redacted].
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

7.5.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

a. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

b. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

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.

c. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

7.5.3. AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Sponsor in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

7.5.4. Assessment of Severity

The severity of each AE will be graded by the Investigator according to the current version of the NCI CTCAE (v4.03). The criteria can be found at http://ctep.cancer.gov/reporting/ctc.html.

For AEs not listed in the NCI-CTCAE, the following similar grading system should be used:

- Grade 1 Mild AE
- Grade 2 Moderate AE
- Grade 3 Severe AE
- Grade 4 Life-threatening or disabling AE
- Grade 5 Death related to AE

Severity, which is a description of the intensity of manifestation of the AE, is distinct from *seriousness*, which implies a subject outcome or AE-required treatment measure associated with a threat to life or functionality. An AE assessed as Grade 4 based on the NCI CTCAE grades may or may not be assessed as serious based on the seriousness criteria.

The severity rating must be recorded on the appropriate AE reporting page of the subject's eCRF.

7.5.5. Assessment of Causality

The Investigator will assess the relationship between the investigational product and the AE by answering 'yes' or 'no' to the question: 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?' If it is deemed that there is a reasonable causal relationship between the AE and investigational product, it is to be considered as "related".

- The investigator is obligated to assess the relationship between each study intervention (pembrolizumab, nivolumab, and indoximod) and each occurrence of each AE/SAE.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** Sponsor**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

7.5.6. Follow Up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed eCRF.
- The investigator will submit any updated SAE data to Sponsor within 24 hours of receipt of the information.

7.5.7. Reporting of SAEs

- Investigators must immediately report to the Sponsor any serious adverse events whether or not they are considered related to the investigational agent(s)/intervention.
- The SAE must initially be reported within 24 hours of learning of the SAE, followed by a complete SAE report within 3 calendar days of the initial 24-hour report.
- Refer to the Study Manual for copies of the forms and instructions for reporting to the Sponsor.
- 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 in eCRF).

The Site Investigator will notify the IRB and 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.

7.5.8. Exposure to Study Drug During Pregnancy

The effects of indoximod on the developing human fetus are unknown. Based on their actions, both pembrolizumab and nivolumab can cause fetal harm when administered to pregnant women. 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 effective contraception prior to study entry and for the duration of study treatment and for a minimum of 4 months (for those who receive pembrolizumab) and a minimum of 5 months (for those who receive nivolumab) after completion of study treatment. More conception guidance is provided in Appendix 4.

The Investigator must report any pregnancy (including the pregnancy of a male subject's partner), even if no AE has occurred, on a Pregnancy Report Form within 24 hours of the Investigator becoming aware of the pregnancy. See the Study Manual for a copy of the form and instructions on how to submit this information to the Sponsor.

Female Subjects who become pregnant while on the study will be immediately discontinued from study treatment, and complete the End of Treatment visit at 30 days post-last dose follow-up period, reporting all AEs including any related to the pregnancy. In addition, the Investigator will make every attempt to confirm the outcome of the pregnancy and report this on a follow-up Pregnancy Report form.

7.6. Treatment of Overdose

No cases of overdose with indoximod have been reported. If overdose occurs, the Medical Monitor should be contacted and subjects should be closely monitored and supportive care given as necessary.

7.7. [redacted]

[redacted]

7.7.1.1. [redacted]

[redacted]:


ECG

logged and stored at -65°C to -95°C in a frost-free freezer until ready for shipment to XenoBiotic [redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]rt of infusion)

[redacted]

7.7.2. [redacted] With protocol Version 4: The phase 3 study will not proceed.

[redacted]

	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

7.8. Biomarkers

[redacted]

Tumor Tissue Samples

[redacted]

8. Statistical Considerations

8.1. Statistical Hypotheses

Phase 3 - **With protocol Version 4: The phase 3 study will not proceed.**

The co-primary efficacy endpoints are

1. Progression-free survival (PFS) time which is defined as time from date of randomization until the earliest date of disease progression per RECIST 1.1, or death from any cause, whichever comes first. Patients who have neither progressed nor died will be censored at the last tumor assessment date for the endpoint PFS and will be assessed per RECIST 1.1.
2. Overall survival (OS) is defined as the time from the date of randomization until death from any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.

The first tumor assessment test will be conducted at 9 weeks (+/- 1 week) followed by assessments every 9 weeks (+/- 1 week) for duration of study participation.

The null (H_{PFS_0}) and alternative hypotheses (H_{PFS_1}) for PFS are as follows:

H_{PFS0}: There is no difference in the PFS time between treatment groups.

H_{PFS1}: There is a difference in the PFS time between treatment groups.

The null (H_{OS_0}) and alternative hypotheses (H_{PFS_1}) for OS are as follows:

H_{OS_0}: There is no difference in the OS time between treatment groups.

H_{OS_1}: There is a difference in the OS time between treatment groups.

In the analysis of the first co-primary endpoint, PFS, a log-rank test will be used to test for a difference in the time to PFS between treatment groups.

In the analysis of the second co-primary endpoint, OS, a log-rank test will be used to test for a difference in the time to OS between treatment groups.

The null hypothesis will be rejected in favor of the alternative hypothesis if either of the co-primaries is significant at the 2-sided p-value for the treatment group difference from the above corresponding primary analysis is less than 0.025.

Separate Kaplan-Meier (KM) plots for PFS and for OS time will be presented for each treatment group.

The above primary analysis and KM plots will be based on the Intent-to-Treat (ITT) population. In a further sensitivity analysis, the primary analysis will be repeated using the Per-Protocol Set (PPS).

8.2. Sample Size Determination

8.2.1. Sample Size Considerations - With protocol Version 4: The phase 3 study will not proceed.

Each of the co-primaries, PFS and OS, will be allocated 0.025 2-sided.

This trial will compare PFS and OS for the combination indoximod and pembrolizumab/ nivolumab versus pembrolizumab/nivolumab alone.

It is assumed that the comparators, nivolumab and pembrolizumab will perform similarly.

For PFS, pembrolizumab alone PFS survival was acquired from the survival curves from Keynote 066. PFS survival information for the combination, indoximod and pembrolizumab, was available from interim results of the single-arm trial NLG2103.

Data were plotted from available pembrolizumab trials and indoximod interim data and time-dependent failure rates were extracted from these plots and were used in the sample size calculations.

There are several limitations that affect the calculations.

For checkpoint inhibitors, T. T. Chen (JNCI J Natl Cancer Inst (2015) 107(9)) notes that delayed treatment effects as well as a “floor” are common.

The term “floor” refers to the situation in which the survival curves, rather than following a constant risk model (exponential), exhibit a risk which decreases over time, approaching a horizontal asymptote with some percentage of patients remaining essentially risk-free for the remainder of the trial. T.T. Chen refers to this a “cure rate model”.

For the PFS, the data beyond month 10 in these sources is extremely limited. So it remains an open question as to whether a floor exists for pembrolizumab, and if so, what that floor is (i.e., what proportion of patients will remain event free for the remainder of the trial. For sample size

calculations, it is necessary to make assumptions for the curve beyond 10 months. A number of trial configurations were investigated. The final power calculations were based on the following assumptions:

(i) From months 11 through 15, the survival curves continue to decline at the same rate as observed during months 3-10, and

(ii) after month 15, the curves are essentially horizontal, i.e., no further events are observed.

For OS, although a cure rate might exist, the survival curves for Keynote 006 do not show this, so there was no cure rate assumption for OS.

For each of the co-primary endpoints, the final analysis will be event-driven. Based on a variety of considerations for the two co-primary endpoints, a sample size of 600 patients was selected.

The number of events to trigger an analysis for PFS is 415 and for OS the trigger is 325 events. Hazard ratios are 0.69 for PFS and 0.67 for OS.

Power calculations for both PFS and OS were based on the following assumptions:

1. N = 600 patients across approximately 125 clinical trial sites (projecting 4-5 subjects per site with a maximum enrollment per site of 45 subjects (7.5% of total) allowed)
2. Randomization 1:1.
3. Enrollment: 15 months
4. Expected trial length to achieve number of events: 30 months PFS, 60 months OS.
5. Significance Level for each co-primary endpoint: 0.025 2-sided
6. Loss: 1% per year
7. Length of delayed treatment effect: 2 months PFS, 1 month OS
8. The effect of interim analyses were not taken into account here, but will be assessed later:

The assumed failure rates for PFS are

Table 1 Assumed Conditional Failure Rates (annual) For PFS

Month	Indoximod Combination	Pembrolizumab
0-2	.55797	.55797
2-3	.65701	.97922
3-4	.8685	.84671
4-6	.65674	.58204
6-15	.47474	.62154
15+	.001	.001

The assumption that there are no events beyond month 15 leads to an approximate cure rate for PFS of about 37% for the combination arm, 25% for the pembrolizumab alone arm. For PFS, the observed difference between the two observed survival curves determined the treatment effect.

The assumed failure rates for OS are:

Table 2 Assumed Conditional Failure rates (annual) For OS

	Conditional Annual Failure Rate	
Months	Pembrolizumab	Indoximod Combination
1	.3846	.3846
2-3	.3846	.2692
4-9	.3200	.2240
10+	.1600	.1120

For OS, the treatment effect after the delay was assumed to be 30%.

The power under these assumptions is about

- 91.2% for PFS,
- 85.9% for OS.

Power calculations were based on the method of Lakatos (1988), which is implemented in PASS 15.

For PFS (Table 1), the time dependent rates for the control group were obtained from Robert C et al. (Robert, Caroline, et al. "Pembrolizumab versus ipilimumab in advanced melanoma." *New England Journal of Medicine* 372.26 (2015): 2521-2532) – the Keynote 006 trial, Figure 1. The time dependent rates for the combination arm were based on NewLink clinical trial NLG2103. For OS (Table 2), the time-dependent failure rates for the control group were also obtained from Keynote 006, Figure 2.

Figure 1 PFS curves from Keynote 006 (Robert et al NEJM)

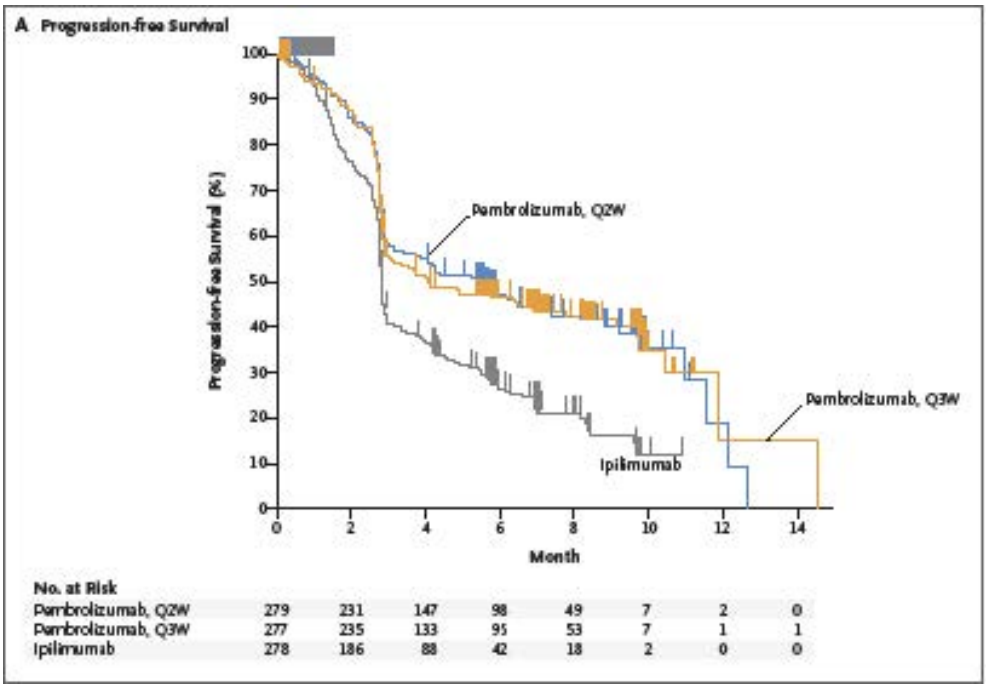


Figure 2 From Robert, Caroline, et al. "Pembrolizumab versus ipilimumab in advanced melanoma." New England Journal of Medicine 372.26 (2015): 2521-2532.

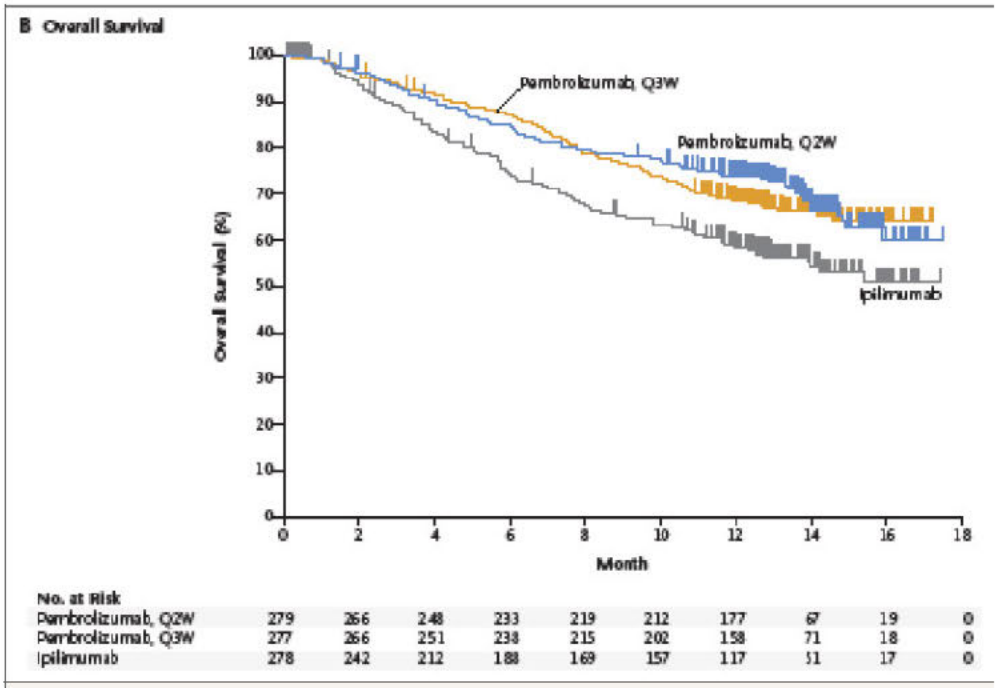


Figure 1. Kaplan–Meier Estimates of Progression-free and Overall Survival.

Shown are rates of progression-free survival as of September 3, 2014 (Panel A), and overall survival as of March 3, 2015 (Panel B), in the intention-to-treat population among patients receiving pembrolizumab every 2 weeks (Q2W) or every 3 weeks (Q3W) or ipilimumab.

8.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled Set	The enrolled set is all subjects who are enrolled into the study and provide informed consent.
Safety Analysis Set (SAF)	The SAF will consist of all randomized patients who received at least one dose of the randomized treatment during the study. This population will be used for all safety analysis. Subjects will be analyzed according to the treatment actually taken.
Intent-to-Treat (ITT)	The ITT is defined as all randomized patients. All efficacy analyses will be performed on the ITT. Patients will be analyzed according to the treatment they are assigned to at randomization, irrespective of what treatment they actually received.
Per-Protocol Set (PPS)	The PPS will be a subset of the FAS that do not have major protocol deviations considered having a serious impact on the efficacy results. Patients with protocol deviations resulting in exclusion from PPS will be identified prior to database lock.
[redacted]	[redacted]

8.4. Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

8.4.1. Efficacy Analyses

Phase 3 Efficacy Endpoints - With protocol Version 4: The phase 3 study will not proceed.

Endpoint	Statistical Analysis Methods
Primary	The co-primary efficacy endpoints below will be analyzed using ITT and the PPS: 1. Progression-free survival (PFS) time which is defined as time from date of randomization until the earliest date of disease progression per RECIST 1.1, or death from any cause, whichever comes first. Patients who have neither progressed nor died will be censored at the last tumor assessment date for the endpoint PFS and will be assessed per RECIST 1.1. 2. OS is defined as the time from the date of randomization until death from any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive. The primary analysis for both PFS and OS will be stratified by checkpoint inhibitor treatment (pembrolizumab or nivolumab).
Secondary	The following secondary efficacy endpoint will be analyzed using ITT and the PPS: • Objective response rate (ORR): The first tumor assessment test will be conducted at 9 weeks followed by assessments every 9 weeks for duration of study participation. Defined as patients who have a best response as complete or partial response based on RECIST 1.1. An overall false-positive rate of 5% level for the above key secondary efficacy endpoint will be maintained, in that no significance of the key secondary endpoint will be claimed unless either of the co-primary statistical analyses is significant at the 2.5% level. We will compare response rates in the study groups using the stratified Miettinen and Nurminen method (1985).

8.4.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

The safety and tolerability of the pembrolizumab/nivolumab plus indoximod combination will be determined by reported AEs, SAEs, RLTs, physical examination findings, vital sign measurements, 12-lead ECG readings, clinical laboratory evaluations, and treatment discontinuation due to toxicity. All summaries will be prepared for the Safety Analysis Population.

For each safety parameter, the last assessment made before the first dose of the indoximod for each period will be used as the baseline for all analyses of that safety parameter.

8.4.2.1. Regimen-limiting Toxicities

RLTs will be reported as AEs and summarized separately by schedule and cohort for the Safety Analysis Population.

8.4.2.2. Adverse Events

All subjects will be assessed regularly for the occurrence of AEs from the time of first dose of the indoximod until 30 days after the last dose, initiation of new systemic anticancer therapy, or death, whichever comes first.

The incidence of treatment-emergent AEs (TEAEs) will be summarized and tabulated using the Medical Dictionary for Regulatory Terms (MedDRA) by System Organ Class (SOC) and Preferred Term (PT). An AE occurring during the treatment period will be considered a TEAE if it was not present before the first dose of indoximod or if it was present before the first dose of indoximod but increased in severity during the treatment period. If more than one AE is reported before the first dose of indoximod and is coded to the same PT, the AE with the greatest severity will be used as the benchmark for comparison with the AEs that were also coded to that PT and that occurred during the treatment period. An AE that occurs more than 30 days after the last dose of indoximod will not be counted as a TEAE, unless recommended by the Medical Monitor or Investigator.

All AEs captured in the database will be included in by-subject data listings including those that are not treatment-emergent (ie, were reported between the time the ICF was signed until the date of the first indoximod dose). Only TEAEs will be summarized in tables.

TEAEs will be coded using the most current version of MedDRA available at the time of study start and data will be summarized for each indoximod dose level within a schedule by System Organ Class (SOC) and preferred term for the Safety Population. The number and percent of subjects reporting each TEAE will be summarized, as well as the number of TEAEs. A subject with 2 or more TEAEs within the same level of summarization (ie, SOC or preferred term) will be counted only once in that level using the most severe event or most related (for the relationship to study medication table). Percentages will be based upon the number of subjects in the Safety Population within each indoximod dose level within a schedule.

Additional summary tables will be generated for grade 3 or higher TEAEs, TEAEs considered related to indoximod, TEAEs by severity and relationship, deaths, DLTs, SAEs, and TEAES leading to treatment discontinuation.

A by-subject AE data listing, including verbatim term, SOC, preferred term, treatment, severity, outcome, and relationship to treatment, will be provided. Separate listings will be generated for deaths, DLTs, SAEs and AEs leading to treatment discontinuation.

8.4.2.3. Clinical Laboratory Parameters

For chemistry, coagulation and hematology parameters, laboratory measurements including actual values at the visit and their changes from baseline during the treatment period, will be summarized. In addition, the maximum and minimum post-treatment values will be presented.

Shift tables from baseline to the worst post-baseline category during the treatment period will be provided for chemistry parameters and hematology parameters. The possible categories in shift tables could include "normal" and "abnormal" based on normal ranges, along with clinical significance information if applicable. Both scheduled and unscheduled post baseline values during the treatment period will be considered.

All clinical laboratory data will be listed by subject. Values outside the normal ranges will be flagged and toxicity grades will be displayed for relevant parameters.

8.4.2.4. Vital Signs

Vital signs will be summarized by indoximod dose level within a schedule using descriptive statistics (mean, standard deviation, median, minimum, and maximum) and presented for each timepoint, including change from baseline, for the Safety Analysis Population. Clinically significant post-baseline vital sign findings will be reported as AEs. A by-subject data listing of all vital sign data will be generated.

8.4.2.5. Electrocardiograms

Heart rate, RR interval, PR interval, QT interval, and QTcB and/or QTcF interval will be summarized by indoximod dose level within a schedule using descriptive statistics (mean, standard deviation, median, minimum, and maximum) and presented for each timepoint, including change from baseline, for the Safety Analysis Population. The mean of triplicate values at the screening visit will be used to calculate the baseline value.

Clinically significant post-baseline ECG findings will be reported as AEs. A by-subject data listing of all ECG data will be generated.

The number and percentage of subjects with elevated QTc values (> 450 msec, > 480 msec, and > 500 msec) at baseline and end of treatment will be presented. In addition, the number and percentage of subjects with QTc values that increase by > 30 msec and > 60 msec from baseline to end of treatment will be presented.

A shift table from baseline to the worst post-baseline values during the treatment period will be provided for QTcF and QTcB intervals. The following categories will be used: ≤ 450 msec, > 450 and ≤ 480 msec, > 480 and ≤ 500 msec, and > 500 msec.

8.4.2.6. Physical Examinations

Detailed information on the physical examinations will be listed by subject. Clinically significant post-baseline physical examination findings will be reported as AEs.

8.4.3. Other Analyses

[redacted]

8.5. Interim Analyses

8.5.1. Interim Analysis Plan - With protocol Version 4: The phase 3 study will not proceed.

Interim analyses are planned in this study for two purposes: (i) as a check on the sample size assumptions with possible midcourse correction, and (ii) interim assessment of efficacy in the case that superiority of the experimental treatment is sufficiently compelling that it would be unethical to continue to treat patients with the inferior drug.

i. As a check on sample size assumptions with possible mid-course correction.

Three issues in the sample size calculations are of particular importance

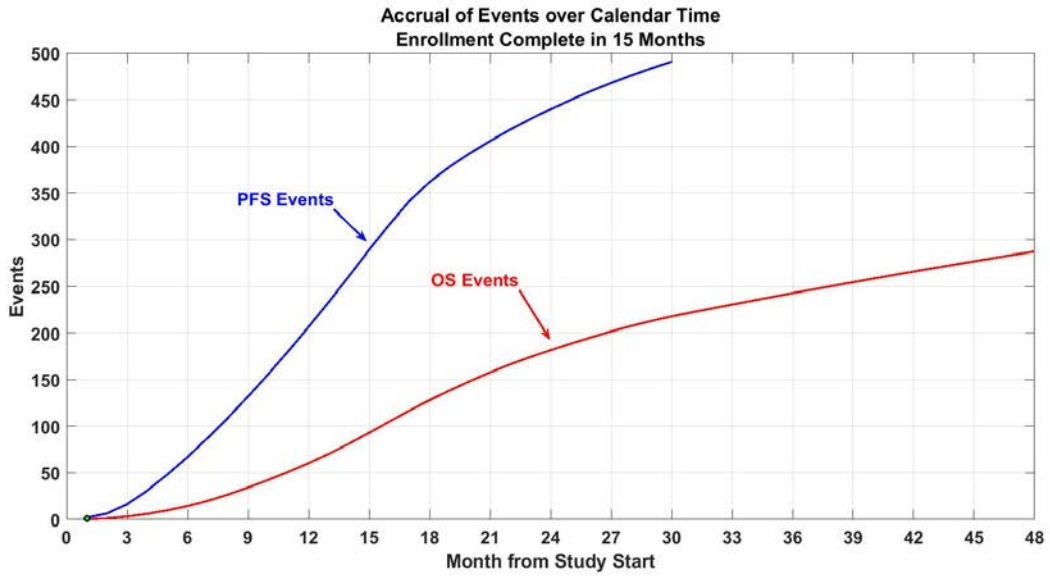
a. The data used for estimating sample size relied on the use of a non-randomized control. This was because the only data available for the combination arm is from a single arm study, and the most relevant data for the control arm is from a trial of a different active therapy. Interim data will be based on randomized data of the treatment arms on the target population.
b. A delayed treatment effect is possible. Its existence and length have yet to be determined and quantified.
c. A "floor" or "cure rate" is likely. Its existence and the proportion "cured" have yet to be determined and quantified.

Interim analyses for both PFS and OS could shed light on all three factors, which in turn could be used for mid-course correction. To maintain the significance at the desire level, the approach of Cui, Hung and Wang (1999) (Cui, Hung, and H. M. Hung. "Wang, (1999)."Modification of Sample Size in Group Sequential Clinical Trials."." *Biometrics* 55: 853-857) will be used. This method also integrates well with the group-sequential design and analysis.

For mid-course corrections, the timing of the interim analysis with respect to the accrual of events is critical. The interim must occur early enough for the mid-course correction to be useful, but late enough for there to be sufficient data for a reasonably informed decision. If there is a delayed treatment effect, there must be enough data to quantify that effect. For PFS, the time lag in applying RECIST criteria for establishing progression must be built into the interim design.

Figure 3 provides projections of the accrual of such events based on the time-dependent risks assumed in the sample size calculations for the configuration currently regarded as most likely.

Figure 3 Accrual of Events over Calendar Time Based on Time-Dependent Event Rates Expected for PFS and for OS.



ii. Group-Sequential Design Issues.

With the co-primary endpoints of PFS and OS, issues arise. In particular, PFS events will accrue much more quickly than OS events.

By design, the alpha was allocated equally to each of the co-primary endpoints. Even if there was no interim analysis, the PFS events are projected to reach the designated total for the final analysis at about month 30.

In order to maintain maximum power for the final PFS analysis, while meeting the demand for an interim analysis for efficacy, a Lan-DeMets spending function will be designed to test the interim, spending about 0.001/2 of the .05/2 alpha allocated to the PFS co-primary. This single interim for PFS efficacy would have to take place when about half the total 491 PFS events occur. Referencing Figure 3, this would occur at about 13 months. Allowing 3 months for full determination of PFS status through month 13 leads to an expected interim meeting at about 16 months. OS will not be examined for efficacy at this interim. The PFS interim for mid-course correction is expected to take place at the same meeting.

Using similar rationale, the single interim for OS efficacy would take place at about month 22; half of the designated maximum OS event should occur at about 21 months, and for OS data, the data should be ready of the meeting in about 1 month. At that meeting, both mid-course correction for OS and early termination for efficacy would be considered. An additional consideration is that

increasing sample size for OS when early trial termination for superior efficacy of PFS is likely could be counterproductive.

Developing group-sequential spending functions to meet these demands when hazards and hazard ratios are time-dependent is complex, and is still underway.

The Statistical Analysis Plan will describe the planned interim analyses in greater detail.

The interim analyses will be conducted by an independent statistician and analyzed by the independent DSMC. The DSMC will take all appropriate measures to avoid accidental transfer of unblinded data or analysis results to the Sponsor or other blinded parties. The DSMC is charged with providing recommendations to the Sponsor based on their review.

8.5.2. Independent Data Safety Monitoring Committee (DSMC)

This study will be overseen by an independent Data Safety Monitoring Committee (DSMC) which will operate according to FDA Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees – OMB Control No. 0910-0581) and the Committee for Medicinal Products for Human Use (CHMP) Guideline on Data Monitoring Committees – EMEA/CHMP/EWP/5872/03). The DSMC will be independent and will follow an agreed Charter and will give recommendations on continuation of the study. They may suggest changes to study conduct and will review data against pre-agreed stopping rules.

8.5.2.1. DSMC Composition

The DSMC is comprised of four voting members, a non-voting member (ad-hoc clinical expert), a statistician and a secretary to the DSMC.

8.5.2.2. DSMC Operations

During the dose escalation Phase 2, the DSMC will review [redacted] safety data. They will review other data as the need arises, in agreement with the Sponsor and as detailed in minutes of DSMC meetings and, as necessary, in an amended Charter. The DSMC will review data towards or at the end of each dose cohort and/or at other times as the need arises and will provide recommendations on study conduct, including on progression to the next cohort based on pre-agreed definitions of Regimen Limiting Toxicity (RLT) and Maximum Tolerated Dose (MTD). They will also give a recommendation on the dose for the Phase 3 part of the trial, based on these and other factors as become apparent during the dose escalation phase.

With protocol Version 4: The phase 3 study will not proceed.
During the Phase 3 part of the trial, the DSMC will review accrual information and safety data such as listings and natures of adverse events as well as other data as the need arises in agreement with the Sponsor and as detailed in minutes of DSMC meetings and, as necessary, in an amended Charter. The DSMC will review the safety of the study drugs and procedures on a quarterly basis, or at other times as the need arises, while any subject is still receiving study drug.

In Phase 3, an interim safety analysis will be performed by the DSMC when 60 subjects have been treated with at least one cycle of therapy. The DSMC will conduct a thorough safety review of unblinded safety data. Reports of the adverse events and treatment related toxicity will be generated. The safety and tolerability of the combination of indoximod with pembrolizumab/nivolumab will be assessed by evaluating the proportion of patients experiencing Grade 3 or higher non-hematologic AEs, death due to any cause, and SAEs for each arm of the randomized portion of the study. If the cumulative incidence of treatment related Grade 3 or higher AEs, deaths, other SAEs or frequency of relapsed or refractory disease in the indoximod arm exceeds the control arm by >25%, study accrual will be held until complete analysis of the data is preformed and no definitive toxicity pattern is identified.

8.6. Changes in the Conduct of the Study or Planned Analyses

Any changes from the analyses planned in the protocol will be documented in the SAP which will be finalized prior to database lock. Any changes in the analyses performed after the SAP has been finalized will be documented in the Clinical Study Report (CSR).

If any amendments to this protocol are necessary, the Sponsor will propose them in writing to the Investigator. Any amendments proposed by the Investigator will be reviewed and approved by the Sponsor prior to submission for IRB review and implementation. No protocol amendment may be implemented (with the exceptions noted below) before it has been submitted to the Regulatory Agency and approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC). In addition, the Investigator signature page must be signed and submitted to the Sponsor.

If the protocol is amended to eliminate or reduce the risk to subjects, the amendment may be implemented before IRB/IEC review and approval. However, the IRB/IEC must be informed in writing of such an amendment, and approval must be obtained within reasonable time limits.

Protocol deviations brought to the attention of the Sponsor after their occurrence will only be recognized and assessed for ethical, medical, scientific, and regulatory implications and for impact on the subject's participation in the study, and will be documented. Such deviations cannot be waived.

Protocol violations (which are deviations that have a major impact on the subject's rights, safety, or well-being or the integrity and authenticity of the study data) can never be waived.

9. Supporting Documentation and Operational Considerations

9.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

Ethical Considerations
This study will be performed in accordance with the protocol, the Declaration of Helsinki, the ICH Harmonized Tripartite Guideline for GCP, and all applicable local regulatory requirements. The study will be conducted in full compliance with FDA guidelines for GCP and in accordance with the ethical principles that have their origins in the Declaration of Helsinki and 21 CFR §312.120.

Institutional Review Board
It is the responsibility of the Investigator to obtain the approval of the Independent Ethics Committee (IEC) / Institutional Review Board (IRB) before the start of the study. A copy of the approval letter will be supplied to the Sponsor, along with a roster of IEC / IRB members. During the course of the study, the Investigator or designee will provide timely and accurate reports to the IEC / IRB on the progress of the study at appropriate intervals (not to exceed 1 year) and at the completion of the study. Investigator or designee will notify the IEC / IRB of serious AEs (SAEs) or other important safety findings. The study protocol, informed consent form (ICF), information sheet advertisements (if any), and amendments (if any) will be approved by the IRB at each study center in conformance CFR, Title 21, Part 56.

Subject Information and Consent
Before the start of any study-related procedures are undertaken, the Investigator or designee must obtain written, informed consent from each study in accordance with US federal regulations (21 CFR §50) and the ICH document "Guidance for Industry – E6 Good Clinical Practice: Consolidated Guidance". Informed consent will be obtained by discussing with the subject the purpose of the study, the risks and benefits, the study procedures, and any other information relevant to the subject.

The Investigator or designee must explain to the subject that for purposes of evaluating the study results, that subject's private health information obtained during the study may be shared with the Sponsor, regulatory agencies, and IECs / IRBs, before enrolling that subject into the study. It is the Investigator's (or designee's) responsibility to obtain permission to use private health information per the Health Information Portability and Accountability Act (HIPAA) from each subject, or if appropriate, the subject's legal representative.

The subject or his/her legal representative will document his/her informed consent by signing the current version of the written, IRB-approved ICF in the presence of a witness. The person who conducted the informed consent discussion with the subject and/or subject's legal representative must also sign the ICF. The subject is given a fully executed copy of the ICF bearing all appropriate signatures, and the original must be maintained in the clinical master files at the site.

The Investigator, or designee, is responsible for the content of the ICF, but the original and any updated versions must be approved by the Sponsor prior to submission to the IRB/IEC. The ICF should also include any additional information required by local laws relating to institutional review. All active Subjects participating on the protocol must be re-consented each time the ICF is updated and re-approved by the IRB/IEC.

Study Management and Investigator Obligations

Investigator and Clinical Sites
The PI at each study center (clinical site) is the individual responsible for ensuring that the investigation is conducted according to the signed Investigator's statement, the protocol, and ICH GCP guidelines at his/her site.

The PI at each clinical site will be responsible for the management of the study, which will include but not be limited to oversight of other designated study Investigators and study staff conducting any activities related to the study, maintenance of the study file and subject records, correspondence with the IRB, and completion of the electronic case report forms (eCRFs).

Data Monitoring
Before the first subject is dosed in the study, a Sponsor representative will meet with the Investigator and clinical site study staff to review the procedures for conducting the study and to train the staff on recording the data on the eCRFs using the electronic data capture (EDC) system. The Sponsor representative will periodically monitor the progress of the study by conducting on–site visits. The Sponsor representative will also be able to review query statuses remotely, which may warrant more frequent communication with the Investigators and clinical site study staff.

The Investigator will make available to the Sponsor representative the source documents, the signed consent forms, all other study-related documents, and the computer that accesses the eCRFs. The Investigator or designee will be responsible for reviewing eCRFs, resolving data queries generated by the Sponsor via the system, providing missing or corrected data, approving all changes to the data, and endorsing the subject data within the EDC system. This approval method will include applying an electronic signature, a uniquely assigned username and a password that together will represent a traditional handwritten signature.

Data Recording and Documentation
Data collection will involve the use of the Sponsor electronic data capture (EDC) system, to which only authorized personnel will have access. In addition to periodic monitoring occurring within the system by Sponsor personnel, programmatic edit checks will be used to review the data for completeness, logic, and adherence to study protocol. As a result of this monitoring and these checks, queries may be issued electronically to the clinical study center and answered electronically by that study center. The identifying information (assigned username, date, and time) for both the originator of the query (if created during the monitoring process) and the originator of the data change (if applicable), as well as the Investigator's approval of all changes performed on his or her Subjects' data, will be collected.

All data collected in the context of this study will be stored and evaluated according to regulatory requirements and applicable guidance for electronic records. Data will be stored and evaluated in such a way as to guarantee subject confidentiality in accordance with the legal stipulations applying to confidentiality of data. Study records (e.g., copies of eCRFs, regulatory documents, etc.) will be retained at the study center, along with adequate source documentation, according to FDA and ICH requirements. All study records must be available for inspection by the Sponsor, its authorized representatives, and FDA officials.

Retention and Review of Records

The PI must maintain the documentation relating to this study. If the Sponsor, the FDA, or another regulatory authority wishes to review any documentation relating to the study, the PI must permit access to such records.

The PI must retain a copy of all records that support the eCRFs for this study (e.g., ICFs, clinical laboratory reports, source documents, indoximod dispensing records) for a period of at least 15 years after study completion unless local regulations or study center policies require a longer retention period or otherwise notified in writing by the Sponsor.

If the PI retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a suitable alternate custodian employee of the study center or to a suitably qualified and responsible third party. The Sponsor must be notified in writing of the name and address of the new custodian before such transfer is made.

No study records shall be destroyed without notifying and giving the Sponsor the opportunity to arrange long-term storage for such study records or to authorize in writing the destruction of records after the required retention period.

Subject Confidentiality

All subject records will only be identifiable by a unique subject identification number. Subjects' names or identifying information other than the data as specified for the eCRF collection are not to be transmitted to the Sponsor. The PI will keep a master subject list on which the subject number and full name, address, and telephone number of each subject are listed.

Study Sponsorship

The Sponsor for this study is:

NEWLINK GENETICS CORPORATION

The Sponsor Study Director and contact person is:

Eugene Kennedy, MD
Chief Medical Officer
NewLink Genetics Corporation
Email: gkennedy@linkp.com

NewLink Genetics Corporation

2503 South Loop Drive, Suite 5100
Ames, IA 50003
Telephone: 515-296-5555
Facsimile: 515-296-3556
www.linkp.com

Study Audits and Inspections
The study may be evaluated by the Sponsor and/or designees and government inspectors who must be allowed access to eCRFs, source documents, and other study files. Sponsor audit reports will be kept confidential. The Investigator should promptly notify Sponsor of any audits scheduled by any regulatory authorities, and promptly forward copies of audit reports.

Study Termination
The Sponsor reserves the right to terminate the study in its entirety or at a specific study center at any time.

Reporting and Publication
All data generated in this study will be the property of the Sponsor. An integrated clinical and statistical report will be prepared at the completion of the study.

Publication of the results by the Investigators will be subject to the signed contractual agreement between the PI and the Sponsor

9.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in the table below will be performed by the local laboratories.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Protocol-Required Clinical Laboratory Assessments

Lab Test	*Parameters*	*Timing*
Chemistry	Sodium, potassium, magnesium, calcium, chloride, glucose, blood urea nitrogen (BUN), creatinine, total protein, alkaline phosphatase, albumin, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), phosphorus.	• Pre-study • Weekly during Cycle 1 and then Day 1 of each subsequent Cycle • EOT Visit • Per SOC during follow-up
Hematology	Total white blood cell count (WBC), WBC differential to include neutrophils, lymphocytes, monocytes, basophils, and eosinophils, red blood cell count (RBC), hemoglobin level, hematocrit level, platelet count.	• Pre-study • Weekly during Cycle 1 and then Day 1 of each subsequent Cycle • EOT Visit • Per SOC during follow-up
Coagulation	Prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR)	• Pre-study • EOT Visit
Urinalysis	Specific gravity, pH, protein, glucose, ketones, bilirubin, and blood.	• Pre-study • As clinically indicated during treatment • EOT Visit
Pregnancy test*	Urine pregnancy test or Serum β–hCG as confirmation of positive urine test *only for women of child-bearing potential	• Pre-study • Every 3 – 4 weeks depending on PD-1 Schedule • EOT Visit
Pituitary	Luteinizing hormone (LH) and follicle stimulating hormone (FSH)	• Pre-study • Day 1 of each Cycle
Endocrine	Free T4, thyroid-stimulating hormone (TSH), and adrenocorticotropic hormone (ACTH) levels.	• Pre-study • Day 1 of each Cycle
Pancreatic	Amylase and lipase enzymes	• Pre-study • Day 1 of each Cycle

Investigators must document their review of each laboratory safety report.

9.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Reporting Serious Adverse Event and Serious Unexpected Adverse Reactions

Any death, serious adverse event (SAE)*, or serious unexpected suspected adverse reaction (SUSAR)** occurring in a subject while receiving study drug (investigational medicinal product) or within 30 days of receiving study drug, even though the event may not appear to be study-drug related, **must be promptly reported** (within 24 hours) by email, telephone, or facsimile to the **24-Hour Emergency and SAE Submission Line.** Ensure that the event is identified on the reporting form as "serious" (see definitions below).

SAE IMMEDIATE NOTIFICATION METHODS	
SAE REPORT FORM SUBMISSION email or fax	1. Submit SAE Form via email: INCDrugSafety@INCResearch.com 2. Submit SAE form via fax: 1-877-464-7787

Contact for Urgent Medical or Eligibility Questions

For urgent medical study questions, contact by telephone the **Study Safety Medical Monitor** and/or the alternative contacts. Responses will be provided within 24 hours. For subject eligibility questions contact by telephone or email the **Study Safety Medical Monitor** and/or the alternative contacts. Responses will be provided 1 business day. **For emergency issues contact the 24-Hour Hotline.**

EMERGENCY CONTACT INFORMATION		
Role in Study	**Contact Name**	**Email Address / Telephone**
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		[redacted]
[redacted]	[redacted]	[redacted]

9.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Contraception Guidance:

Male and Female participants

Male and female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the following table.

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent [a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In this case, two highly effective methods of contraception should be utilized during the treatment period and for at least 120-150 days (4-5 months) after the last dose of study intervention

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

The Investigator must report any pregnancy (including the pregnancy of a male subject's partner), even if no AE has occurred, on a Pregnancy Report Form within 24 hours of the Investigator becoming aware of the pregnancy. See the Study Manual for a copy of the form and instructions on how to submit this information to the Sponsor.

Female Subjects who become pregnant while on the study will be immediately discontinued from study treatment, and complete the End-of-Treatment visit at 30 days post-last dose follow-up period, reporting all AEs including any related to the pregnancy. In addition, the Investigator will make every attempt to confirm the outcome of the pregnancy and report this on a follow-up Pregnancy Report form.

Based on their actions, both pembrolizumab and nivolumab can cause fetal harm when administered to pregnant women. 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 effective contraception prior to study entry and for the duration of study treatment and for a minimum of 4 months (for those who receive pembrolizumab) and a minimum of 5 months (for those who receive nivolumab) after completion of study treatment.

9.5. Appendix 5: ECOG Performance Status

Level	ECOG*
0	Normal activity
1	Symptoms but ambulatory
2	In bed <50% of time
3	In bed >50 % of time
4	100 % bedridden
5	Dead

* As published in American Journal of Clinical Oncology:

Oken M, Creech RH, Tormey DC, Horton J, Davis TE, McFadden E, Carbone PP. Toxicity and response criteria of the eastern cooperative oncology group. *Am J Clin Oncol.* (CCT). 1982; 5: 649-655.

Credit to Eastern Cooperative Oncology Group, Robert Comis MD, Group Chair

9.6. Appendix 6: NYHA Functional Classification

The New York Heart Association (NYHA) Functional Classification places subjects in one of four categories based on how much they are limited during physical activity.

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while *at rest*. Mostly bedbound subjects.

9.7. Appendix 7: RECIST 1.1 Guideline

The publication with the RECIST v.1.1 criteria can be accessed at:

[redacted]

9.8. Appendix 8: List of Abbreviations

ACTH	Adrenocorticotropic Hormone
AE	Adverse Event
B-HCG	Beta Human Chorionic Gonadotropin
CBC	Complete Blood Count
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
[redacted]	[redacted]
eCRF	Electronic Case Report Form
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonization
INR	International Normalized Ratio
IP	Investigational Product
IV	Intravenous
LH	Luteinizing Hormone
MTD	Maximum Tolerated Dose
ORR	Objective Response Rate
OS	Overall Survival
PD	Progression of Disease
PFS	Progression-Free Survival
PK	Pharmacokinetic
PR	Partial Response
PT	Prothrombin Time
RECIST	Response Evaluation Criteria in Solid Tumors
RLT	Regimen Limiting Toxicity
SAE	Serious Adverse Event
TFTs	Thyroid Function Tests

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