Statistical Analysis Plan

NCT03301636

Sponsor Name:	**NewLink Genetics Corporation**
Protocol Number and Title:	**NLG2107** **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**
Protocol Version and Date:	**Version 1.0 21-Aug-2017** **Version 1.1 18-Sep-2017** **Version 2.0 08-Nov-2017** **Version 3.0 30-Mar-2018** **Version 4.0 27-Aug-2018**
Syneos Health (Formerly INC Research) Project Code:	**1010280**
Author:	[redacted]
SAP Version:	**V1.0 for Phase 2**
SAP Version Date:	**04-Dec-2019**

Notice of Confidential and Proprietary Information:

The information contained in this document is confidential belonging to NewLink Genetics Corporation. Acceptance of this document constitutes agreement by the recipient that no information contained herein will be published or disclosed without prior written authorization from an official of NewLink Genetics Corporation. However, this document may be disclosed to appropriate Institutional Review Board and Ethics Committees or duly authorized representatives of a national regulatory authority under the condition that they are requested to keep it confidential. In the event of an actual or suspected breach of this obligation, Syneos Health (formerly INC Research) should be notified promptly.

Revision History

Version #	Date (dd-mmm-yyyy)	Revision Summary
0.1	30-Mar-2018	Initial Release Version of Phase 2 SAP
0.2	31-May-2018	2nd draft Version of Phase 2 SAP based on the updated protocol and the comments from NewLink Genetics Corporation
1.0	18-Nov-2019	Draft Final SAP updated based on protocol V4.0 and comments from NewLink Genetics Corporation
1.0	04-Dec-2019	Finalized SAP updated based on comments from NewLink Genetics Corporation

I confirm that I have reviewed this document and agree with the content.

TABLE OF CONTENTS

1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
ADA	Anti-Drug Antibody
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
AUC_{0-12}	Area under the plasma concentration-time curve from time zero to 12 hours post-dose
$AUC_{0-12,ss}$	Area under the plasma concentration-time curve from time zero to 12 hours post-dose at steady state
AUC_{0-24}	Area under the plasma concentration-time curve from time zero to 24 hours post-dose
$AUC_{0,24,ss}$	Area under the plasma concentration-time curve from time zero to 24 hours at steady state
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to last measurable concentration (or 72 hours) post-dose
AUC_{0-inf}	Area under the curve extrapolated to infinity
BLQ	Below Limit of Quantification
CI	Confidence Interval
C_{max}	Maximum Serum Concentration
$C_{max,ss}$	Maximum Serum Concentration at Steady State
C_{min}	Minimum Serum Concentration
$C_{min,ss}$	Minimum Serum Concentration at Steady State
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
ICH	International Conference on Harmonization
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Description
MTD	Maximum Tolerated Dose
N/A	Not Applicable
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
PK	Pharmacokinetic
[redacted]	[redacted]
PO	Orally
PT	Preferred Term
RECIST	Response Evaluation Criteria in Solid Tumors
RLT	Regimen Limiting Toxicity
RP3D	Recommended Phase 3 Dose
QTc	Corrected QT Interval
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
$t_{1/2}$	Terminal Elimination Half Life
$t_{1/2,ss}$	Terminal Elimination Half Life at Steady State
TEAE	Treatment Emergent Adverse Event
TLF	Table, Listing and Figure
T_{max}	Time to Maximum Serum Concentration
$T_{max,ss}$	Time to Maximum Serum Concentration at Steady State
WHO DD	World Health Organization Drug Dictionary

2. PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures of the Phase 2 portion of the study which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. RESPONSIBILITIES

Syneos Health (formerly INC Research) will perform the statistical analyses and are responsible for the production and quality control of tables, listings, and figures (TLFs) of the Phase 2 portion, except for the exploratory endpoints (i.e. concentration-QT analysis). Based on protocol Version 4, the phase 3 study will not proceed, so the analysis of the Phase 3 portion will not be performed.

2.2. TIMINGS OF ANALYSES

The primary analysis of safety, tolerability [redacted] is planned after all Phase 2 subjects complete the final study visit or terminate early from the study in Phase 2 portion of the study.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

The primary objective (Phase 2) is 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.

3.2. EXPLORATORY OBJECTIVE

The exploratory objective (Phase 2) is to assess the QT prolongation potential of indoximod. Full detail of the concentration-QT analysis will be provided in a separate SAP.

3.3. BRIEF DESCRIPTION

The Phase 2 portion of this study is an open-label, dose-escalation study to establish the Phase 3 dose of indoximod given in combination with pembrolizumab or nivolumab, 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.

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.

[redacted]

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 3 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 3 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 3 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 2 or more patients at a particular dose level experience RLTs and the next lower dose has 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.

3.4. SUBJECT SELECTION

Male or female adult patients with unresectable stage III or IV advanced melanoma who meet all eligibility criteria will be selected. The detailed inclusion/exclusion criteria can be found in the study protocol Sections 5.1 and 5.2.

3.5. SAMPLE SIZE DETERMINATION

The Phase 2 sample size will be 12-18 subjects (depending on dose escalation) – 3 to 6 subjects per dose level.

3.6. TREATMENT ASSIGNMENT AND BLINDING

The Phase 2 is an open-label study and has no randomization/ blinding.

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

Table 1. Dose Levels of the Phase 2 Portion

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 Day 1 of each 21-day cycle. Nivolumab will be dosed on Day 1 of each 14-day cycle. During Cycle 1, subjects will take the first dose of indoximod on Day 1 and not take another dose until Day 4; from Cycle 2, indoximod will be dosed twice daily on all days of each cycle.

3.7. ADMINISTRATION OF STUDY MEDICATION

3.7.1. 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 study medication should be taken twice daily (Q12 hours) in a continuous fashion.

3.7.2. 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.

3.8. STUDY PROCEDURES AND FLOWCHART

The schedule of activities for Phase 2 can be found in Appendix 1.

4. ENDPOINTS

4.1. EFFICACY ENDPOINTS

The Phase 2 efficacy endpoints include results of the tumor assessments and response evaluations by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria. The efficacy data will be listed but not summarized.

4.2. [redacted]

[redacted].

4.3. SAFETY ENDPOINTS

For Phase 2, the safety and tolerability of the pembrolizumab/nivolumab plus indoximod combination will be determined by reported AEs, serious AEs (SAEs), RLTs, physical examination findings, vital sign measurements, 12-lead electrocardiogram (ECG) readings, clinical laboratory evaluations, and treatment discontinuation due to toxicity.

5. ANALYSIS SETS

5.1. ENROLLED SET - PHASE 2

The Enrolled Set will include all subjects who are enrolled into the Phase 2 portion of the study and provide informed consent.

5.2. SAFETY ANALYSIS SET (SAF) - PHASE 2

The Safety Analysis Set (SAF) – Phase 2 will include all subjects who receive at least 1 dose of any study treatment (indoximod, pembrolizumab, or nivolumab) during the Phase 2 portion of the study. This SAF will be used for all safety analysis. Subjects will be analyzed according to the treatment actually taken.

5.3. [redacted]

[redacted].

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. GENERAL METHODS

All relevant subject data for Phase 2 portion of the study will be included in listings. All subjects entered into the database will be included in subject data listings. The listings will be generally sorted by the dose level and then Subject ID, unless specified otherwise.

All applicable data will be summarized by dose level and overall for the Phase 2 portion, unless specified otherwise. In addition, data will be summarized by visit and/or time-point where appropriate. Unscheduled or repeat assessments will not be included in summary tables, but will be included in listings.

Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. The same number of decimal places as in the raw data will be presented when reporting the minimum and maximum, 1 more decimal place than in the raw data will be presented when reporting the mean and median, and 2 more decimal places than in the raw data will be presented when reporting the SD.

Descriptive statistics for categorical/qualitative data will include frequency counts and percentages. The total number of subjects in the dose level (N) for a given population will be used as the denominator for percent calculations, unless stated otherwise in the table shell. All percentages will be presented with 1 decimal point, unless specified otherwise. Percentages equal to 100 will be presented as 100% and percentages will not be presented for zero frequencies.

All analyses and summaries will be produced using SAS® Version 9.3 (or higher).

6.2. KEY DEFINITIONS

6.2.1. Baseline

Baseline is defined as the last non-missing assessment before the first dose of any study treatment in Phase 2, unless specified otherwise.

6.2.2. Change from Baseline

Change from baseline will be calculated for the post-baseline assessment as:

Change from baseline = post-baseline value – baseline value

6.2.3. Duration of Treatment (Weeks)

Duration of treatment is defined as the time from the date of the first dose to the date of last dose of any study treatment (indoximod, pembrolizumab, or nivolumab) in Phase 2. This will be calculated as (date of last dose – date of first dose +1)/7.

6.2.4. Treatment-emergent Adverse Event (TEAE)

A TEAE is an AE that occurs or increases in severity after administration of the first dose of indoximod and through 30 days after the last dose of indoximod in Phase 2.

6.3. MISSING DATA

For the purposes of assessing treatment emergence for AEs or classifying medications into prior/concomitant, the following algorithms will be used for partially missing dates.

For start dates of events:

- The day and month are missing: if the subject started receiving indoximod in the reported year, the first dose date of indoximod will be used as the start date; otherwise '1 January' will be used as the start date.

- The day is missing: if the subject started receiving indoximod in the reported month and year, the first dose date of indoximod will be used as the start date; otherwise, the first day of the reported month and year will be used as the start date.

For stop dates of events:

- The day and month are missing: if the final visit is in the reported year, the date of final visit will be used as the stop date; otherwise, '31 December' will be used as the stop date.

- The day is missing: if the final visit is in the reported month and year, the date of final visit will be used as the stop date; otherwise, the end of the reported month and year will be used as the stop date.

If an AE has the start date completely missing and the stop date on/after the first dose date of indoximod, this AE will be considered as treatment emergent.

If a medication has the stop date completely missing, this medication will be considered as ongoing and concomitant.

6.4. VISIT WINDOWS

The visits recorded in database will be used for all analyses, except for End of Treatment (ET) visit. For subjects who early discontinue from study treatment, the ET visit will be mapped to the closest scheduled visit based on the following algorithms.

Phase 2 Schedule	Target Scheduled Visit	Mapping Window, inclusive
Schedule A (Indoximod + Pembrolizumab)	Last Cycle x Day 1	From (date of Cycle x Day 1) to (date of Cycle x Day 1 + 3 days)
	Last Cycle x Day 8	From (date of Cycle x Day 1 + 4 days) to (date of Cycle x Day 1 + 10 days)
	Last Cycle x Day 15	After (date of Cycle x Day 1 + 11)
Schedule B (Indoximod + Nivolumab)	Last Cycle x Day 1	From (date of Cycle x Day 1) to (date of Cycle x Day 1 + 3 days)
	Last Cycle x Day 8	After (date of Cycle x Day 1 + 4 days)

7. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

7.1. SUBJECT DISPOSITION AND WITHDRAWALS

For subject study status, the number and percentage of subjects for each of the following categories will be presented for the Phase 2 portion of the study.

- Subjects in Enrolled Set – Phase 2 (the number only)
- Subjects in SAF – Phase 2
- Subjects in [redacted]– Phase 2
- Subjects who completed the Phase 2 study
- Subjects who discontinued the Phase 2 study treatment by primary reason of discontinuation.
- Subjects who discontinued the Phase 2 study by primary reason of discontinuation.

For all categories of subjects, percentages will be calculated using the number of subjects from Enrolled Set – Phase 2 unless otherwise specified.

The data for subject disposition, protocol deviation, eligibility, and whether a subject is included in the analysis sets will be listed.

7.2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Descriptive statistics will be summarized for the demographic characteristics and disease characteristics based on the SAF – Phase 2. Listings will also be presented for the demographic characteristics and disease characteristics, respectively.

7.2.1. Demographic Characteristics

The following variables will be summarized: age (years), gender, race, height (cm), and weight (kg).

7.2.2. Disease Characteristics

The following variables will be summarized: BRAF mutation status, number of disease sites, T Stage, N stage, M stage, and stage at Screening.

7.3. MEDICAL HISTORY

7.3.1. Medical History

Medical history abnormalities will be coded to Medical Dictionary for Regulatory Activities (MedDRA®) terms. The version used will be specified in the data display footnote. Medical history will only be listed but not summarized.

7.3.2. Prior Anticancer Radiotherapy

A listing will be provided for the prior anticancer radiotherapy.

7.3.3. Prior Anticancer Surgery

A listing will be provided for the prior anticancer surgery.

7.3.4. Prior Anticancer Medication

A listing will be provided for the prior anticancer medication.

7.4. MEDICATION AND PROCEDURE

7.4.1. Prior and Concomitant Medication

Medications will be recorded on the electronic case report form (eCRF), and will be coded using the World Health Organization Drug Dictionary (WHO DD).

Prior medications will be any medications that started and stopped prior to the first dose of indoximod. Concomitant medications will be any medications that started or continued after the first dose of indoximod.

Prior and concomitant medications will be tabulated and summarized by dose level. Medications will be sorted alphabetically by ATC term and then preferred term within ATC term.

Prior and concomitant medications will be listed in the same table; a column will be included in the listing to indicate if the medication is prior or concomitant.

7.4.2. On-Study Therapeutic Procedure

A listing will be provided for the on-study therapeutic procedures.

8. EFFICACY

8.1. TUMOR ASSESSMENTS

Tumor assessments will be performed for target lesions, non-target lesions, and new lesions at baseline and every 9 weeks (± 1 week) after baseline.

The tumor measurement data and radiological assessment data will be listed.

8.2. RESPONSE EVALUATIONS

Tumor response will be assessed by RECIST 1.1 criteria at each tumor assessment time point, which includes the overall response, and individual assessment of target lesions, non-target lesions, and new lesions.

The tumor response data will be listed.

9. [redacted]

[redacted]

9.1. [redacted]

[redacted]

[redacted]

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

Table 3. [redacted]

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

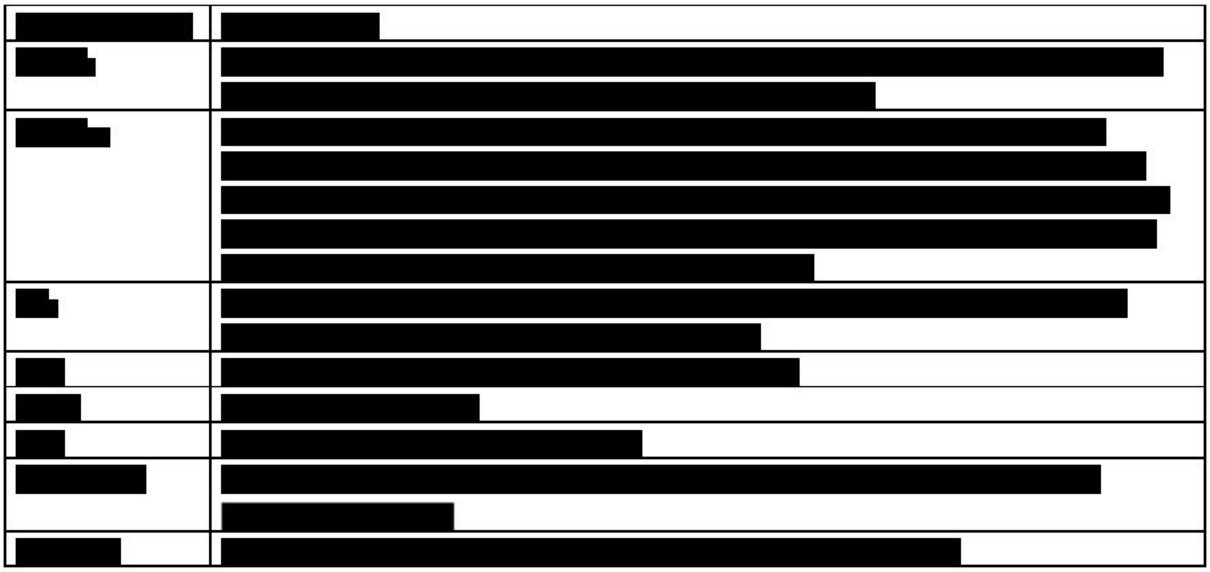
9.2. [redacted]

[redacted]

[redacted]

Table 4. [redacted]

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



9.3. [redacted]

[redacted]

[redacted]

[redacted]

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

[redacted]

[redacted]

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

9.4. [redacted]

[redacted]

[redacted]

- [redacted]

[redacted]

[redacted]

[redacted]

9.5. [redacted]

[redacted]

10. SAFETY

SAF - Phase 2 will be used for all safety analysis of the Phase 2 portion of the study.

10.1. EXTENT OF EXPOSURE AND COMPLIANCE

Exposure of the study treatments (indoximod, pembrolizumab, and nivolumab) will be summarized by dose level and overall for the Phase 2 portion of the study. The following variables will be summarized:

- Maximum number of cycles started
- Number of subjects who started the maximum cycle of 1, 2, 3, 4, and so on
- Duration of treatment (weeks), defined as Section 6.2.3

The following variables will be summarized separately for each study treatment (indoximod, pembrolizumab, and nivolumab) by dose level and overall for the Phase 2 portion of the study.

- Number of administrations (for pembrolizumab and nivolumab) or tablets taken (for indoximod) per subject
- The total dose (mg) received per subject
- Number of subjects with dose interruption/delay
- Number of subjects with dose modification (for pembrolizumab and nivolumab only)
- Number of subjects with compliance percentage of <85% on 2 sequential cycles (for indoximod only)

The listings of study treatment exposure and administration will be provided.

10.2. DOSE LIMITING TOXICITIES (DLT)

The DLTs will be reported as AEs and summarized separately by dose level and overall for Phase 2. In addition, the DLTs will be listed.

10.3. ADVERSE EVENTS

The AEs will be coded to system organ class (SOC) and preferred term (PT) using the MedDRA dictionary. The version used will be specified in the data display footnote.

The National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) will be used to assess the severity of AEs. If severity is missing, the event will be listed as missing severity but summarized as a CTCAE Grade 3.

The relationship of each AE to each study treatment (indoximod, pembrolizumab, and nivolumab) will be classified as related or unrelated. If relationship is missing, the event will be listed as missing relationship but summarized as related.

Summaries will focus on the TEAEs, defined in Section 6.2.4. The TEAEs will be summarized by dose level and overall for Phase 2. The number and percent of subjects reporting each TEAE will be summarized, as well as the number of TEAEs (if applicable). A subject with 2 or more TEAEs within the same level of summarization (i.e., SOC or PT) will be counted only once in that level using the most severe event or most related event.

Summaries presenting the frequency of AEs by SOC and PT will be sorted by descending frequency of SOC for the 'Total' column and then, within a SOC, by descending frequency of PT for the 'Total' column.

The following summary tables will be provided:

- An overall summary of the frequency of subjects reporting all TEAEs, serious TEAEs, TEAEs with CTCAE Grade 3 or higher, indoximod-related TEAEs, TEAEs leading to indoximod discontinuation, and TEAEs with fatal outcome.
- TEAEs by SOC and PT
- Serious TEAEs by SOC and PT
- TEAEs with CTCAE Grade 3 or higher by SOC and PT
- Indoximod-related TEAEs by SOC and PT
- TEAEs leading to indoximod discontinuation by SOC and PT
- TEAEs with fatal outcome by SOC and PT
- TEAEs by SOC and PT, and by maximum CTCAE grade
- TEAEs by SOC and PT, and by maximum relationship to indoximod
- TEAEs by SOC and PT, and by maximum relationship to pembrolizumab
- TEAEs by SOC and PT, and by maximum relationship to nivolumab

All AEs will be listed by dose level and then subject number of Phase 2. Separate listings will be produced for serious TEAEs, TEAEs leading to indoximod discontinuation, and TEAEs with fatal outcome. In addition, the listing of all deaths (regardless of cause) will be provided.

10.4. LABORATORY EVALUATIONS

The following laboratory tests will be performed locally to evaluate the safety profile: clinical chemistry (including endocrine, pituitary, and pancreas function tests), hematology (including coagulation), urinalysis, and pregnancy.

For each laboratory parameter, the actual values and changes from baseline (if applicable) will be summarized and the frequency of subjects with clinically significant abnormal laboratory values will be tabulated for baseline and each scheduled post-baseline visit, by dose level and overall for Phase 2. In addition, the maximum and minimum post-baseline values will be summarized, if applicable.

Shift tables ('Normal', 'Abnormal, Not Clinically Significant', and 'Abnormal, Clinically Significant') from baseline to the worst post-baseline category during treatment period will be provided for the clinical chemistry and hematology parameters. Both scheduled and unscheduled post-baseline values during treatment period will be considered.

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

10.5. VITAL SIGNS

The vital sign measurements include blood pressure (systolic and diastolic), pulse rate, respiration rate, and body temperature.

For each vital sign parameter, the actual values and changes from baseline (if applicable) will be summarized for baseline and each scheduled post-baseline visit by dose level and overall for Phase 2.

All vital signs measurements will be listed.

10.6. 12-LEAD ELECTROCARDIOGRAM (ECG)

12-lead ECG measurements will be performed in triplicate at the scheduled time points, including the heart rate, RR interval, PR interval, QT interval, QTcB and/or QTcF interval. ECG overall interpretation will also be collected on the eCRF.

For summary purposes, the mean of the available repeat measurements at a scheduled time point will be used for each continuous parameter; the worst case of interpretation

categories ('Normal', 'Abnormal, Not Clinically Significant', and 'Abnormal, Clinically Significant') at a scheduled time point will be used.

For each continuous parameter, the actual values and changes from baseline (if applicable) will be summarized for baseline and each scheduled post-baseline time point by dose level and overall for Phase 2.

The number (percentage) of subjects with elevated QTc values ('>450 msec', '>480 msec', and '>500 msec') at baseline and end of treatment will be presented; the number (percentage) of subjects with QTc values which increase by >30 msec and >60 msec from baseline to end of treatment will be presented, by dose level and overall for Phase 2.

A shift table from baseline to the maximum post-baseline values during the treatment period will be provided for QTcF and QTcB intervals, based on the categories ('≤450 msec', '>450 and ≤480 msec', '>480 and ≤500 msec', and '>500 msec').

For ECG overall interpretation, the number (percentage) of subjects with individual categories ('Normal', 'Abnormal, Not Clinically Significant', and 'Abnormal, Clinically Significant') will be summarized for baseline and each scheduled post-baseline time point by dose level and overall for Phase 2.

All ECG measurements and overall interpretation results will be listed.

10.7. 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).

Clinically significant physical examination findings will be reported on medical history or AE eCRFs.

The date of physical examinations will be listed.

10.8. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

The ECOG performance status will be based on 6-grade scale (e.g. 0=normal activity; 5=dead).

The number (percentage) of subjects with individual categories of ECOG performance status will be summarized for baseline and each scheduled post-baseline visit by dose level and overall for Phase 2.

All ECOG performance status data will be listed.

10.9. [redacted]

[redacted]

11. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

Although mentioned in Protocol Section 7.7.1.2, the PK and immunogenicity analysis of Permbrolizumab/Nivolumab are excluded from the final analysis.

12. REFERENCE LIST

1. Gough K, Hutchinson M, Keene O, Byrom B, Ellis S, Lacey L, McKellar J. Assessment of Dose Proportionality: Report from the Statisticians in The Pharmaceutical Industry/Pharmacokinetics UK joint working party. Drug Inf J. 1995; 29:1039-1048.
2. Hummel J, McKendrick S, Brindley C and French, R. Exploratory assessment of dose proportionality: review of current approaches and proposal for a practical criterion. Pharmaceut. Statist. 2009; 8: 38-49.

13. PROGRAMMING CONSIDERATIONS

13.1. GENERAL CONSIDERATIONS

- One SAS program can create several outputs.
- One output file can contain several outputs.
- Output files will be delivered in Word format (.rtf).
- Numbering of TLFs will follow International Conference on Harmonization (ICH) E3 guidance.

13.2. TABLE, LISTING, AND FIGURE FORMAT

13.2.1. General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8.
- The data displays for all TLFs will have a minimum 1-inch blank margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified.
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm^2, C_{max}) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

13.2.2. Headers

- All output should have the following header at the top left of each page:
  NewLink Genetics Corporation Protocol NLG2107
  Draft/Final Run
- All output should have Page n of N at the top or bottom right corner of each page. The TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.

13.2.3. Display Titles

- Each TLF should be identified by the designation and a numeral. (i.e., Table 14.1.1). The title is centered. The analysis set should be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
(XX Analysis Set)

13.2.4. Column Headers

- Column headings should be displayed immediately below the solid line described above in initial upper-case characters.
- Analysis set sizes will be presented for each study group in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of subjects in the analysis set.

13.2.5. Body of the Data Display

13.2.5.1. General Conventions

Data in columns of a table or listing should be formatted as follows:

- alphanumeric values are left-justified;
- whole numbers (e.g., counts) are right-justified;
- numbers containing fractional portions are decimal aligned.

13.2.5.2. Table Conventions

- If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
mild	0
moderate	8
severe	3

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups should be included.

- P-values should be output in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places. Any p-value less than 0.001 will be presented as <0.001. If the p-value should be less than 0.0001 then present as <0.0001. If the p-value is returned as >0.999 then present as >0.999.

13.2.5.3. Listing Conventions

- Listings will be sorted for presentation in order of study groups, subject number, visit/collection day, and visit/collection time.
- Dates should be printed in SAS® DATE9.format (“ddMMMyyyy”: 01JUL2000). Missing portions of dates should be represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as “N/A”, unless otherwise specified.
- All observed time values must be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.

13.2.5.4. Figure Conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint values will be displayed on the Y-axis.

13.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with “Note:” if it is an informational footnote, or with 1, 2, 3, etc. if it is a reference footnote. Each new footnote should start on a new line where possible.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source.

14. QUALITY CONTROL

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. Syneos Health (formerly INC Research) Standard Operating Procedures (SOPs) 03.010 and 03.013 provide an overview of the development of such SAS programs.

Syneos Health (formerly INC Research) SOP 03.009 describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

15. INDEX OF TABLES

The following tables will be produced (table numbers and titles may be different in the final versions):

Header	Table Number	Name	Analysis Set
14.		Tables and Figures Referred to but not Included in the Text	
14.1		Demographic Data Summary Tables	
14.1.1		Subject Disposition	
	14.1.1.1	Summary of Subject Disposition	Enrolled Set – Phase 2
14.1.2		Demographic and Baseline Characteristics	
	14.1.2.1	Summary of Demographic Characteristics	SAF – Phase 2
	14.1.2.2	Summary of Disease Characteristics	SAF – Phase 2
14.1.3		Medications	
	14.1.3.1	Prior Medications	SAF – Phase 2
	14.1.3.2	Concomitant Medications	SAF – Phase 2
14.1.4		Treatment Compliance	
	14.1.4.1	Summary of Maximum Cycles Started and Duration of Treatment	SAF – Phase 2
	14.1.4.2	Summary of Exposure for Indoximod	SAF – Phase 2
	14.1.4.3	Summary of Exposure for Pembrolizumab	SAF – Phase 2
	14.1.4.4	Summary of Exposure for Nivolumab	SAF – Phase 2
[redacted]		[redacted]	
[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
14.3		Safety Data Summary Tables	
14.3.1		Adverse Events	
	14.3.1.1	Overall Summary of Treatment-Emergent Adverse Events	SAF – Phase 2
	14.3.1.2	Incidence of Dose Limiting Toxicities	SAF – Phase 2
	14.3.1.3	Incidence of Treatment-Emergent Adverse Events	SAF – Phase 2
	14.3.1.4	Incidence of Serious Treatment-Emergent Adverse Events	SAF – Phase 2
	14.3.1.5	Incidence of Treatment-Emergent Adverse Events with CTCAE Grade 3 or Higher	SAF – Phase 2
	14.3.1.6	Incidence of Indoximod-related Treatment-Emergent Adverse Events	SAF – Phase 2
	14.3.1.7	Incidence of Treatment-Emergent Adverse Events Leading to Indoximod Discontinuation	SAF – Phase 2
	14.3.1.8	Incidence of Treatment-Emergent Adverse Events with Fatal Outcome	SAF – Phase 2
	14.3.1.9	Incidence of Treatment-Emergent Adverse Events by Maximum CTCAE Grade	SAF – Phase 2
	14.3.1.10	Incidence of Treatment-Emergent Adverse Events by Maximum Relationship to Indoximod	SAF – Phase 2
	14.3.1.11	Incidence of Treatment-Emergent Adverse Events by Maximum Relationship to Pembrolizumab	SAF – Phase 2
	14.3.1.12	Incidence of Treatment-Emergent Adverse Events by Maximum Relationship to Nivolumab	SAF – Phase 2
14.3.4		Laboratory Data	SAF – Phase 2
14.3.4.1.1		Clinical Chemistry	SAF – Phase 2
	14.3.4.1.1.1	Summary of Clinical Chemistry	SAF – Phase 2
	14.3.4.1.1.2	Proportions of Subjects with Clinically Significant Clinical Chemistry	SAF – Phase 2

Header	Table Number	Name	Analysis Set
		Values	
	14.3.4.1.1.3	Shift Table of Clinical Chemistry	SAF – Phase 2
14.3.4.1.2		Hematology	
	14.3.4.1.2.1	Summary of Hematology	SAF – Phase 2
	14.3.4.1.2.2	Proportions of Subjects with Clinically Significant Hematology Values	SAF – Phase 2
	14.3.4.1.2.3	Shift Table of Hematology	SAF – Phase 2
14.3.4.1.3		Urinalysis	
	14.3.4.1.3.1.1	Summary of Urinalysis (Continuous)	SAF – Phase 2
	14.3.4.1.3.1.2	Summary of Urinalysis (Categorical)	SAF – Phase 2
	14.3.4.1.3.2	Proportions of Subjects with Clinically Significant Urinalysis Values	SAF – Phase 2
14.3.4.2		Vital Signs	
	14.3.4.2.1	Summary of Vital Signs	SAF – Phase 2
14.3.4.3		Electrocardiogram (ECG)	
	14.3.4.3.1	Summary of Electrocardiogram (ECG)	SAF – Phase 2
	14.3.4.3.2	Proportions of Subjects with Elevated QTcF and QTcB Values	SAF – Phase 2
	14.3.4.3.3	Shift Table of QTcF and QTcB Intervals	SAF – Phase 2
	14.3.4.3.4	Summary of Electrocardiogram (ECG) Overall Interpretation	SAF – Phase 2
14.3.4.4		Eastern Cooperative Oncology Group (ECOG) Performance Status	
	14.3.4.4.1	Summary of Eastern Cooperative Oncology Group (ECOG) Performance Status	SAF – Phase 2

If ICH standard sections are removed from the report or additional sections added, the highest level section number (14) may change. Templates are provided in Attachment 1.

16. INDEX OF FIGURES

The following figures will be produced (figure numbers and titles may be different in the final versions):

Header	Figure Number	Name	Analysis Set
[redacted]		[redacted]	
[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]

Templates can be found in Attachment 2.

17. INDEX OF LISTINGS

Data collected in the database will be listed. Numbering of listings may be adjusted to accommodate split listings or listings that are omitted due to no records.

Header	Listing Number	Name	Analysis Set
16.2		Subject Data Listings	
16.2.1		Subject Disposition	
	16.2.1.1	Subject Disposition	Enrolled Set - Phase 2
16.2.2		Protocol Deviations	
	16.2.2.1	Protocol Deviations	Enrolled Set - Phase 2
16.2.3		Patients excluded from the Analysis	
	16.2.3.1	Eligibility	Enrolled Set - Phase 2
	16.2.3.2	Analysis Sets	Enrolled Set - Phase 2
16.2.4		Demographic Data	
	16.2.4.1	Demographic Characteristics	Enrolled Set - Phase 2
	16.2.4.2	Disease Characteristics	Enrolled Set - Phase 2
	16.2.4.3	Medical History	Enrolled Set - Phase 2
	16.2.4.4	Prior Anticancer Radiotherapy	Enrolled Set - Phase 2
	16.2.4.5	Prior Anticancer Surgery	Enrolled Set - Phase 2
	16.2.4.6	Prior Anticancer Medication	Enrolled Set - Phase 2
	16.2.4.7	Prior and Concomitant Medication	Enrolled Set - Phase 2
	16.2.4.8	On-Study Therapeutic Procedure	Enrolled Set - Phase 2
16.2.5		Compliance Data	
	16.2.5.1	Exposure of Study Treatment	Enrolled Set - Phase 2
	16.2.5.2	Study Treatment Administration – Indoximod	Enrolled Set - Phase 2
	16.2.5.3	Study Treatment Administration – Pembrolizumab or Nivolumab	Enrolled Set - Phase 2
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
16.2.6		Individual Efficacy Response Data	
	16.2.6.1.1	Tumor Assessment - Target Lesions	Enrolled Set - Phase 2
	16.2.6.1.2	Tumor Assessment - Non-Target Lesions and New Lesions	Enrolled Set - Phase 2
	16.2.6.2	Tumor Response Evaluation by RECIST 1.1	Enrolled Set - Phase 2
	16.2.6.3	Radiological Assessment	Enrolled Set - Phase 2
16.2.7		Adverse Event Listings	
	16.2.7.1	Adverse Events	Enrolled Set - Phase 2
	16.2.7.2	Dose Limiting Toxicities	Enrolled Set - Phase 2
	16.2.7.3	Serious Treatment-Emergent Adverse Events	Enrolled Set - Phase 2
	16.2.7.4	Treatment-Emergent Adverse Events Leading to Indoximod Discontinuation	Enrolled Set - Phase 2
	16.2.7.5	Treatment-Emergent Adverse Events with Fatal Outcome	Enrolled Set - Phase 2
	16.2.7.6	Death (Regardless of Cause)	Enrolled Set - Phase 2
16.2.8		Listing of Individual Laboratory Measurements by Patient	
	16.2.8.1.1	Clinical Chemistry	Enrolled Set - Phase 2
	16.2.8.1.2	Hematology	Enrolled Set - Phase 2
	16.2.8.1.3	Urinalysis	Enrolled Set - Phase 2
	16.2.8.1.4	Pregnancy Test	Enrolled Set - Phase 2
	16.2.8.2.1	Vital Signs	Enrolled Set - Phase 2
	16.2.8.2.2	Electrocardiogram (ECG)	Enrolled Set - Phase 2
	16.2.8.2.3	Physical Examination	Enrolled Set - Phase 2
	16.2.8.2.4	Eastern Cooperative Oncology Group (ECOG) Performance Status	Enrolled Set - Phase 2
	16.2.8.2.5	Tumor Tissue Collection	Enrolled Set - Phase 2

Templates of the listings are provided in Attachment 3. These templates show what information will be contained in the listings but the actual layout (e.g. order of

columns, additional columns) may change to reflect what is actually received. Listings may be split into multiple listings if there are too many data points to fit on one page. Numbering of listings may be adjusted to accommodate split listings, listings that are added and/or listings that are omitted due to no records. If ICH standard sections are removed from the report or additional sections added, the highest level section number (16) may change.

18. MOCK-UPS

Attachment 1: Planned Table Shells

Attachment 2: Planned Figure Shells

Attachment 3: Planned Listing Shells

19. APPENDIX

Appendix 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.

		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		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]														
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] per Section 7.7

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
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.							

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]														
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]														

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] per Section 7.7

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.							