# STATISTICAL ANALYSIS PLAN

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

## NLG-2104

## A Phase 1/2 Study of Indoximod in Combination with Gemcitabine and Nab-Paclitaxel in Patients with Metastatic Adenocarcinoma of the Pancreas

**IND Number:** [redacted]

**Date of Plan:** 22 January 2019

**Based on:** Protocol Version 4 (25 JUL 2016)

CRF Version 2

## SPONSOR:

NewLink Genetics Corporation

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

# Statistical Analysis Plan Approval

| | |
|---|---|
| **SAP:** | NLG-2104 SAP |
| **SAP Version:** | Final Version 2.0 |
| **Sponsor Representative:** | Eugene P. Kennedy, MD<br>Chief Medical Officer, NewLink Genetics |
| **Approval Signature:** | [redacted] |
| **Date:** | [redacted] |
| **Protocol Version:** | Version 4 (25 JUL 2016) |
| **CRF Version:** | Version 2 |
| **SAP Author:** | [redacted] |
| **SAP Author Approval Signature:** | [redacted] |
| **Date:** | 22 January 2019 |

Changes from SAP V1.0:

| Change | Reason for Change |
|---|---|
| Removed duration of complete response tables and figures | Not enough data to support tables and figures |
| Added listing for regimen limiting toxicities | Omitted in V1.0 |
| Removed table 14.1.11 (ECGs at Baseline) | Same data is also captured in tables |
| Removed table 14.1.11 and replaced with ECG values/results tables 14.3.5.1 and 14.3.5.2 | Needed 2 tables (one for values and one for results) and moved to safety section |

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# 1. LIST OF ABBREVIATIONS

**Table 1: List of Abbreviations**

| Abbreviation | Term |
|---|---|
| BID | twice daily |
| CR | complete response |
| CRF | case report form |
| ECOG | Eastern Cooperative Oncology Group |
| HR | hazard ratio |
| irRC | Immune related response criteria |
| IV | Intravenously |
| NE | not evaluable |
| OS | overall survival |
| PD | progressive disease |
| PFS | progression-free survival |
| RP2D | recommended phase 2 dose |
| RECIST | response evaluation criteria in solid tumors |
| RLT | regimen limiting toxicity |
| SAP | statistical analysis plan |
| WHO | World Health Organization |

# 2. INTRODUCTION

This is a non-randomized open-label Phase 1/2 trial designed to evaluate the combination of the immunotherapeutic agent indoximod and the standard of care chemotherapy gemcitabine plus nab-paclitaxel in patients with metastatic adenocarcinoma of the pancreas. The phase 1 portion was designed to identify the regimen-limiting toxicity (RLT) and recommended phase 2 dose (RP2D) for the combination. The phase 2 portion of the study evaluates the potential efficacy of this combination. All patients will receive the standard 28-day gemcitabine plus nab-paclitaxel regimen. Twice daily oral indoximod will be administered concurrently in continuous 28 day cycles. The Phase 2 expansion cohort requires paired biopsies prior to treatment and prior to the start of Cycle 2. Drug dosing is the same as in Phase 2.

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

## 3.1. Protocol and Case Report Form Version

This SAP is based on NLG-2104 Protocol Version 4 dated 25 JUL 2016 and case report forms (CRFs) version 2.

## 3.2. Study Objectives

### 3.2.1. Primary

The primary objective(s) of the study is:

- Phase 1 component: To characterize the regimen limiting toxicity (RLT) and determine a recommended phase 2 dose of indoximod when administered with a standard of care chemotherapy backbone consisting of gemcitabine plus nab-paclitaxel.

- Phase 2 component: To evaluate efficacy as determined by overall survival (OS) in patients with metastatic adenocarcinoma of the pancreas.

### 3.2.2. Secondary

The secondary objectives of the study are:

- To examine biomarker responses of gemcitabine and nab-paclitaxel with indoximod.
- To determine the response rate of the combination indoximod with gemcitabine plus nab-paclitaxel.
- To determine the time to progression and progression-free survival with the combination indoximod with gemcitabine plus nab-paclitaxel.

## 3.3. Study Endpoints

### 3.3.1. Primary

- The primary efficacy endpoint for the Phase 2 component is Overall Survival (OS).

### 3.3.2. Secondary

- Progression Free Survival (PFS)

- To examine biomarker responses of patients treated with gemcitabine and nab-paclitaxel with indoximod.

- To determine the response rate, duration of response, and duration of overall CR of patients treated with gemcitabine and nab-paclitaxel with indoximod using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria.

- To determine the time to progression of patients treated with gemcitabine and nab-paclitaxel with indoximod.

# 4. STUDY DESIGN

This is a Phase 1/2 trial designed to evaluate the combination of the immunotherapeutic agent indoximod and the standard of care chemotherapy gemcitabine plus nab-paclitaxel in patients with metastatic adenocarcinoma of the pancreas. The phase 1 portion is designed to identify the regimen-limiting toxicity (RLT) and recommended phase 2 dose (RP2D) for the combination. The phase 2 portion of the study will evaluate the potential efficacy of this combination. All patients will receive the standard 28-day gemcitabine plus nab-paclitaxel regimen. Twice daily oral indoximod will be administered concurrently in continuous 28 day cycles. Drug dosing will be the same as in Phase 1. (Figure 1).

In the phase 1 portion, dose escalation of indoximod will begin at 600mg twice daily and potentially escalate to 1200 mg twice daily. There will be no intra-patient dose escalation. The standard of care backbone chemotherapy is associated with significant toxicities that may confound efforts to define the true toxicity of indoximod when added to this backbone. The high rate of toxicity of the backbone regimen may result in an inaccurate rejection of all dose levels of any new agents when added. It has been recommended in these situations that a "pragmatic" approach be adopted for determining dose-limiting toxicities. In this approach, only grade 3 and 4 toxicities that are attributable to the test agent *and* result in the delay of the administration of the backbone chemotherapy, gemcitabine plus nab-paclitaxel, will be considered as regimen limiting. Additionally, any toxicities not before seen with either the backbone chemotherapy alone or with indoximod alone will be considered regimen associated toxicities and not ascribed to either agent in isolation. The period for determination of dose-limiting toxicities will be the initial 28 days of treatment. The recommended phase 2 dose will include an assessment of toxicities that occur at later time points.

Dosage Escalation: Phase 1 component: Patients will be assigned in cohorts of three. Dose escalation will occur according to a standard 3 x 3 dose escalation design in 28 day cycles.

| Dose Level | Indoximod DOSE (oral) | Nab-paclitaxel (IV) | Gemcitabine (IV) |
|---|---|---|---|
| 1 | 600 mg BID x 28 days | 125 mg/m$^2$ weekly x 3 | 1000 mg/m$^2$ weekly x 3 |
| 2 | 1000 mg BID x 28 days | 125 mg/m$^2$ weekly x 3 | 1000 mg/m$^2$ weekly x 3 |
| 3 | 1200 mg BID x 28 days | 125 mg/m$^2$ weekly x 3 | 1000 mg/m$^2$ weekly x 3 |

Regimen Limiting Toxicities are defined as:

- Any grade 4 non-hematological toxicity that is related to indoximod, with the exception of alopecia or nausea;
- Any grade 3 non-hematological toxicity that is related to indoximod that results in the delay of administration of the backbone chemotherapy (gemcitabine plus nab-paclitaxel) by more than 4 weeks;
- Grade 4 thrombocytopenia (<25,000/μL) attributable to indoximod that results in the

delay of administration of the backbone chemotherapy for more than 4 weeks;

- Grade 4 (<500/μL) neutropenia lasting more than 7 days, or Grade 3 (<1000/μL) febrile neutropenia, attributable to indoximod;

- Delay in starting the second cycle of the backbone therapy by more than 4 weeks due to any additional toxicities attributable to test agent indoximod.

AEs not known and expected from gemcitabine plus nab-paclitaxel and not seen in phase 1/2 indoximod studies will be considered regimen associated toxicities initially. Any grade 3 or higher regimen toxicity of this nature mandates a conference call within the next 3 business days between investigators and sponsor to discuss attribution and response.

Phase 2: Once a RP2D is determined, the phase 2 portion of the study will be initiated. In both phase 1 and phase 2, every 2 cycles patients will have repeat imaging to assess response. Corollary biomarkers will be assessed at the same interval as will PET-CT after the 1st 8 week cycle. Up to 18 patients will be enrolled in the phase 1 portion of the study and 80 patients will be enrolled in the phase 2 portion. Once a RP2D is determined, treatment will commence with oral indoximod concurrent with the first backbone chemotherapy cycle.

Patients will receive gemcitabine plus nab-paclitaxel on a standard 4 week cycle schedule. Oral indoximod will continue throughout.

After the first two cycles of backbone chemotherapy, interval assessments will be performed. These will include CT or MRI (consistent with patient's baseline imaging modality) as well as PET in up to 30 patients at selected institutions for research purposes. Biochemical assessments will be performed as well as per the study calendar. Patients continuing on treatment will have imaging and biochemical assessment after every two cycles (with research PET performed after the first 2 cycles only).

Treatment may continue until patient has treatment limiting toxicity, progression of disease, withdrawals consent, or is considered to no longer be in adequate physical condition for additional therapy by the treating physician.

Phase 2 Expansion Cohort: Once the Phase 2 cohort fills, additional patients will be enrolled in an expansion cohort that requires paired pre-treatment and on-treatment biopsies of the same lesion. Biopsies must be done percutaneously, preferably by ultrasound guidance. No endoscopic or laparoscopic biopsies are allowed. No lung lesions are allowed due to the high risk of complication (pneumothorax) with multiple core needle biopsies.

The first biopsy is to be done prior to study treatment. The second biopsy is to be done during study week 8 (Cycle 2 week 4). Study treatment in the Phase 2 expansion will otherwise follow the treatment plan for Phase 2 (see section 4.4 of the protocol for more information regarding the expansion cohort).

Figure 1: **Study Design**

**TREATMENT SCHEMATIC**
**Phase 1 and Phase 2**

**Study Day -30 to –0**
Patients prescreened for protocol eligibility
↓
**Cycle 1 Day 1**
Indoximod (dose dictated by escalation level) po daily starts and continues throughout study Nab-paclitaxel 125 mg/m$^2$ given intravenously over 30 to 40 minutes followed by Gemcitabine 1000 mg/m$^2$ intravenously over 30 to 40 minutes
↓
**Cycle 1 Day 8**
Nab-paclitaxel 125 mg/m$^2$ given intravenously over 30 to 40 minutes followed by Gemcitabine 1000 mg/m$^2$ intravenously over 30 to 40 minutes
Indoximod po continues
↓
**Cycle 1 Day 15**
Nab-paclitaxel 125 mg/m$^2$ given intravenously over 30 to 40 minutes followed by Gemcitabine 1000 mg/m$^2$ intravenously over 30 to 40 minutes
Indoximod po continues
↓
**Cycle 1 Day 22**
Rest from Chemotherapy
Indoximod (dose dictated by escalation level) po daily continues
↓
**Cycle 2 Day 1**
Nab-paclitaxel 125 mg/m$^2$ given intravenously over 30 to 40 minutes followed by Gemcitabine 1000 mg/m2 intravenously over 30 to 40 minutes
Indoximod po continues
↓
**Cycle 2 Day 8**
Nab-paclitaxel 125 mg/m$^2$ given intravenously over 30 to 40 minutes followed by Gemcitabine 1000 mg/m$^2$ intravenously over 30 to 40 minutes
Indoximod po continues
↓
**Cycle 2 Day 15**
Nab-paclitaxel 125 mg/m$^2$ given intravenously over 30 to 40 minutes followed by Gemcitabine 1000 mg/m$^2$ intravenously over 30 to 40 minutes
Indoximod po continues
↓
**Cycle 2 Day 22**
Rest from Chemotherapy
Indoximod (dose dictated by escalation level) po daily continues Evaluate for Response (imaging and biomarkers)
↓
**Treatment may continue until disease progression or significant toxicity**

## 4.1. Sample Size Considerations

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

Phase 2 component: The primary objective of the Phase 2 component is to assess the efficacy of indoximod in combination with gemcitabine plus nab-paclitaxel as determined by overall survival (OS) in patients with metastatic adenocarcinoma of the pancreas.

Assuming an expected median OS of 8.5 months for patients treated with gemcitabine plus nab-paclitaxel based on historical data[1]approximately 56 OS events would be required to detect with 80% power and one-sided significance level of 0.05 an increase in median OS of 30% (12.14 months). A total of 80 patients will be enrolled to account for up to 30% of patients being non-evaluable or lost to follow-up. No patients from Phase 1 will roll over into Phase 2.

Phase 2 biopsy cohort: The endpoint of the biopsy cohort is to obtain pre- and post-treatment tumor biopsies that can be analyzed retrospectively upon completion of the trial to gain insight into the scientific basis for any observed treatment effect and possibly guide future trial design and patient selection. As this is an exploratory effort, no formal sample-size estimation can be performed. According to general guidelines regarding the sample size for pilot or translational studies, a sample size of up to 40 patients would provide a reasonable precision for the estimation of pilot information.

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

## 4.2. Schedule of Assessments

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

## Table 2: Schedule of Assessments

| | Pre Study | Cycle 1 | | | | Additional Cycles | | | | FUV |
|---|---|---|---|---|---|---|---|---|---|---|
| | | D1 | D8 | D15 | D22 | D1 | D8 | D15 | D22 | |
| Nab-Paclitaxel | | **A** | **A** | **A** | | **A** | **A** | **A** | | |
| Gemcitabine | | **B** | **B** | **B** | | **B** | **B** | **B** | | |
| Indoximod | | **C** | **C** | **C** | **C** | **C** | **C** | **C** | **C** | |
| Informed consent | X | | | | | | | | | |
| Demographics | X | | | | | | | | | |
| Medical history | X | | | | | | | | | |
| Concurrent meds | X | X---------- | | | | | | | ----------X | |
| Physical exam | X | X | | | | X | | | | X |
| Vital signs | X | X | X | X | | X | X | X | | X |
| Height | X | | | | | | | | | |
| Weight | X | X | | | | X | | | | X |
| Performance status | X | X | | | | X | | | | X |
| CBC w/diff, plts | X | X | X | X | | X | X | X | | X |
| Serum chemistry | X | X | X | X | | X | X | X | | X |
| CA19-9/CEA | X | | | | | | | **D** | | |
| C-Reactive Protein | | X | | X | | X | | X | | |
| PT, PTT, INR | X | | | | | | | | | |
| Urinalysis | X | | | | | | | | | |
| EKG | X | | | | | | | | | |
| Adverse event evaluation | X | X ---------- | | | | | | | ---------- X | |
| Tumor measurements | X | **Tumor measurements are completed at each radiologic evaluation.** | | | | | | | | |
| Radiologic evaluation (CT or MRI) | X | **CT or MRI to be completed every 2 cycles** | | | | | | | | |
| PET Scan | X | | | | | | | **E** | | |
| B-HCG | X | | | | | | | | | |
| [redacted] | | [redacted] | | [redacted] | | [redacted] | | [redacted] | | |
| Blood for future testing | | **G** | | | | **G** | | | | |
| Archival tumor tissue | | **H** | | | | | | | | |
| Blood & PBMC | | **I** | Every 2 months during active treatment | | | | | | | |
| Paired Core Needle Bx | X | | | | | End of Cycle 2 | | | | |

**Calendar Notes:**

**A**: Nab-paclitaxel 125 mg/m$^2$ IV

**B**: Gemcitabine 1000 mg/m$^2$ IV

**C**: Indoximod PO - dose determined by escalation or phase 2 dose

**D**: CA19-9 or CEA to be performed at completion of every 2 cycles

**E**: PET Scan (at selected institutions only) to be completed at baseline and once at end of the first 2 cycles

**F**: [redacted]

**G**: Blood for future testing – Sample sent same day, on room air, overnight express to NewLink Genetics for banking. Samples should not be shipped on Fridays or day before U.S. holidays.

**H**: Archival tumor tissue is obtained if possible.

**I**: Drawn pre-drug administration and then every 2 months during treatment (see section 12.5 of the protocol)

# 5. DATA HANDLING DEFINITIONS AND CONVENTIONS

## 5.1. Scheduled Study Evaluations and Study Periods

### 5.1.1. Day 1

Day 1 is the date of first dose of treatment with study drug. Study drug is defined as any of the following: indoximod, gemcitabine or nab-paclitaxel.

### 5.1.2. Study Day

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

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

### 5.1.3. Baseline Value

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

### 5.1.4. Enrollment Date

The date the patient signed informed consent.

### 5.1.5. End of Treatment Value

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

### 5.1.6. Cycle Length and Duration

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

**For purposes of exposure evaluation:** Cycle 1 Day 1 is defined as the day of the first dose of Study drug. The end of the first cycle of therapy is the earlier of: (1) 28 calendar days (inclusive) later; or (2) permanent discontinuation of Study drug. Subsequent cycles are the periods starting 1 day after the end of the previous cycle and ending the earlier of: (1) 28 calendar days (inclusive) later; or (2) permanent discontinuation of study medication.

## 5.2. Variable Definitions

### 5.2.1. Age

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

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

### 5.2.2. Body Mass Index (BMI)

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

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

### 5.2.3. Body Surface Area (BSA)

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

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

### 5.2.4. Concomitant Medication

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

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

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

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

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

# 6. STATISTICAL METHODOLOGY

## 6.1. General Methodology

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

## 6.2. Analysis Populations

### 6.2.1. Safety Population

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

### 6.2.2. Intent-to-Treat Population

The intent-to–treat population will include all patients receiving at least 1 dose of study drug.

### 6.2.3. Efficacy Evaluable (EE) Population

The EE population consists of all patients enrolled in phase 2 except those included in the biopsy cohort (subjects 016 through 117) who have received at least one cycle of therapy and have had their disease re-evaluated through radiographic imaging and assessed according to RECIST version 1.1 at least once post baseline. EE will also include any patients who exhibit objective disease progression by radiographic imaging assessment according to RECIST version 1.1 prior to the end of cycle 1.

### 6.2.4. Efficacy Evaluable Including Biopsy Cohort (EEBC) Population

The EEBC consists of all patients enrolled in phase 2 who have received at least one cycle of therapy and have had their disease re-evaluated through radiographic imaging and assessed according to RECIST version 1.1 at least once post baseline. EEBC will also include any patients who exhibit objective disease progression by radiographic imaging assessment according to RECIST version 1.1 prior to the end of cycle 1.

# 7. BASELINE, EXPOSURE, AND DISPOSITION VARIABLES AND ANALYSES

Unless otherwise stated, all analyses in this section will be performed on the safety population and presented by study phase. All data that is summarized will be supported by a patient level data listing. Additional listings may described in the relevant section.

## 7.1. Disposition of Patients

The number and percentage of patients who were enrolled, enrolled and not treated, in the safety population, who completed at least 1 cycle of treatment, in the EE population, in the EEBC population, who were withdrawn from treatment (with a primary reason for treatment withdrawal), and who were withdrawn from the study (with a primary reason for study withdrawal) will be summarized for all patients by study phase.

## 7.2. Demographics and Baseline Disease Characteristics

The following demographic and baseline characteristics will be summarized for the safety and EEBC populations: age, sex, race, ethnicity, weight (by gender), height, BMI, BSA, baseline ECOG performance status. Additionally, staging information of histological type, primary tumor (T) stage, regional lymph node (N) stage, distant metastasis (M) stage, and pathologic stage grouping will be summarized separately.

## 7.3. Protocol Deviations

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

## 7.4. Medical History

Medical history will be coded using MedDRA dictionary. Medical history will be summarized by CTCAE grade within each body system.

## 7.5. Physical Exam

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

## 7.6. Concomitant Medication

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

## 7.7. Prior Systemic and Radiation Therapy

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

## 7.8. Exposure

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

- **Number of Cycles Started**: Number of cycles started will be the number of cycles with a nonzero dose of any study drug.
- **Number of Cycles Completed**: Number of cycles completed will be the number of cycles where all 3 doses of nab-paclitaxel or gemcitabine were administered.
- **Duration of Treatment**: The number of study days between Day 1 and the last nonzero dosing record of study drug taken by the patient. If the last dosing record is non-zero and has a missing end date, then the last day of treatment is defined as the earliest of: (1) the end-of-treatment visit; (2) date of death; or, (3) the last on-study visit.
- **Total Dose**: The total dose administered across the duration of the study for each study medication as recorded on the CRF.
- **Total Average daily dose**: average daily dose is the total dose (mg)/duration of treatment (days)
- **Assigned Dose (use BSA for each cycle):**

- **Relative Dose Intensity**:

Nab-Paclitaxel/ Gemcitabine relative dose intensity (%) = 100× [total dose (mg)/assigned dose (mg)]

## 7.9. Indoximod Compliance

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

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

# 8. EFFICACY

## 8.1. General Considerations

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

## 8.2. Phase 1 Component Primary Endpoints

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

An RLT is defined in Section 4.

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

## 8.3. Efficacy Hypotheses

**Overall Survival (Primary Endpoint):** Administration of indoximod in combination with standard of care treatment gemcitabine plus nab-paclitaxel improves OS in patients with metastatic adenocarcinoma of the pancreas.

**Progression-Free Survival (Secondary Endpoint):** Administration of indoximod in combination with standard of care treatment gemcitabine plus nab-paclitaxel improves PFS in patients with metastatic adenocarcinoma of the pancreas.

**Best Overall Response Rate (Secondary Endpoint):** Administration of indoximod in combination with standard of care treatment gemcitabine plus nab-paclitaxel improves Best ORR in patients with metastatic adenocarcinoma of the pancreas.

## 8.4. Analysis of the Primary Efficacy Parameter

### 8.4.1. Overall Survival (OS)

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

Kaplan-Meier methods will be used to estimate the survival time distribution and the median, $25^{th}$ and $75^{th}$ percentiles of survival (in weeks) by study phase and overall. Confidence intervals

around median survival time will be calculated using the method of Brookmeyer and Crowley[3], which is the default method within SAS version 9.3. Figures for Kaplan-Meier estimates will also be presented. OS will be summarized for the EEBC population and the ITT population.

## 8.5. Analysis of the Secondary Efficacy Parameters

### 8.5.1. Progression-Free Survival (PFS)

PFS will be calculated from the date of enrollment to the time of CT scan documenting relapse or other unambiguous indicator of disease development), or date of death, whichever occurs first. Patients who have no documented relapse as defined by RECIST and are still alive prior to the database lock, or who dropout prior to study end, will be censored at the date of the last radiological evidence documenting absence of relapse. For patients with no post-baseline radiographic imaging, PFS will be censored at the end of treatment (EOT) or end of study (EOS) visit date, whichever is later. In these cases if the reason for EOT or EOS is disease progression, the patient will not be censored, but will be considered to have progressed on the date of EOT or EOS. PFS will be summarized for the EEBC population and the ITT population.

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

### 8.5.2. Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. For patients who do not have measurable disease, overall response can be assessed using Table 3. Response rate is defined as the percentage of patients with either complete or partial response while on study. Response rates will be presented by for target and non-target lesions, by study phase and overall, and 95% confidence intervals based on the normal approximation to the binomial will be presented for response rates.

**Table 3: RECIST Evaluation Criteria for Overall Response: For Patients with Measurable Disease (i.e., Target Disease)**

| Target Lesions | Non-Target Lesions | New Lesions | Overall Response | Best Overall Response when Confirmation is |
|---|---|---|---|---|
| CR | CR | No | CR | > 4 weeks Confirmation** |
| CR | Non-CR/Non-PD | No | PR | ≥ 4 weeks Confirmation** |
| CR | Not evaluated | No | PR | |
| PR | Non-CR/Non-PD/not evaluated | No | PR | |
| SD | Non-CR/Non-PD/not evaluated | No | SD | documented at least once ≥ 4 weeks from baseline** |

| | | | | |
|---|---|---|---|---|
| PD | Any | Yes or No | PD | no prior SD, PR or CR |
| Any | PD*** | Yes or No | PD | |
| Any | Any | Yes | PD | |

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

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

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

**Table 4: RECIST Evaluation Criteria for Overall Response: For Patients with Non-Measurable Disease (i.e., Non-Target Disease)**

| Non-Target Lesions | New Lesions | Overall Response |
|---|---|---|
| CR | No | CR |
| Non-CR/non-PD | No | Non-CR/non-PD* |
| Not all evaluated | No | not evaluated |
| Unequivocal PD | Yes or No | PD |
| Any | Yes | PD |

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

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

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

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

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

Time to treatment discontinuation will also be summarized.

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

### 8.5.3. Overall Response using Immune Related Response Criteria (iiRC)

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

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

irPR: decrease in tumor burden > 50% relative to baseline confirmed by a consecutive assessment at least 4 weeks after first documentation

irSD: not meeting criteria for irCR or irPR, in absence of irPD

irPD: increase in tumor burden > 25% relative to nadir (minimum recorded tumor burden) confirmed by a repeat, consecutive assessment no less than 4 weeks from the date first documented

irRC rate is defined as the percentage of patients with either irCR or irPR while on study.

Immune related response rates will be presented for target and non-target lesions, by study phase and overall, and 95% confidence intervals based on the normal approximation to the binomial will be presented for response rates.

# 9. SAFETY AND TOLERABILITY

## 9.1. General Considerations

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

## 9.2. Adverse Events

### 9.2.1. Adverse Event Definitions

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

Adverse events will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0 or later preferred term and system organ class. Severity of AEs will be described and graded using the NCI CTCAE version 4.03. NCI CTCAE grading reference can be found at https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

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

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

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

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

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

### 9.2.2. Adverse Event Summaries

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

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

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

- Number (%) of patients reporting TEAEs by system organ class and preferred term.
- Number (%) of patients reporting Serious TEAEs by system organ class and preferred term.
- Number (%) of patients reporting Indoximod-related Serious AEs by system organ class and preferred term.
- Number (%) of patients reporting CTCAE Grade 3 or 4 TEAEs by system organ class and preferred term.
- Number (%) of patients reporting CTCAE Grade 3 or 4 indoximod-related TEAEs by system organ class and preferred term.
- Number (%) of patients reporting TEAEs by CTCAE Grade system organ class and preferred term.
- Number (%) of patients reporting Fatal AEs by system organ class and preferred term.
- Number (%) of patients reporting indoximod-related AEs by system organ class and preferred term.
- Number (%) of patients reporting gemcitabine -related AEs by system organ class and preferred term.
- Number (%) of patients reporting nab-paclitaxel-related AEs by system organ class and preferred term.
- Number (%) of patients reporting treatment regimen-related AEs by system organ class and preferred term (related to any of the 3 study treatments).
- Number (%) of patients reporting treatment-emergent AEs by preferred term in descending order of frequency (for all patients).

The TEAEs occurring in ≥ 5% of the safety population are called frequently reported AEs and will be summarized by MedDRA preferred term for all TEAEs as well as indoximod related TEAEs.

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

## 9.3. Clinical Laboratory Tests

### 9.3.1. Laboratory Value Definitions

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

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

## 9.4. Vital Signs

The actual value and change from baseline to each visit will be summarized for vital signs (systolic blood pressure, diastolic blood pressure, heart rate, respiration rate, and body temperature). Potentially clinically significant vital sign abnormalities are defined in Table 5. The number and percent of patients with potentially clinically significant post-baseline vital sign values will be summarized over all post-baseline visits.

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

**Table 5: Criteria for Potentially Clinically Significant (PCS) Vital Sign Abnormalities**

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

## 9.5. Electrocardiograms

Twelve-lead electrocardiograms (ECGs) will be obtained for each patient during the study in accordance with Table 2. The baseline values will be summarized for ECG parameters. ECG results including abnormalities will also be tabulated.

## 9.6. ECOG/Karnofsky Performance Status

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

## 10. [redacted]

[redacted]

# 11. REFERENCES

1. Von Hoff, D.D., Randomized phase III study of weekly *nab*-paclitaxel plus gemcitabine versus gemcitabine alone in patients with metastatic adenocarcinoma of the pancreas (MPACT). 2013 Gastrointestinal Cancers Symposium Abstract LBA148.

2. Hintze, J. (2013). PASS 12. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com.

3. Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics 1982;38:29-41.

# 12. PLANNED TABLES, LISTINGS, AND FIGURES

## 12.1. Tables

| Table No | Title | Population |
|---|---|---|
| 14.1.1 | Patient Disposition by Study Phase | All Patients |
| 14.1.2.1 | Summary of Demographics and Baseline Disease Characteristics by Study Phase | Safety Population |
| 14.1.2.2 | Summary of Demographics and Baseline Disease Characteristics | EEBC Population |
| 14.1.3 | Summary of Histology by Study Phase | Safety Population |
| 14.1.4 | Summary of Medical History by Study Phase | Safety Population |
| 14.1.5 | Summary of Baseline Physical Examination by Study Phase | Safety Population |
| 14.1.6 | Summary of Concomitant Medications by Study Phase | Safety Population |
| 14.1.7 | Summary of Prior Systemic Therapy by Study Phase | Safety Population |
| 14.1.8 | Summary of Prior Radiation Therapy by Study Phase | Safety Population |
| 14.1.9.1 | Summary of Exposure to Indoximod by Study Phase | Safety Population |
| 14.1.9.2 | Summary of Exposure to Gemcitabine by Study Phase | Safety Population |
| 14.1.9.3 | Summary of Exposure to Nab-paclitaxel by Study Phase | Safety Population |
| 14.1.10 | Summary of Regimen Limiting Toxicities (RLTs) Phase 1 Only | Safety Population |
| | | |
| 14.2.1.1 | Summary of Overall Survival | EEBC Population |
| 14.2.1.2 | Summary of Overall Survival by Study Phase | ITT Population |
| 14.2.2.1 | Summary of Progression-free Survival Using RECIST Criteria | EEBC Population |
| 14.2.2.2 | Summary of Progression-free Survival Using RECIST Criteria by Study Phase | ITT Population |
| 14.2.3.1 | Summary of Best Overall Response Using RECIST Criteria | EEBC Population |
| 14.2.3.2 | Summary of Best Overall Response Using RECIST Criteria by Study Phase | ITT Population |
| 14.2.4.1 | Summary of Duration of Overall Response Using RECIST Criteria | EEBC Population |
| 14.2.4.2 | Summary of Duration of Overall Response Using RECIST Criteria by Study Phase | ITT Population |
| 14.2.5.1 | Summary of Duration of Stable Disease Using RECIST Criteria | EEBC Population |
| 14.2.5.2 | Summary of Duration of Stable Disease Using RECIST Criteria by Study Phase | ITT Population |
| 14.2.6.1 | Summary of Duration of Partial Response Using RECIST Criteria | EEBC Population |
| 14.2.6.2 | Summary of Duration of Partial Response Using RECIST Criteria by Study Phase | ITT Population |
| 14.2.7.1 | Summary of Time to First Response Using RECIST Criteria | EEBC Population |
| 14.2.7.2 | Summary of Time to First Response Using RECIST Criteria by Study Phase | ITT Population |
| 14.2.8.1 | Summary of Time to Progression Using RECIST Criteria | EEBC Population |
| 14.2.8.2 | Summary of Time to Progression Using RECIST Criteria by Study Phase | ITT Population |
| 14.2.9 | Summary of Time to Treatment Discontinuation by Study Phase | ITT Population |
| 14.2.10 | Summary of Best Overall Response Using Immune Related Response Criteria (irRC) by Study Phase | ITT Population |
| 14.2.11 | Summary of Best Response for Non-Target Lesions by Study Phase | ITT Population |
| 14.3.1 | Overall Summary of Treatment-Emergent Adverse Events by Study Phase | Safety Population |
| 14.3.2.1 | Summary of Treatment-Emergent Adverse Events By MedDRA System Organ Class, Preferred Term and Study Phase | Safety Population |
| 14.3.2.2 | Summary of Serious Treatment-Emergent Adverse Events By MedDRA System Organ Class, Preferred Term and Study Phase | Safety Population |
| 14.3.2.3 | Summary of CTCAE Grade 3 and 4 Treatment-Emergent Adverse Events By MedDRA System Organ Class, Preferred Term and Study Phase | Safety Population |
| 14.3.2.4 | Summary of CTCAE Grade 3 and 4 Indoximod-Related Treatment-Emergent Adverse Events By MedDRA System Organ Class, Preferred Term and Study Phase | Safety Population |

| Table No | Title | Population |
|---|---|---|
| 14.3.2.5 | Summary of Treatment-Emergent Adverse Events By MedDRA System Organ Class, Preferred Term, CTCAE Grade and Study Phase | Safety Population |
| 14.3.2.6 | Summary of Fatal Adverse Events By MedDRA System Organ Class, Preferred Term, and CTCAE Grade by Study Phase | Safety Population |
| 14.3.2.7 | Summary of Indoximod-Related Treatment-Emergent Adverse Events By MedDRA System Organ Class, Preferred Term and Study Phase | Safety Population |
| 14.3.2.8 | Summary of Indoximod-Related Serious Treatment-Emergent Adverse Events By MedDRA System Organ Class, Preferred Term and Study Phase | Safety Population |
| 14.3.2.9 | Summary of Gemcitabine -Related Treatment-Emergent Adverse Events By MedDRA System Organ Class, Preferred Term and Study Phase | Safety Population |
| 14.3.2.10 | Summary of Nab-paclitaxel-Related Treatment-Emergent Adverse Events By MedDRA System Organ Class, Preferred Term and Study Phase | Safety Population |
| 14.3.2.11 | Summary of Treatment-Emergent Adverse Events By MedDRA Preferred Term and Study Phase in Decreasing Order of Frequency | Safety Population |
| 14.3.2.12 | Summary of Treatment Regimen Related Treatment-Emergent Adverse Events By MedDRA Preferred Term and Study Phase in Decreasing Order of Frequency | Safety Population |
| 14.3.2.13 | Summary of Frequent (>=5%) Treatment-Emergent Adverse Events By MedDRA Preferred Term and Study Phase in Decreasing Order of Frequency | Safety Population |
| 14.3.2.14 | Summary of Frequent (>=5%) Treatment Regimen Related Treatment-Emergent Adverse Events By MedDRA Preferred Term and Study Phase in Decreasing Order of Frequency | Safety Population |
| 14.3.3.1 | Summary of Hematology Laboratory Values and Change from Baseline by Visit and Study Phase | Safety Population |
| 14.3.3.2 | Shift Table of Hematology Values - To the Worst Abnormal Value by Study Phase | Safety Population |
| 14.3.3.3 | Summary of Clinically Significant Abnormal Hematology Laboratory Values by Study Phase | Safety Population |
| 14.3.3.4 | Summary of Chemistry Laboratory Values and Change from Baseline by Visit and Study Phase | Safety Population |
| 14.3.3.5 | Shift Summary of Chemistry Values - To the Worst Abnormal Value by Study Phase | Safety Population |
| 14.3.3.6 | Summary of Clinically Significant Abnormal Chemistry Laboratory Values by Study Phase | Safety Population |
| 14.3.3.7 | Summary of Urinalysis Laboratory Results by Visit and Study Phase | Safety Population |
| 14.3.3.8 | Summary of Other Laboratory Values and Change from Baseline by Visit and Study Phase | Safety Population |
| 14.3.4.1 | Summary of Vital Sign Values and Change from Baseline by Visit and Study Phase | Safety Population |
| 14.3.4.2 | Summary of Potentially Clinically Significant Vital Sign Abnormalities by Study Phase | Safety Population |
| 14.3.5.1 | Summary of 12-Lead ECG Values by Study Phase | Safety Population |
| 14.3.5.2 | Summary of 12-Lead ECG Results by Study Phase | Safety Population |
| 14.3.6.1 | Summary of ECOG Status by Visit and Study Phase | Safety Population |
| 14.3.6.2 | Shift Summary of ECOG Status from Baseline to Worst Post-Baseline Status by Study Phase | Safety Population |

## 12.2. Figures

| Figure No | Title | Population |
|---|---|---|
| 14.4.1 | Kaplan-Meier Plot of Overall Survival | EEBC Population |

| Figure No | Title | Population |
|---|---|---|
| 14.4.2 | Kaplan-Meier Plot of Progression-free (RECIST) Survival | EEBC Population |
| 14.4.3 | Kaplan-Meier Plot of Duration of Overall Response (RECIST) | EEBC Population |
| 14.4.4 | Kaplan-Meier Plot of Duration of Stable Disease (RECIST) | EEBC Population |

## 12.3. Listings

| Listing No | Title |
|---|---|
| 16.1.1 | Patient Enrollment and Disposition Status by Study Phase and Dose |
| 16.1.2 | Patient Demographics by Study Phase and Dose |
| 16.1.3 | Medical History by Study Phase and Dose |
| 16.1.4 | Staging by Study Phase and Dose |
| 16.1.5 | Protocol Deviations/Violations by Study Phase and Dose |
| 16.1.6 | Physical Exam Findings by Study Phase and Dose |
| 16.1.7 | ECOG/Karnofsky Performance Status by Study Phase and Dose |
| 16.1.8 | Concomitant Medications by Study Phase and Dose |
| 16.1.9 | Concomitant Procedures by Study Phase and Dose |
| 16.1.10 | Prior Systemic Therapy by Study Phase and Dose |
| 16.1.11 | Prior Radiation Therapy by Study Phase and Dose |
| 16.1.12 | Imaging by Study Phase and Dose |
| 16.1.13 | Regimen Limiting Toxicities |
| 16.2.1 | Study Drug Compliance and Exposure by Study Phase and Dose |
| 16.2.2 | Gemcitabine and Nab-Paclitaxel Administration by Study Phase and Dose |
| 16.2.3 | Indoximod Administration by Study Phase and Dose |
| 16.3.1 | Target Lesions – RECIST by Study Phase and Dose |
| 16.3.2 | RECIST Response by Study Phase and Dose |
| 16.3.3 | Measurable Lesions (irRC) by Study Phase and Dose |
| 16.3.4 | Non-Target Lesions RECIST and irRC by Study Phase and Dose |
| 16.3.5 | irRC Response by Study Phase and Dose |
| 16.3.6 | Survival Status by Study Phase and Dose |
| 16.3.7 | Overall Survival Events and Assessments by Study Phase and Dose |
| 16.3.8 | Death Report Information by Study Phase and Dose |
| 16.3.9 | Regimen Limiting Toxicities |
| 16.4.1 | Adverse Events by Study Phase and Dose |
| 16.4.2 | Serious Adverse Events by Study Phase and Dose |
| 16.4.3 | Fatal Adverse Events by Study Phase and Dose |
| 16.4.4 | Grade 3 or 4 Adverse Events by Study Phase and Dose |
| 16.4.5 | Grade 3 or 4 Indoximod-Related Adverse Events by Study Phase and Dose |
| 16.4.6 | Indoximod-Related Adverse Events by Study Phase and Dose |
| 16.4.7 | Gemcitabine-Related Adverse Events by Study Phase and Dose |
| 16.4.8 | Nab-paclitaxel-Related Adverse Events by Study Phase and Dose |
| 16.4.9 | Adverse Events Causing Treatment Discontinuation by Study Phase and Dose |
| 16.5.1 | Chemistry Laboratory Values by Study Phase and Dose |
| 16.5.2 | Abnormal Chemistry Laboratory Values by Study Phase and Dose |
| 16.5.3 | Hematology Laboratory Values by Study Phase and Dose |
| 16.5.4 | Abnormal Hematology Laboratory Values by Study Phase and Dose |
| 16.5.5 | Urinalysis Laboratory Values by Study Phase and Dose |
| 16.5.6 | Other Laboratory Values by Study Phase and Dose |
| 16.5.7 | Pregnancy Test Results by Study Phase and Dose |

| Listing No | Title |
|---|---|
| 16.6.1 | Vital Signs by Study Phase and Dose |
| 16.6.2 | Abnormal Vital Sign Values by Study Phase and Dose |
| 16.7.1 | 12-Lead ECG Values and Interpretation by Study Phase and Dose |
| 16.7.2 | Abnormal 12-Lead ECG Values by Study Phase and Dose |

# APPENDIX A. CLINICAL LABORATORY TESTS

| Serum Chemistry | Hematology | Urinalysis | Other |
|---|---|---|---|
| Alkaline phosphatase | WBC Count | Specific Gravity | C-reactive protein |
| ALT | Neutrophil | Protein | CA 19-9 |
| AST | Eosinophil | Glucose | Carcinoembryonic Antigen (CEA) |
| Bicarbonate | Basophil | pH | INR |
| BUN | Monocyte | Ketones | PT |
| Calcium | Lymphocyte | Bacteria | PTT |
| Chloride | Hemoglobin | RBC | |
| Creatinine | Platelet | WBC | |
| Glucose | | | |
| Potassium | | | |
| Sodium | | | |
| Total Bilirubin | | | |

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

# APPENDIX B. CLINICAL LABORATORY CONVERSION FACTORS*

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

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

# APPENDIX C. PERFORMANCE STATUS CRITERIA

| **ECOG Performance Status Scale** | | **Karnofsky Performance Scale** | |
|---|---|---|---|
| Grade | Descriptions | Percent | Description |
| 0 | Normal activity. Fully active, able to carry on all pre-disease performance without restriction. | 100 | Normal, no complaints, no evidence of disease. |
| | | 90 | Able to carry on normal activity; minor signs or symptoms of disease. |
| 1 | Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work). | 80 | Normal activity with effort; some signs or symptoms of disease. |
| | | 70 | Cares for self, unable to carry on normal activity or to do active work. |
| 2 | In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. | 60 | Requires occasional assistance, but is able to care for most of his/her needs. |
| | | 50 | Requires considerable assistance and frequent medical care. |
| 3 | In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. | 40 | Disabled, requires special care and assistance. |
| | | 30 | Severely disabled, hospitalization indicated. Death not imminent. |
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. | 20 | Very sick, hospitalization indicated. Death not imminent. |
| | | 10 | Moribund, fatal processes progressing rapidly. |
| 5 | Dead. | 0 | Dead. |