Clinical Trial Protocol
NLG-2104

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

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

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PROTOCOL SYNOPSIS:

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

Primary Objective: 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.

Secondary Objectives:

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

Population: Patients with metastatic pancreas cancer who have NOT received any prior chemotherapy agents in the metastatic setting.

Sample Size: Up to 98 patients will be initially enrolled in this study (up to 18 in phase 1, and 80 patients in phase 2).

An additional Phase 2 expansion cohort of up to 40 patients will be added for the purpose of obtaining matched pre-treatment and on-treatment tumor biopsies.

Investigational Drug: Indoximod consists of an inhibitor of the immunoregulatory enzyme, indoleamine 2,3-dioxygenase. Indoximod is a sterile powder mixed with inert ingredients and packaged as 200 mg capsules.

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

Safety Analysis: To establish the safety and the recommended phase 2 dose of indoximod in combination with gemcitabine plus nab-paclitaxel, it is necessary to determine the attribution of all toxicities. However, 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.

Duration of Treatment: Patients may continue on treatment until they experience progressive disease or unacceptable toxicity, require palliative radiotherapy, withdraw consent, or their physician feels it is no longer in their best interest to continue on treatment.

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/m^2 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

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RESEARCH PROTOCOL ABSTRACT

This is a phase 1/2 trial designed to efficiently identify the regimen limiting toxicity (RLT) and recommended phase 2 dose (RP2D) for the combination of the immunotherapeutic agent indoximod when administered in combination with standard of care chemotherapy gemcitabine plus nab-paclitaxel in patients with metastatic adenocarcinoma of the pancreas. All patients will receive the same standard gemcitabine plus nab-paclitaxel regimen, plus indoximod in doses increasing from 600 mg twice daily to, potentially, 1200 mg twice daily. Doses of indoximod will be allocated using a standard three plus three dose escalation. RLT will be considered as 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. Every 2 cycles (8 weeks), patients will have repeat imaging to assess response. Corollary biomarkers will be assessed at the same time points.

1.0 OBJECTIVES

1.1 Primary objectives

Phase 1 component: To characterize the regimen limiting toxicity and recommended phase 2 dose of indoximod when administered with gemcitabine plus nab-paclitaxel.

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

1.2 Secondary objectives

a) To examine biomarker responses of gemcitabine and nab-paclitaxel with indoximod.

b) To determine the response rate of the combination indoximod with gemcitabine plus nab-paclitaxel.

c) To determine the time to progression and progression-free survival with the combination indoximod with gemcitabine plus nab-paclitaxel.

2.0 BACKGROUND

2.1 Adenocarcinoma of the exocrine pancreas

Pancreatic cancer is a major unsolved public health problem in the United States, with approximately 44,000 new cases in the year 2012, making it the tenth most common malignancy in adult men and ninth in women. It ranks as the fourth leading cause of cancer deaths, accounting for 7 % of all cancer-related deaths in the United States. Five-year survival is less than 5% for all stages. Currently, the only potentially curative therapy is surgical resection. Nonetheless, many patients who undergo surgical resection derive limited therapeutic benefit. Survival of patients who undergo surgical resection followed by adjuvant radio-chemotherapy for localized non-metastatic adenocarcinoma of the pancreas is at best 15% at 5 years, and the

median disease free survival is 10-13 months. This uniformly poor prognosis even in the earliest stage disease with best treatment modalities, underscores the need for radical rethinking of our approach to pancreatic cancer. There is a critical need for development of novel therapies with biological activity to improve outcomes in this disease.

In the advanced setting, effective therapeutic options are limited. Gemcitabine has become the standard chemotherapy for treatment of advanced pancreatic cancer for the last 15 years, after demonstration that gemcitabine produced significant improvement in disease-related symptoms and prolonged survival when compared to 5-FU. Since the establishment of gemcitabine as standard chemotherapy for pancreatic adenocarcinoma, multiple trials have evaluated the addition of alternate chemotherapeutic agents to gemcitabine. Of the multiple phase 3 trials preformed, only the addition of erlotinib was shown to have any additional benefit. Recent data from the MPACT trial has shown a significant increase in one and two year survival for the combination of gemcitabine and nab-paclitaxel in the advanced setting. This combination can be considered a current standard of care therapy for metastatic pancreatic adenocarcinoma.

2.2 Immune suppression, pancreatic cancer and Indolamine 2,3 dioxygenase (IDO)

The pancreatic tumor microenvironment is marked by significant immunosuppression [1]. This immune suppression has been reported to be facilitated by a number of soluble factors derived from both the tumor stromal and immune infiltrating compartments [1-3]. One of these factors is indolamine 2,3 dioxygenase or IDO. IDO degrades the essential amino acid tryptophan. IDO has been reported to be produced by stromal, tumor and infiltrating immune cells. The primary effect of IDO is a direct effect of tryptophan depletion. Tryptophan depletion can lead to attenuated proliferation of local pathogens, tumor cells and, more importantly, tumor infiltrating lymphocytes. Local depletion of tryptophan is believed to be immunosuppressive to local T cells. T cells starved of tryptophan are unable to proliferate and are more sensitive to Fas-mediated apoptosis. In addition, it appears that IDO may also induce preferential differentiation of naïve T cells into T regulatory cells that can further accentuate the local immunosuppressive microenvironment. In addition, the metabolites of tryptophan have been reported to be toxic to effector T cells preferentially over TH2-like cells. In pancreatic cancer, Brody et al have demonstrated increased production of both known forms of IDO, IDO1 and IDO2, in the tumor microenvironment. Specifically, primary pancreatic cancer cell lines were able to express IDO after treatment with IFNγ. Interestingly, fresh metastatic pancreatic tumor cells from lymph node metastases also demonstrated IDO expression.

2.3 Indoximod (1-methyl-D-tryptophan, NSC-[redacted]; IND#[redacted], IND#[redacted], IND#[redacted])

A copious amount of literature has developed demonstrating that the IDO-mediated modulation of immune responses is important in autoimmunity and transplantation in addition to regulating immunity in health [2]. It was shown that an inhibitor of the IDO pathway, indoximod, improved anti-tumor T cell responses and slowed the growth of tumors. Subsequently, several other groups have confirmed this finding in other models [3, 4]. This agent was prioritized by NCI's RAID program for clinical development as an IDO pathway inhibitor. An important component of this work included the revelation that the D-isomer was more effective than the L-isomer of the racemic mixture in shrinking tumors. Based on these results it was decided to

continue the development of this drug with the Drug Development Group (DDG) at NCI. Extramural resources were committed to perform the IND-directed preclinical work. They were able to demonstrate good oral bioavailability with favorable pharmacokinetics with once daily dosing. Furthermore, no significant toxicity was observed in animals.

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

Objective responses have been seen in a phase 1b study (Protocol 8784 under IND78060) investigating indoximod given with docetaxel for metastatic solid tumors. Twenty-seven subjects were enrolled onto this study with 22 subjects being evaluable for response. Docetaxel was administered at 60 mg/m^2 intravenously every 3 weeks dose levels 1-4 and 75 mg/m^2 for dose level 5. Indoximod was given at 300, 600, 1000, 2000, and 1200 mg PO twice daily continuously for levels 1-5, respectively. Four patients (2 breast, 1 NSCLC, 1 thymic tumor) achieved a partial response (18%), one patient achieved stable disease for longer than 6 months (4%), nine patients achieved stable disease for less than 6 months (36%), and eight patients had progressive disease (36%). No drug-drug interactions were noted. (Soliman, HH et al. 2014).

2.4 Gemcitabine

Gemcitabine chemotherapy is the standard of care for inoperable pancreatic cancer, although its clinical activity is modest. In the initial phase 2 trial of single-agent gemcitabine, an 11% partial response rate was observed (Casper, Green et al. 1994). A phase 3 randomized study of gemcitabine versus 5-flourouracil in 126 patients reported a 5% objective response rate in the gemcitabine arm, with a median survival of 5.65 months and a 1-year survival rate of 18% (Burris, Moore et al. 1997). Twenty-four percent of patients in the gemcitabine arm experienced a clinical benefit, consisting of improved pain control, performance status, or weight stabilization. In 1996, the US Food and Drug Administration (FDA) approved gemcitabine for the treatment of locally advanced and metastatic pancreatic cancer.

Despite numerous trials of novel agents given alone or in combination with gemcitabine, little has improved upon these very modest results. It was not until the 2005 National Cancer Institute of Canada report of a phase 3 trial of gemcitabine plus erlotinib versus gemcitabine that any combination was shown to be superior to gemcitabine monotherapy. Although statistically significant (hazard ratio 0.82), the absolute improvement in survival, (5.91 months with gemcitabine, 6.24 months with the combination) was once again, exceedingly modest (Moore, Goldstein et al. 2007) and no difference in response rates was seen in the combination arm as compared to gemcitabine alone. As such, although this combination is a licensed indication for pancreatic cancer, gemcitabine plus erlotinib is not a widely accepted standard of care.

2.5 FOLFIRINOX

In the metastatic setting, FOLFIRINOX was compared to standard gemcitabine monotherapy in 342 patients with an ECOG PS0 or 1. The primary endpoint was (OS), with a median OS of 11.1 months in the FOLFIRINOX group vs. 6.8 months in the gemcitabine group (HR for death, 0.57; 95% confidence interval [CI], 0.45 to 0.73; P<0.001). Median progression-free survival (PFS) was 6.4 months in the FOLFIRINOX group and 3.3 months in the gemcitabine group (HR for disease progression, 0.47; 95% CI, 0.37 to 0.59; P<0.001). The objective RR was 31.6% in the FOLFIRINOX group versus 9.4% in the gemcitabine group (P<0.001) (Conroy *et al.* 2011). The toxicities of FOLFIRINOX in this study included moderate to severe fatigue, hematopoietic toxicity, nausea and diarrhea. In practice, individual practitioners and institutions have made changes to the FOLFIRINOX backbone to reduce these toxicities. How these changes may affect the endpoints of PFS and OS in FOLFIRINOX treated patients is not known. However, the overall poor tolerability of this regimen in various groups of patients, especially in older or poorer PS patients, makes this combination difficult to utilize in the majority of pancreatic patients, and therefore it is not universally accepted as first line treatment in metastatic patients. Its toxicities also make it a poor choice to combine with other drugs in new studies such as this one due to possible overlapping toxicity.

2.6 Paclitaxel Albumin-bound Particles (Nab-Paclitaxel)

Nab-paclitaxel is a unique protein formulation of a non-crystalline, amorphous form of paclitaxel in an insoluble particle state. Nab-paclitaxel has been developed to reduce the toxicities associated with Taxol (paclitaxel) Injection (in which paclitaxel - from the native crystalline form - is formulated with Cremophor EL/ethanol as the solvent) while maintaining or improving its chemotherapeutic effect. Nab-paclitaxel has been approved for commercialization in 38 countries, including the United States (US), Canada, the EU, Australia, China, India and Korea for the treatment of women with metastatic breast cancer. Nab-paclitaxel alone and in combination chemotherapy is being evaluated in a number of cancers, including metastatic melanoma, non-small cell lung cancer, pancreatic cancer, and other solid tumors.

A recent phase 3 clinical trial of nab-paclitaxel in combination with gemcitabine in treatment-naïve patients with metastatic pancreatic cancer demonstrated a statistically significant improvement in overall survival compared to patients receiving gemcitabine alone [(median of 8.5 vs. 6.7 months) (HR 0.72, P=0.000015)]. In the MPACT (Metastatic Pancreatic Adenocarcinoma Clinical Trial) study, nab-paclitaxel plus gemcitabine demonstrated a 59% increase in one-year survival (35% vs. 22%, p=0.0002), double the rate of survival at two years (9% vs. 4%, p=0.02), and an improvement in 3 year survival (4% vs. 0%) as compared to gemcitabine alone. Nab-paclitaxel plus gemcitabine also demonstrated a statistically significant improvement in key secondary endpoints compared to gemcitabine alone, including a 31% reduction in the risk of progression or death with a median progression-free survival (PFS) of 5.5 vs. 3.7 months (HR 0.69, P=0.000024) and an overall response rate (ORR) of 23% compared to 7% (response rate ratio of 3.19, p=1.1 x 10-10).

The most common grade ≥ 3 treatment-related adverse events in the study for nab-paclitaxel plus gemcitabine vs. gemcitabine alone were neutropenia (38% vs. 27%), fatigue (17% vs. 7%), and neuropathy (17% vs. 1%). In the nab-paclitaxel plus gemcitabine arm, the median time to

neuropathy improvement was 29 days. There was no difference in serious life threatening toxicity (4% in each arm).

No direct comparison of FOLFIRINOX to gemcitabine and nab-paclitaxel has been made to date, but because of its survival advantage and good tolerability, gemcitabine and nab-paclitaxel is the most widely accepted and utilized first line regimen in metastatic pancreatic cancer.

2.7 Rationale for current study

The observation that inhibition of IDO can augment traditional cytotoxic agents in vivo in murine models provides a rationale for examining it in combination with effective chemotherapy regimens in human subjects. In particular, the traditional resistance of adenocarcinoma of the pancreas to standard chemotherapies and its marked immune suppressive tumor microenvironment suggest that the biologic response modifier indoximod may be particularly interesting. Recent data suggest that the chemotherapeutic regimen including gemcitabine plus nab-paclitaxel is associated with higher response rates and improved overall survival when compared to single agent gemcitabine. This study seeks to examine the additional toxicity of the biologic response modifier indoximod to the backbone chemotherapy of gemcitabine plus nab-paclitaxel and to identify a suitable dose of indoximod for future phase 2 and 3 studies.

2.8 Rationale for Phase 1 design

“Combination” clinical trials of novel biological or immunotherapy agents assess the safety and/or efficacy of a biologic or immunotherapeutic by treating patients with the investigational agent plus a standard-of-care (“backbone”) chemotherapy. While this addresses the ethical concern of treating patients with an investigational agent of unknown efficacy when a standard-of-care chemotherapy (even of modest efficacy) is available, it complicates the assessment of the safety and efficacy of the investigational agent. Phase 1 dose-escalation trials are especially difficult, since patients are generally treated at the MTD of the backbone therapy, which, by definition, already induces significant toxicity in approximately1/6 of patients (the target rate of the 3 + 3 dose-escalation trial design). Phase 1 and early phase 2 trials are typically not large enough to identify even a significant increase of a known backbone toxicity, so a simple randomized trial would be underpowered. We propose a Phase 1 dose-escalation trial of an immunotherapeutic agent that addresses these issues, by escalating against the effect of regimen-limiting toxicity, i.e., toxicity induced by the immunotherapeutic agent that limits the administration of the backbone therapy. Specifically, we define regimen-limiting toxicity (RLT) as a toxicity attributable to the immunotherapy agent that delays the planned administration of the next cycle of the backbone chemotherapy. RLT will usually include all the toxicities that are usually defined as dose-limiting (e.g., Grade 3) non-hematological toxicities and all Grade 4 and 5 toxicities), in addition to less severe toxicities, but it is phenomenological in nature; if a patient’s next cycle of treatment is delayed because of an adverse event caused by treatment, that patient has experienced RLT, irrespective of the severity or nature of the causal toxicity. The goal of the trial will be to find the maximum dose of indoximod that does not induce RLT in more than 1/6 of patients treated with gemcitabine plus nab-paclitaxel. The dose will be allocated using a standard Phase 1 design.

3.0 STUDY POPULATION

Potential patients will be identified from each investigator's and co-investigators' current clinic population at each participating institution, or will be referred by their own physicians. They will be approached and informed of the study by an individual who is involved in their care. No cold-calling will occur, and no advertising will be used. The consent process will be carried out as a joint effort among the subject's physician, the study coordinator, and/or co-investigators on the study.

3.1 Inclusion Criteria:

A patient will be eligible for inclusion in this study only if all of the following criteria are met:

- Patient has definitive histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas. The definitive diagnosis of metastatic pancreatic adenocarcinoma will be made by integrating the histopathological data within the context of the clinical and radiographic data. Patients with islet cell or neuroendocrine neoplasms are excluded.

- Initial diagnosis of metastatic disease must have occurred ≤8 weeks prior to entry in the study.

- Patient has one or more metastatic tumors measurable per RECIST 1.1 by CT scan ≤4 weeks prior to entry into the study (or MRI, if patient is allergic to CT contrast media). Patients cannot have nodal metastases alone even if such nodal metastases are formally considered M1 disease.

- Life expectancy of greater than 3 months.

- Male or non-pregnant and non-lactating female, and ≥18 years of age.

- If a female patient is of child-bearing potential, as evidenced by regular menstrual periods, she must have a negative serum or urine pregnancy test (β-hCG) documented within 7 days prior to the first administration of study drug.

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

- Patients must have received no previous radiotherapy, surgery, chemotherapy or investigational therapy for the treatment of metastatic disease.

- Prior treatment with gemcitabine and/or nab-paclitaxel in the adjuvant setting is allowed, provided at least 6 months have elapsed since completion of the last dose and no lingering toxicities are present.

- Patients who have not received any other immunomodulatory therapies (including vaccines) as treatment for this or any other cancer.

- Patient has adequate biological parameters as demonstrated by the following blood counts at Baseline (obtained ≤14 days prior to treatment initiation):

    - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
    - Platelet count $\geq 75{,}000/mm^3$
    - Hemoglobin (Hgb) ≥ 9 g/dL.

- Patient has the following blood chemistry levels at Baseline (obtained ≤14 days prior to treatment initiation):

    - AST (SGOT), ALT (SGPT) $\leq 2.5 \times$ upper limit of normal range (ULN), unless liver metastases are clearly present, then $\leq 5 \times$ ULN is allowed
    - Albumin ≥ 2.8 g/dL
    - Total bilirubin ≤ ULN, patients with known Gilbert's syndrome allowed up to 3 x ULN.
    - Serum creatinine within normal limits or calculated clearance ≥ 60 mL/min/1.73 m^2 for patients with serum creatinine levels above or below the institutional normal value

- Patient has acceptable coagulation studies (obtained ≤ 14 days prior to randomization) as demonstrated by prothrombin time (PT) and partial thromboplastin time (PTT) within normal limits (± 15%). If the patient is on coumadin we suggest switching the patient to a low molecular weight heparin product including enoxaparin (Lovenox) and fondiparinux (Arixtra), but if not feasible then INR must be ≤ 3.

- Patient has no clinically significant abnormalities in urinalysis results (obtained ≤ 14 days prior to enrollment).

- Patient has a Karnofsky performance status (KPS) ≥ 70.

- Patients should be asymptomatic for jaundice prior to enrollment.

- Pain symptoms should be stable and should not require modifications in analgesic management prior to enrollment.

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

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

3.2 Exclusion Criteria:

A patient will not be eligible for inclusion in this study if any of the following criteria apply:

- Patients may not be receiving (or received prior to enrollment) any other investigational agents for metastatic disease.

- Patient has known brain metastases,

- Patient has only locally advanced disease.

- Lymph node only metastases even if considered M1 disease by official staging criteria.

- Ascites of any measurable amount or any clinical significance. Patients who have previously had ascites that has been drained are also ineligible. Trace ascites on a CT scan is allowed.

- History of malignancy in the last 3 years. Patients with prior history of in situ cancer or basal or squamous cell skin cancer are eligible. Patients with other malignancies are eligible if they were cured by surgery alone or surgery plus radiotherapy and have been continuously disease-free for at least 3 years.

- Patient has active, uncontrolled bacterial, viral, or fungal infection(s) requiring systemic therapy.

- Patient has known historical or active infection with HIV, hepatitis B, or hepatitis C.

- Patients with any active autoimmune disease (i.e. psoriasis, extensive atopic dermatitis, asthma, IBD, M.S., uveitis, vasculitis), chronic inflammatory condition, or any condition requiring concurrent use of any systemic immunosupressants or steroids for any reason would be excluded from the study. Any patient with an allo-transplant of any kind would be excluded as well. This would include those with a xenograft heart valve to avoid the potential risk of any immune reaction causing valvular degeneration. Mild-intermittent asthma requiring only occasional beta-agonist inhaler use or mild localized eczema will not be excluded.

- Patient has undergone major surgery, other than diagnostic surgery (i.e., surgery done to obtain a biopsy for diagnosis without removal of an organ), within 4 weeks prior to Day 1 of treatment in this study.

- Patient has a history of allergy or hypersensitivity to any of the study drugs or any of their excipients.

- Uncontrolled intercurrent illness including, but not limited to, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

- Pregnant women are excluded from this study, breastfeeding should be discontinued.

3.3 Inclusion of Women and Minorities

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

3.4 On Study Tests

3.4.1 Baseline Assessment

- Patients must be entered into the trial and start treatment within 8 weeks of diagnosis of metastatic pancreatic cancer.

- Baseline imaging study (high quality spiral CT with intravenous contrast or MRI if CT contrast allergic) demonstrating measurable metastatic disease must be performed ≤ 30 days prior to entry into study.

- If no PET scan has been performed as part of routine clinical care ≤ 4 weeks prior to entry into the study, one may be performed after entry but prior to the initiation of any treatment. Up to thirty patients will undergo PET evaluation at selected institutions. These are being done for research purposes only and are not intended to impact or direct treatment within the scope of this protocol.

- If patient has any evidence (imaging or biochemical) of biliary obstruction or impending biliary obstruction, a biliary stent (preferably metal) shall be placed prior to entry in the study. If a stent becomes occluded while on trial, it shall be replaced with a metal stent unless there is a clear contra-indication.

3.4.2 Additional On-Study Tests

On-Study and Eligibility Tests will include (See Section 13.0 Study Calendar for details)

- Baseline history and complete physical examination (to include height and weight) within 14 days prior to initiating therapy.

- Serum chemistries including BUN, creatinine, albumin, and glucose; electrolytes including sodium, potassium, and calcium; liver function tests including total bilirubin, AST (SGOT), ALT (SGPT), and alkaline phosphatase to be done within 14 days prior to initiating therapy.

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

- Baseline ECG

- CBC with platelets and 5-part differential (to include neutrophils, lymphocytes, eosinophils, basophils, and monocytes) to be done within 14 days prior to initiating therapy.

- Blood (approximately 4 mL) for measurement of [redacted] at baseline

- Bloods for correlative studies. See section 12.0.

- For Phase 2 expansion cohort, pre-treatment biopsies are required. The lesion to be biopsied must be accessible via percutaneous core needle. No endoscopic or laparoscopic biopsies are allowed. No lung lesions are allowed. Lesions that can be imaged by ultrasound are strongly preferred. If a lesion can be imaged by both ultrasound and CT scan, ultrasound is required unless there are special circumstances. Such cases must be discussed in advance with either the overall study PI or the medical monitor. Each biopsy must consist of four individual core biopsies. Details of biopsy handling are included in the lab manual. A paired on-treatment biopsy of the same lesion performed in the same fashion is also required during study week 8.

4.0 STUDY DESIGN AND METHODS

4.1 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. The Phase 2 expansion cohort will require paired biopsies prior to treatment and prior to the start of Cycle 2. Drug dosing will be the same as in Phase 2.

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-subject dose escalation. Regimen-limiting toxicity will be considered as those toxicities related to indoximod that significantly limit the administration of the backbone chemotherapy gemcitabine plus nab-

paclitaxel. 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.

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.

4.2 Phase 1 treatment plan

The phase 1 portion of the study will be a dose escalation study of indoximod against the standard gemcitabine plus nab-paclitaxel 4 week schedule. A standard 3+3 dose escalation design will be used. Escalation will be done against regimen limiting toxicities as described in sections 4.2.1 and 4.2.2.

4.2.1 Definition of Regimen-Limiting Toxicity (RLT)

The standard chemotherapy regimen gemcitabine plus nab-paclitaxel is one of the new backbone chemotherapy regimens to which new agents will be added for patients with adenocarcinoma of the pancreas. To describe the safety and determine a RP2D of the new agent indoximod in combination with gemcitabine plus nab-paclitaxel, it is necessary to determine the attribution of all toxicities. However, when gemcitabine plus nab-paclitaxel is administered as standard regimen, it is associated with significant toxicities [9] that may confound efforts to define the true toxicity of new agents added to this backbone. The danger is that the high rate of toxicity of the backbone regimen will result in an unacceptably high rate of rejecting all dose levels of new agents. It has been recommended in these situations that a “pragmatic” approach be adopted for determining any additional toxicity due to the test agent [10]. In this approach, only grade 3 and 4 toxicities that are attributable to the test agent (indoximod) and result in the delay of the administration of the backbone chemotherapy, gemcitabine plus nab-paclitaxel, will be considered as regimen limiting. Thus, for purposes of the dose escalation in this trial, Regimen Limiting Toxicity will be 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.

4.2.2 Dose Escalation Rules

Each cycle is 28 days. Patients will continue until they experience disease progression or toxicity.

The different dose-levels are defined in Table 1.

Table1. Dose levels (Phase 1 portion).

Dose Level	Indoximod DOSE (oral)	Nab-paclitaxel (IV)	Gemcitabine
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

Patients will be assigned in cohorts of three.

Dose escalation will occur according to the following schema:

Number of Patients with RLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enroll next three patients at the next higher dose level.
≥2 out of 3	Dose escalation will be stopped. Next lower dose will be declared MTD. If only three patients were enrolled at lower dose level, an additional three patients will be enrolled.
1 out of 3	3 more patients are enrolled at this dose. • If 0 of 3 of these experience a RLT, escalate to next level • If 1 or more of these experience RLT, dose escalation is stopped and next lower dose is declared MTD

MTD will be declared to be the highest dose at which ≤ 1 out of 6 patients experiences a RLT. If 0 out of 3 patients experience a RLT at dose level 3, the cohort will be expanded to 6 to assure that ≤ 1 out of 6 patients experience a RLT at that dose and establish it as the RP2D. MTD in this

context is considered a function of indoximod in this combination and not a MTD for indoximod in any other context / combination.

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.

The initial dose of Indoximod will be 600 mg BID. If a RLT is reported at Dose Level 1, a lower dose cohort may be added after consultation between the Investigators, Medical Monitor and Sponsor, depending on the cumulative safety data. The protocol will be amended at that time accordingly.

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 a 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.

4.3 Phase 2 Treatment Plan

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.

4.4 Phase 2 Expansion Cohort Treatment Plan

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.

Each biopsy is to consist of four core needle samples of tumor. No FNA's are allowed. Patients have to have a lesion that can be biopsied with a core needle to be eligible. Lesions that can be imaged by ultrasound are strongly preferred. If a lesion can be imaged by both ultrasound and CT scan, ultrasound is required unless there are special circumstances. Such cases must be discussed in advance with either the overall study PI or the medical monitor. Details of biopsy handling are included in the lab manual.

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.

4.5 Follow-up Phase

Once patients are no longer receiving treatment or are removed from study treatment for any of the reasons listed in sections 6 or 7, they will be followed monthly for a period of 6 months. Follow up may consist of either in-person or by telephone assessment as the patient's clinical condition dictates.

Once 6 months have passed from the end of treatment, patients will be followed every 3 months until death or three years has elapsed.

5.0 REGISTRATION PROCEDURES

5.1 Registration Process

All patients must be registered on study before beginning therapy.

All patients must have a: (1) signed Informed Consent Document and, (2) a completed Eligibility Checklist Form before registration on the study. To register a subject for this protocol, an authorized physician or their designee must FAX or EMAIL the subject information to the NewLink Genetics Registration Office or the site's designated CRA between the hours of 8:30 A.M. and 5:00 P.M. Central Standard Time, Monday through Friday. (FAX: (515) 296-3556; EMAIL: PatientRegistrations@linkp.com). No evening, weekend or holiday registrations will be permitted. Once eligibility is confirmed, NewLink will FAX or EMAIL a confirmation of registration to the site.

A file of copies of all reports, laboratory studies and other pertinent information documenting the subject's eligibility for study will be maintained in the Clinical Research Office of NewLink Genetics Corporation.

6.0 STUDY MEDICATIONS AND PROCEDURES

6.1 Study Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are also described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Table 2 Dosing Schedule

Week	1	2	3	4	5	6	7	8	9	10	11	12
Cycle	Cycle 1				Cycle 2				Cycle 3 onward			
Indoximod	X	X	X	X	X	X	X	X	X	X	X	X
Nab-Paclitaxel/ Gemcitabine	X	X	X	-	X	X	X	-	X	X	X	-

6.2 Indoximod Administration

Patients will receive indoximod every day starting on the day of the first dose of chemotherapy. Capsules of indoximod are available in 200 mg strengths. Indoximod will be administered in divided doses (BID), once in the morning and once in the evening. Patients should not eat or drink anything other than water for 1 hour prior to taking the medication and 1 hour after taking the medication. Patients should be told to swallow whole capsules without chewing. No specific premedications are required.

6.3 Gemcitabine Plus Nab-Paclitaxel Administration

6.3.1 Premedication

Please see gemcitabine and nab-paclitaxel prescribing information for premedication

6.3.2 Treatment and Dosing

Patients will receive nab-paclitaxel plus gemcitabine with 125 mg/m^2 nab-paclitaxel as a 30- to 40-minute infusion (maximum infusion time not to exceed 40 minutes) followed by 1000 mg/m^2 gemcitabine as a 30- to 40-minute infusion (maximum 40 minutes) for 3 weeks followed by a week of rest.

6.4 Supportive Care and Concomitant Medications

- All standard of care anti-emetics, anti-diarrheals, antibiotics are permitted.
- Use of growth factor support as primary prophylaxis to prevent neutropenia is not prohibited. An ANC < 1500 on day 1 of any cycle will require the use of growth factor

for all remaining cycles unless otherwise not indicated. Choice of growth factor is at the investigator's discretion

- Erythropoiesis-stimulating agents (ESA) can be utilized as per institutional guidelines and as per the ESA APPRISE (Assisting Providers and cancer Patients with Risk Information for the Safe use of ESAs) program requirements.

- Because of the risk of sepsis with gemcitabine plus nab-paclitaxel, especially in those patients who have biliary stents due to biliary obstruction, patients must be instructed to begin taking either ciprofloxacin 500mg BID orally (or amoxicillin/clavulanate 875 BID orally if allergic to ciprofloxacin or similar drugs) for any fever > 100. 5 deg F (38.3 C). They should then call their treating physician and be evaluated as soon as clinically indicated.

- Concomitant medications should be avoided with the exception of analgesics (only acetaminophen or narcotics may be given for pain), chronic treatments for concomitant medical conditions, or agents required for life threatening medical problems.

- No additional chemotherapy, immunotherapy, or other anti-tumor therapy is permitted during the study.

6.5 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for until one of the following criteria applies

- Unacceptable adverse event(s)
- Disease progression per immune-related criteria AND RECIST criteria
- Intercurrent illness that prevents further administration of treatment
- Patient decides to withdraw from the study
- Patient inability to be compliant with study treatment in opinion of investigator defined as missing infusional treatments for non-medical reasons or complying with oral treatments below an 85% threshold on two sequential study visits
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

7.0 KNOWN TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

7.1 Indoximod Toxicities

The most common adverse reactions (≥10% incidence) are: fatigue, nausea, vomiting, diarrhea, anorexia, and anemia.

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

7.2 Gemcitabine Toxicities

Hematologic - In studies in pancreatic cancer, myelosuppression is the dose-limiting toxicity with gemcitabine, but <1% of patients discontinued therapy for anemia, leukopenia, or thrombocytopenia. Red blood cell transfusions were required by 19% of patients. The incidence of sepsis was less than 1%. Petechiae or mild blood loss (hemorrhage), from any cause, was reported in 16% of patients; less than 1% of patients required platelet transfusions. Patients should be monitored for myelosuppression during gemcitabine therapy and dosage modified or suspended according to the degree of hematologic toxicity. Rare (<1%) incidence of autoimmune related thrombocytopenias have been described, which can be life threatening.

Gastrointestinal - Nausea and vomiting were commonly reported (69%) but were usually of mild to moderate severity. Severe nausea and vomiting (World Health Organization [WHO] Grade 3/4) occurred in <15% of patients. Diarrhea was reported by 19% of patients, and stomatitis by 11% of patients.

Hepatic - In clinical trials, Gemzar was associated with transient elevations of one or both serum transaminases in approximately 70% of patients, but there was no evidence of increasing hepatic toxicity with either longer duration of exposure to gemcitabine or with greater total cumulative dose. Serious hepatotoxicity, including liver failure and death, has been reported very rarely in patients receiving gemcitabine.

Renal - In clinical trials, mild proteinuria and hematuria were commonly reported. Hemolytic Uremic Syndrome (HUS) has been reported rarely (0.25%) with the use of gemcitabine. Renal failure may not be reversible even with discontinuation of therapy and dialysis may be required.

Fever - The overall incidence of fever was 41%. This is in contrast to the incidence of infection (16%) and indicates that gemcitabine may cause fever in the absence of clinical infection. Fever was frequently associated with other flu-like symptoms and was usually mild and clinically manageable.

Rash - Rash was reported in 30% of patients. The rash was typically a macular or finely granular maculopapular pruritic eruption of mild to moderate severity involving the trunk and extremities. Pruritus was reported for 13% of patients.

Pulmonary - In clinical trials, dyspnea, unrelated to underlying disease, has been reported in association with gemcitabine therapy. Dyspnea was occasionally accompanied by bronchospasm. Pulmonary toxicity has been reported with the use of gemcitabine. The etiology of these effects is unknown. If such effects develop, gemcitabine should be discontinued. Early use of supportive care measures may help ameliorate these conditions.

Edema - Edema (13%), peripheral edema (20%), and generalized edema (<1%) were reported. Less than 1% of patients discontinued due to edema.

Flu-like Symptoms - "Flu syndrome" was reported for 19% of patients. Individual symptoms of fever, asthenia, anorexia, headache, cough, chills, and myalgia were commonly reported. Fever and asthenia were also reported frequently as isolated symptoms. Insomnia, rhinitis, sweating, and malaise were reported infrequently. Less than 1% of patients discontinued due to flu-like symptoms.

Infection - Infections were reported for 16% of patients. Sepsis was rarely reported.

Alopecia - Hair loss, usually minimal, was reported by 15% of patients.

Neurotoxicity - There was a 10% incidence of mild paresthesias and a <1% rate of severe paresthesias.

Sepsis

Interstitial pneumonitis – Rare but can be life threatening and requires removal from study.

7.3 Nab-paclitaxel Toxicities

Myelosuppression, predominantly neutropenia - Grade 4 neutropenia was reported and typically resolved in <7 days and did not require colony stimulating factor support.

Peripheral neuropathy, predominantly sensory - Grade 3 peripheral neuropathy was reported and typically improved to Grade 1 or 2 within 21 days of interrupting the dose. Following resolution of the peripheral neuropathy to acceptable levels, clinicians were able to restart dosing at a lower dose level.

Nausea and vomiting - Nausea and vomiting were seen, typically at Grade 1 or 2 levels. This AE responded well to standard anti-emetic regimens.

Myalgias and arthralgias - Myalgias and arthralgias were reported and typically were Grade 1 or 2; these were responsive to standard acetaminophen-containing medication.

Mucositis - Mucositis was reported typically Grade 1 or 2. It was not dose-limiting.

Alopecia - Alopecia was reported by most patients and was similar to that seen with Taxol.

Sepsis

Interstitial Pneumonitis – Rare but can be life threatening and requires removal from study.

7.4 Dose Omissions for Indoximod

Any missed doses are not made up. Dosing continues on the next dose.

7.5 Dose Omissions for Gemcitabine and/or Nab-paclitaxel

Day 1 dose missed: If a dose is held or missed that was to be given on Day 1 of a cycle, that cycle will not begin until the day the first dose of the cycle is given.

Day 8 dose missed: If a Day 8 dose is missed, the cycle continues and that dose is not given. The dose is not made up and the cycle remains 28 days.

Day 15 dose missed: If a day 15 dose is missed, the ensuing week (days 15-21) are considered to be the rest week and the cycle is shortened to 21 days. The next cycle is unaffected.

The maximum days between doses should never exceed 28 days (except for peripheral neuropathy, see below).

7.6 Dose Modification for Indoximod

In general, indoximod was very well tolerated in both phase 1 trials and seldom required any dose reductions. If a dose reduction is deemed necessary due to intolerance from taking the required number of pills or grade 3-4 nausea, a one-time dose reduction of 200 mg is permitted. If this is not tolerated, then discontinuation of the study treatment is required however, all patients will still be followed per section 4.4.

7.7 Dose Modifications for Gemcitabine and/or Nab-paclitaxel

Doses will be reduced for hematologic and other toxicities. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Toxicities will be graded using the NCI CTCAE Version 4.0.

Two levels of dose modifications are permitted according to the criteria below. If a toxicity requiring dose modification occurs following the second dose reduction of either study drug, further treatment should be discontinued.

Table 3: Dose Modifications

Dose Level	Nab-paclitaxel Dose (mg/m^2)[a]	Gemcitabine (mg/m^2)[b]
Study Dose	125	1000
-1	100	800
-2	75	600

Dose reductions may or may not be concomitant. Please refer to Table 4 and Table 5 for specific recommendations regarding dose modifications for Day 1 of each cycle for hematologic and non-hematologic toxicity, respectively. Please refer to Table 6 and Table 7 for specific recommendations regarding dose modifications within a cycle for hematologic and non-hematologic toxicities, respectively. A maximum of 2 dose level reductions are allowed.

Patients experiencing study drug-related toxicities that require a delay in scheduled nab-paclitaxel or gemcitabine dosing for ≥ 21 days will be discontinued from further treatment in this study (except for peripheral neuropathy and edema; see below). When a dose reduction is required, no dose re-escalation will be permitted for the duration of study treatment (except for peripheral neuropathy and edema and with the exception mentioned in Table 6 namely: on Day

15, re-escalation with granulocyte-colony stimulating factor (G-CSF) support is permitted, after a previous dose reduction on Day 8 of the same cycle).

Dose Modifications at Day 1

In the event dose modifications are required at the beginning of a cycle due to AEs or hematologic toxicities, doses of nab-paclitaxel and gemcitabine may be adjusted as detailed in Table 4 and Table 5 as presented below:

Table 4: Dose Modifications for Day 1 of Each Cycle (Hematologic Toxicity)

Treatment day counts and toxicity			
ANC		**Platelets**	**Timing**
$\geq 1.5 \times 10^9$/L	And	$\geq 100 \times 10^9$/L	Treat on time
$< 1.5 \times 10^9$/L	Or	$< 100 \times 10^9$/L	Delay by 1 week intervals until recovery

Key: ANC = Absolute neutrophil count.

Table 5: Dose Modifications for Day 1 of Each Cycle (Non-Hematologic Toxicity)

Non Hematologic Toxicity and/or Dose Hold with Previous Cycle	
Toxicity/dose held	**Gemcitabine + nab-paclitaxel dose this cycle**
Grade 0, 1 or 2 toxicity	Same as Day 1 of previous cycle (except for Grade 2 cutaneous toxicity where doses of gemcitabine and nab-paclitaxel should both be reduced to next lower dose level
Grade 3 toxicity[i)]	Decrease gemcitabine and nab-paclitaxel to next lower dose level
Grade 4 toxicity[ii)]	Off protocol treatment
Dose held in 2 previous consecutive cycles	Decrease gemcitabine to next lower dose level and continue throughout the rest of treatment

Key: CTCAE = Common terminology criteria for adverse events.

[i)] If the toxicity only affects neuropathy, then only nab-paclitaxel should be reduced (please see Section 7.7).

[ii)] Pulmonary embolism (a Grade 4 toxicity in the CTCAE tables) if mild or a symptomatic, will be exempt from this requirement (please see Section 7.7).

Dose Adjustments within a Treatment Cycle

In the event that patients must have treatment delayed within a treatment cycle due to toxicities, those doses held during a cycle will not be made up. Dose modifications due to hematologic toxicity (as represented by the blood counts and toxicities, below) within a treatment cycle should be adjusted as outlined in Table 6.

Table 6: Dose Modifications for Hematologic Toxicity within a Cycle

Day 8 Blood Counts	Day 8 Nab-paclitaxel	Day 8 Gemcitabine	Day 15 Blood Counts	Day 15 Nab-paclitaxel	Day 15 Gemcitabine	Any Day Nab-paclitaxel	Any Day Gemcitabine
ANC >1000 and Platelets ≥75,000	100%	100%	ANC >1000 and Platelets ≥75,000	100%	100%		
			ANC 500-1000 or Platelets 50,000-74,999	Full Dose (treat on time) + G-CSF[a]	Full Dose (treat on time) + G-CSF[a]		
			ANC <500 or Platelets <50,000	Hold + G-CSF[a]	Hold + G-CSF[a]		
ANC 500-1000 [b] or Platelets 50,000-74,999	Decrease dose by 1 level (treat on time)	Decrease dose by 1 level (treat on time)	ANC >1000 and Platelets ≥75,000	Return to Previous Dose level (treat on time) + G-CSF[a]	Return to Previous Dose Level (treat on time) + G-CSF[a]		
			ANC 500-1000 or Platelets 50,000-74,999	Same Dose (as Day 8, treat on time) + G-CSF[a]	Same Dose (as Day 8, treat on time) + G-CSF[a]		
			ANC <500 or Platelets <50,000	Hold + G-CSF[a]	Hold + G-CSF[a]		
ANC <500[a] or Platelets <50,000	Hold	Hold	ANC >1000 and Platelets ≥75,000	Decrease Day 8 dose by 1 level (treat on time) + G-CSF[a]	Decrease Day 8 dose by 1 level (treat on time) + G-CSF[a]		
			ANC 500-1000 or Platelets 50,000-74,999	Decrease Day 8 dose by 1 level (treat on time) + G-CSF[a]	Decrease Day 8 dose by 1 level (treat on time) + G-CSF[a]		

Day 8 Blood Counts	Day 8 Nab-paclitaxel	Day 8 Gemcitabine	Day 15 Blood Counts	Day 15 Nab-paclitaxel	Day 15 Gemcitabine	Any Day Nab-paclitaxel	Any Day Gemcitabine
			ANC <500 or Platelets <50,000	Hold + G-CSF[a]	Hold + G-CSF[a]		
Febrile Neutropenia (Grade 3 or 4)[c]						Hold. Upon resuming dosing, decrease to next lower level and do not re-escalate throughout the rest of treatment.	Hold. Upon resuming dosing, decrease to next lower dose level and do not re-escalate throughout the rest of treatment.
Recurrent Febrile Neutropenia (Grade 3 or 4)[b]						Decrease to next lower dose level and do not re-escalate throughout the rest of treatment.	Decrease 2 dose levels (to 600 mg/m^2) and do not re-escalate throughout the rest of treatment.

Table 6: Dose Modifications for Hematologic Toxicity within a Cycle

Abbreviations: ANC = Absolute neutrophil count; G-CSF = Granulocyte colony stimulating factor.

a G-CSF is optional if descent only affects platelets.

b If patients do not experience resolution of neutropenia within 21 days, despite uninterrupted G-CSF treatment, study treatment will be discontinued.

c Febrile patients (regardless of neutrophil count) should have their chemotherapy treatment interrupted. A full sepsis diagnostic work-up should be performed while continuing broad spectrum antibiotics. If cultures are positive, the antibiotic may or may not be changed, depending on the sensitivity profile of the isolated organism. Patients with persisting fever after 3 weeks, despite uninterrupted antibiotic treatment, will discontinue study treatment. Febrile neutropenic patients can also receive G-CSF, in addition to antibiotic treatment, to hasten the resolution of their febrile neutropenia (following current institutional guidelines). In all cases, blood counts must have returned to baseline levels before resuming chemotherapy treatment.

Dose modifications may also be made for non-hematological toxicity within a cycle as specified in Table 7.

Table 7: Dose Modifications for Non-Hematological Toxicity within a Cycle

CTCAE Grade	Percent of Day 1 Nab-paclitaxel + Gemcitabine Dose
0-2 (and Grade 3 nausea/vomiting and alopecia)	100%[a]
3 (except nausea/vomiting and alopecia)	Hold either one or both drugs[a] until resolution to ≤Grade 1. Then resume treatment at the next lower dose level.
4	Hold[b, c]

Abbreviations: CTCAE = Common terminology criteria for adverse events.
a: Except for cutaneous toxicity: please see below.
b: This decision as to which drug should be modified will depend upon the type of non-hematologic toxicity seen and which course is medically most sound in the judgment of the physician/investigator.
c: Pulmonary embolism (a Grade 4 toxicity in the CTCAE tables) if mild or asymptomatic, will be exempt from this requirement (please see below).

Peripheral Neuropathy
Nab-paclitaxel treatment should be withheld in patients who experience grade 3 or worse peripheral neuropathy. Gemcitabine and indoximod administration can continue during this period. Nab-paclitaxel treatment may be resumed at the next lower dose level in subsequent cycles if the peripheral neuropathy improves to grade 1 or better. Patients experiencing peripheral neuropathy that requires a delay in scheduled nab-paclitaxel dosing for ≥ 21 days will discontinue study treatment through treatment cycle 4. If a patient has completed 4 or more cycles of study treatment, then patients may continue on study treatment cycles of indoximod and gemcitabine alone. If the peripheral neuropathy improves to grade 1 or better during subsequent treatment cycles, nab-paclitaxel may be resumed as part of study treatment at the discretion of the treating physician. The time to resolution to grade 1 should be the adverse event duration used for adverse event reporting.

Edema
Patients who have completed 4 or more cycles of study treatment and experience clinically significant edema can continue on with study treatment cycles consisting of indoximod and gemcitabine alone. Nab-paclitaxel can be resumed as part of the study regimen at the discretion of the treating physician if the edema improves to grade 1 or better during subsequent study treatment cycles.

Cutaneous Toxicity
Patients who develop grade 2 or 3 cutaneous toxicity should have their dose reduced to the next lower dose level for both drugs. If the patient continues to experience these reactions, despite dose reduction, treatment should be discontinued. Patients who develop grade 4 cutaneous toxicity should have treatment discontinued.

Gastrointestinal Toxicity
If grade 3 mucositis or diarrhea occurs, study drug should be withheld until resolution to grade 1 or better, then reinstituted at the next lower dose level of both drugs. Patients who develop grade 4 mucositis or diarrhea should have treatment discontinued.

Pulmonary Embolism
Asymptomatic or clinically mild pulmonary embolism can be treated with low-molecular-weight heparin without interruption of therapy. Moderate to severe pulmonary embolism will require permanent discontinuation of treatment.

Interstitial Pneumonitis
During study participation, patients should be carefully monitored for signs and symptoms of pneumonitis (i.e., episodes of transient or repeated dyspnea with unproductive persistent cough or fever) and, if observed, immediate clinical evaluation and timely institution of appropriate management (emphasizing the need for corticosteroids if an infectious process has been ruled out as well as appropriate ventilation and oxygen support when required). Administration of all agents administered under this protocol should be permanently discontinued upon making a diagnosis of interstitial pneumonitis.

Colony Stimulating Factor Administration
Colony stimulating factors may Fe given according to institutional guidelines for the treatment of neutropenic fever or infections associated with neutropenia and for the prevention of febrile neutropenia in patients with an ANC <500 cells/μL. Patients not experiencing resolution of neutropenia within 21 days, despite uninterrupted G-CSF treatment, will discontinue study treatment.

Prophylaxis Against Sepsis
Due to the incidences of non-neutropenic sepsis, at the first occurrence of fever ≥ 38.5 °C (regardless of neutrophil count), institution of ciprofloxacin (500 mg orally, twice daily)—or amoxicillin/clavulanate (Augmentin®, 500 mg orally, 2-3 times daily) in patients with allergy to fluoroquinolones—should be initiated. On their first visit, patients should be provided with enough ciprofloxacin (or the alternative antibiotic) for use at home, and they should be instructed to begin taking it when they first record a temperature of ≥ 38.5 °C (or if they feel they are developing a fever and a thermometer is not available). They should also immediately contact their physician for guidance on where to go for blood counts to be evaluated for sepsis as soon as possible. Hospitalization or evaluation in the emergency room may be required depending on the clinical presentation. Further treatment and duration of anti-biotic therapy is to be determined by the treating physician,

Hypersensitivity Reactions
Hypersensitivity reactions are not expected with either nab-paclitaxel or gemcitabine. If they do occur, minor symptoms such as flushing, skin reactions, dyspnea, hypotension, or tachycardia may require temporary interruption of the infusion. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized

urticaria require immediate discontinuation of study drug administration and aggressive symptomatic therapy.

Patients who develop a severe hypersensitivity reaction should not be re-challenged.

Erythocyte Stimulating agents (ESA)

ESA can be utilized as per institutional guidelines and as per the ESA APPRISE (Assisting Providers and cancer Patients with Risk Information for the Safe use of ESAs) program requirements.

8.0 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with indoximod administered in this study can be found in Section 7.1. Refer to the prescribing insert for docetaxel adverse events.

8.1 [redacted]

The 200 mg capsules are white opaque hard gelatin capsules.

Storage: Stored at controlled room temperature (59-77°F) and a storage area daily temperature log should be maintained and available for monitoring at all times.

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

Route of Administration: Oral

Agent Ordering and Agent Accountability: As required by FDA regulations for all drug storage, procurement and usage are carefully monitored and documented. The Principal Investigator will oversee this process and delegate responsibility as needed to conduct the trial under Good Clinical Practices. A careful inventory is maintained at each of the clinical sites. A Study Agent Order Form will be made available to all participating sites. The PI or designated individual will:

- Complete a Study Agent Order form and send to NewLink Genetics. NewLink will make the appropriate arrangements for the shipment of the drug from the manufacturer.
- Upon receipt of the investigational drug, inventory the shipment ensuring that the information on the packing slip matches exactly with what has been sent to the site, including the amount, lot numbers and quantity, and document the results of this inventory on the provided inventory form.
- Promptly bring any discrepancies, breakage or evidence of tampering to the attention of NewLink Genetics.
- Retain a copy of the shipping inventory, packing slips, and documentation of inventory in the study's records.

8.2 Gemcitabine pharmaceutical information:

For complete details see package insert.

Chemical Name: 2'-deoxy-2'2'-difluorocyti-dine monohydrochloride

Mode of Action: Gemcitabine inhibits DNA synthesis in tumor cells by competing with deoxycytidine triphosphate for incorporation into DNA. Gemcitabine metabolites also inhibit enzymes in DNA synthesis. Finally, gemcitabine is masked from DNA repair enzymes with the addition of one additional nucleotide after gemcitabine is in the DNA chain.

How Supplied: Gemcitabine is supplied in 200 mg and 1000 mg vials. Two hundred mg vials are reconstituted in 5 cc sodium chloride then diluted to a concentration of as low as 0.1 mg/ml if necessary for infusion. The dose is usually given over 30 minutes. One thousand mg vials are reconstituted with 25 cc sodium chloride. It is stored at room temperature until given.

Storage: See package insert.

Stability: See package insert.

Route of Administration: Intravenous

Supply: Commercially available

8.3 Nab-paclitaxel pharmaceutical information:

For complete information please see package insert

Nab-paclitaxel is a Cremophor EL-free, albumin-bound paclitaxel particle with a mean size of approximately 130 nm

Chemical Name: 5β,20-Epoxy-1,2α,4,7β,10β,13αhexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3phenylisoserin

Mode of Action: Nab-paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. Paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis

How Supplied: Nab-paclitaxel is supplied as a white to yellow, sterile, lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous infusion. Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin

Storage: See package insert

Stability: See package insert

Route of Administration: Intravenous

Supply: Commercially available

9.0 CLINICAL AND LABORATORY EVALUATIONS

9.1 Pretreatment Evaluations (See Study Calendar, Section 13.0):

The following are the required pre-study evaluations:

- History and physical examination including height, weight, vital signs and blood pressure, and determination of performance status by the ECOG scale (Appendix A).

- Standard blood work (within 14 days) to include: CBC with differential, platelets, PT, PTT, total bilirubin, AST, ALT, alkaline phosphatase, sodium, potassium, bicarbonate, chloride, BUN, Cr, glucose, calcium, CA 19-9, CEA, and a pregnancy test if of child-bearing potential as defined by ECOG. These tests involve taking 1 tablespoon of venous blood.

- ECOG defines a female of childbearing potential as any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:
  1) Has not undergone a hysterectomy or bilateral oophorectomy; or
  2) Has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Baseline imaging studies (within 30 days prior to study enrollment) including:

- Contrast-enhanced, pancreas mass protocol helical CT scan of the chest, abdomen and pelvis.

- If a patient has a known sensitivity to CT contrast media, high quality MRI with contrast may be used

- PET scan in up to 30 patients at selected institutions for research purposes only will be performed no more than 30 days prior to study initiation. If PET has not been performed at time of enrollment into study, it must be performed prior to starting study treatment.

Biopsy procedure to confirm pancreatic adenocarcinoma:

- Methods may include fine-needle aspiration (FNA) via imaging guidance or during endoscopic ultrasound (EUS), endoscopic brushing at the time of ERCP, or laparoscopic directed needle biopsy.

- Biopsy of distant disease site is preferred to make diagnosis of metastatic disease.

- If biopsy of distant site is considered unwarranted by study investigator and treating physician then metastatic disease can be diagnosed by biopsy of primary tumor in combination with imaging studies (PET positive liver lesions for example).

Biliary stent placement by PTC or ERCP to relieve obstructive jaundice (dilated biliary tree and a serum bilirubin level > normal or AST/ALT > 3x normal) is required prior to starting treatment on study.

- ERCP or PTC is a procedure which allows the doctor to take detailed X-rays of the bile duct and/or pancreas and to relieve obstruction of the biliary tree. For this study metallic biliary stents may be used to drain the biliary tree and are preferred. If a stent becomes occluded, it shall be replaced with a metal stent unless there is a specific contra-indication.

Electrocardiogram (EKG)

Research bloods: See section 12.0

Core Needle Biopsy of Tumor in Phase 2 Expansion Cohort

- For Phase 2 expansion cohort, pre-treatment biopsies are required. The lesion to be biopsied must be accessible via percutaneous core needle. No endoscopic or laparoscopic biopsies are allowed. No lung lesions are allowed. Lesions that can be imaged by ultrasound are strongly preferred. If a lesion can be imaged by both ultrasound and CT scan, ultrasound is required unless there are special circumstances. Such cases must be discussed in advance with either the overall study PI or the medical monitor. Each biopsy must consist of four individual core needle biopsies. FNA is not acceptable. Details of biopsy handling are included in the lab manual. A paired on-treatment biopsy of the same lesion performed in the same fashion is also required during study week 8. Patients who cannot undergo a second biopsy for compelling medical reasons (determined by discussion between the treating physician, PI, and Sponsor) may stay on study. In the case of significant clinical response, if a previously biopsied lesion is no longer available, an alternate lesion may be biopsied but such a situation must be documented.

9.2 Evaluations during Treatment

The following evaluations will be performed during the study:

Day 1, 8 and 15 of each cycle:

- Measurements of vital signs
- Weight and determination of performance status to be completed on Day 1 of each cycle
- CBC, differential, and platelets, serum chemistry tests (1 tablespoon of venous blood) including total bilirubin, AST, ALT, alkaline phosphatase, serum electrolytes (sodium, potassium, chloride, CO_2), BUN, Cr, glucose, calcium. If patients are found to have ANC < 500, daily CBC will be performed until ANC > 500.
- Review of concurrent medications
- Adverse event evaluation

Core Needle Biopsy during Study Week 8 (Prior to Start of Cycle 3)

- A core needle biopsy of the same lesion performed in the same fashion as the pre-treatment study biopsy must be performed

Evaluations Following Completion of Cycle 2 (And Every 2 Cycles Thereafter)

The following evaluations will be performed at the completion of every 2 cycles:

- Serum CA 19-9
- If a patient had a normal CA 19-9 at the beginning of the study but an abnormal CEA, then a CEA will be drawn instead and used to follow the patient.
- Interval imaging study of the same modality used at beginning of study

- PET scan (done only once at the end of the first two cycles in up to 30 patients at selected institutions for research purposes)
- Study bloods: See section 12.0

10.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The list of AEs (Section 7.1) and the characteristics of an observed AE (NCI Common Terminology Criteria for Adverse Events Version 4.03 (CTCAE 4.03)) will determine whether the event requires expedited reporting in addition to routine reporting.

10.1 Adverse Event Reporting

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

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

The P.I. will notify the IRB and NewLink Genetics (Study Sponsor) who in turn will notify the FDA and other regulatory agencies of all serious adverse events as required by law or regulation. All participating investigators will be notified of IND Safety Reports by Investigator Alerts sent through email. Serious Adverse Event (AE) Reporting by investigators will be done as outlined in Table 6.

Definitions for reporting purposes:

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

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

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

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

- fatal

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

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

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

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

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

SAE reporting timelines are defined as:

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

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

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

Hospitalization, Prolonged Hospitalization or Surgery

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

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

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

SAE Reporting Form and Content: For those events that meet the criteria for serious as listed above, please complete a Serious Adverse Event Reporting Form. This form will be provided by NewLink Genetics. Please send to NewLink Genetics within the time frames listed above. Please FAX to (515) 296-3556 or EMAIL to **SAE_Reporting@linkp.com**. Please call (515) 598-2935 with any reporting questions. You may also contact and send this form to the CRA designated for your site.

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

10.2 Routine Adverse Event Reporting

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

10.3 Reporting Requirements for Baseline Adverse Events

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

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

10.4 Adverse Event Case Report Form

All adverse events (regardless of grade and attribution) observed while on study and for 30 days after last dose of treatment, must be recorded on the adverse event case report form. After 30 days from last dose of treatment, only adverse events that are related to the study drug/ combination are required to be recorded on the adverse event forms.

10.5 Pregnancy

The teratogenic potential of indoximod is unknown. During the course of the study, all women of childbearing potential who are participants and all spouses of participants must be instructed to contact the Principal Investigator immediately if pregnancy is suspected. Pregnancy in a participant or partner of a participant who is receiving treatment will be reported following procedures for a SAE (although it will not be coded as a SAE). The event will be recorded in the pregnancy CRF. If pregnancy is suspected in a participant or partner of a participant prior to study drug administration, the study drug will be withheld until the β-hCG test result is available. If pregnancy is confirmed, the patient will not receive study drug and will be withdrawn from the study. If pregnancy is suspected while the patient is receiving study drug, the study drug will be immediately withheld until the result of a β-hCG test result is available. If pregnancy is confirmed, the patient will be permanently discontinued from the study in an appropriate manner. Protocol-required procedures for study discontinuation will be performed unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate follow-up procedures should be considered, if indicated. In addition, the Principal Investigator will report pregnancy-related follow-up information, including perinatal and neonatal outcomes to the IRB. Infants will be monitored for a minimum of eight weeks.

11.0 COSTS AND PAYMENTS

The study drug indoximod will be provided at no cost to patients or their insurance companies. Gemcitabine plus nab-paclitaxel is a standard of care treatment. As a result, patients and/or their insurance will be billed in the standard fashion for Gemcitabine plus nab-paclitaxel treatment. There will be no cost to patients for the doctor's time, procedures and supplies (as described in the Description and Procedures section of the consent form) that are solely related to this study. Patients will be billed in the standard fashion for the routine clinical care that they receive, and either the subject or their insurance provider will be responsible for this payment. Patients will not be paid for participating in this study.

[redacted]

13.0 STUDY CALENDAR

	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)

14.0 MEASUREMENT OF EFFECT

14.1 Antitumor Effect

For the purposes of this study, patients should be re-evaluated for response approximately every 8 weeks during treatment.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1). Changes in the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

Both RECIST criteria and immune criteria for response will be used to determine progression. Patients must meet definition of progression under both criteria to be considered as having progressed.

14.1.1 Definitions:

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with indoximod.

Evaluable for objective response. Only those patients who have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

14.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$20 mm by chest x-ray, as $\geq$10 mm with CT scan, or $\geq$10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be $\geq$15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

14.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Chest x-ray Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. CT scans have slice thickness greater than 5 mm, are not acceptable. High quality MRI is also acceptable.

Ultrasound Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy Can be used to evaluate presence of metastatic disease and / or resectabilty prior to surgery when treating physicians believe procedure is clinically indicated.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Ascites or effusions The cytological confirmation of the neoplastic origin of any effusion or ascites that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET While FDG-PET response assessments need additional study, it is reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring.
d) A ‘positive’ FDG-PET scan lesion is defined as one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic

quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

The PET scan done for research purposes only at selected institutions will not be used to determine progression under RECIST criteria.

14.2 Response Criteria

14.2.1 Evaluation of Target Lesions

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

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

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

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

14.2.2 Evaluation of Non-Target Lesions

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

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

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

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

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

14.2.3 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 with Measurable Disease (i.e., Target Disease)

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

** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

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		

14.2.4 Duration of Response

Duration of overall response: 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).

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

Duration of stable disease: 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.

14.3 Overall Survival

For all patients, OS will be calculated from the date of randomization to the time of death. Patients who are still alive prior to the data cutoff for final efficacy analysis, or who dropout prior to study end, will be censored at the day they were last known to be alive.

14.4 Progression-Free Survival

For all patients, PFS will be calculated from the date of randomization 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 and are still alive prior to the data cutoff for final efficacy analysis, or who dropout prior to study end, will be censored at the date of the last radiological evidence documenting absence of relapse.

14.5 Immune-related Response Criteria

Investigators have relied on Response Evaluation Criteria in Solid Tumors (RECIST) to evaluate antitumor responses to chemotherapeutic agents. However, the responses that are seen with immunotherapeutic agents may extend beyond those of cytotoxic agents and could include responses after disease progression that are not captured by RECIST. The immune-related

response criteria (irRC) may better capture the response patterns observed with some immunotherapeutic agents.

14.5.1 Antitumor response based on total measurable tumor burden

For the immune-related response criteria (irRC), only index and measurable new lesions are taken into account. At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions is calculated. At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions are added together to provide the total tumor burden:

Tumor Burden = $SPD_{\text{index lesions}} + SPD_{\text{new, measurable lesions}}$

14.5.2 Time-point response assessment using irRC

Percentage changes in tumor burden per assessment time point describe the size and growth kinetics of both conventional and new, measurable lesions as they appear. At each tumor assessment, the response inn index and new, measurable lesions is defined based on the change in tumor burden (after ruling our irPD). Decreases in tumor burden must be assessed relative to baseline measurements (i.e., the SPD of all index lesions at screening).

14.5.3 Overall response using the irRC

The overall response according to the irRC is derived from time-point response assessments (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 $\geq$ 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 $\geq$ 25% relative to nadir (minimum recorded tumor burden) confirmed by a repeat, consecutive assessment no less than 4 weeks from the date first documented

15.0 DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

15.1 Regulatory Compliance/Good Clinical Practices

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

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

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

- Signed Confidentiality Agreement
- Signed Clinical Trial Agreement
- Up-to-date signed and dated Curriculum vitae and copies of medical licenses for Principal and sub/co-investigators to be submitted promptly
- Financial Disclosure form for Principal and one sub/co-investigator with financial disclosure forms for all investigators to be submitted promptly
- FDA Form 1572
- IRB approval to conduct the study: IRB-approved informed consent form,
- Name and address of the IRB with the statement that it is organized and operates according to GCP and the applicable laws and regulations
- IRB membership roster
- Local laboratory certifications, its name and address
- Local laboratory normal ranges (a dated copy for tests to be performed during the study).
- Financial agreement, if applicable.
- Signed and dated Investigator Agreement page of the final protocol and amendments, where applicable.

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

Informed Consent
Each subject must give written consent and sign other locally required documents after the nature of the study has been fully explained. The informed consent form must be signed prior to performance of any study-related activity with the exception of baseline imaging (if already obtained within 30 days prior to starting study treatment) and baseline lab studies (if already

obtained within 14 days prior to starting study treatment). The informed consent form that is used must be approved both by the sponsor and by the reviewing IRB. The Informed Consent should be in accordance of the Declaration of Helsinki, current International Conference on Harmonization (ICH) and Good Clinical Practices (GCP) guidelines.

15.2 Administrative Requirements

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

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

Record Retention
In compliance with the ICH/GCP guidelines the investigator/institution will maintain all CRFs and all source documents that support the data collected from each patient, and all trial documents as specified in Essential documents for the Conduct of a Clinical Trial and as specified by the applicable regulatory requirement(s).

The investigator/institution will take measures to prevent accidental or premature destruction of these documents. Essential documents must be retained until at least two years after the last approval of a marketing application in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product.

These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

Case Report Forms (CRF)
CRFs are provided for each patient. Data must be entered onto CRFs in English. All forms must be filled out in black ball-point pen. CRFs must be signed by the investigator where indicated.

All CRF corrections are to be made by the investigator or other authorized study center personnel as instructed on the CRF title page. The investigator must authorize changes to the recorded safety and efficacy data.

The Case Report Forms (CRF) will be designed for the capture of all relevant clinical data for this study. The CRFs are to be completed as soon as possible after the subject's visit, so that they always reflect the latest observations on the patients participating in the trial. All finalized

data will be reviewed and authorized by the Investigator. Copies of CRF data will be retained by the site and Sponsor in accordance with FDA regulations.

Monitoring
All clinical and standard laboratory data specified in this study will be collected and recorded by the nurse coordinator under the supervisions of the Principal Investigator and physician co-investigator

NewLink Genetics (sponsor) will perform on-site monitoring visits as outlined in the Monitoring Plan for this clinical trial. The dates of the visits will be recorded by the monitor in a trial center monitor visit log to be kept at the site. The first routine monitoring visit will usually be made approximately 4 weeks after enrollment has begun at that site. At these visits the monitor will verify the data entered onto the CRFs with the hospital or clinic records (source documents).

At a minimum, source documentation must be available to substantiate patient eligibility and participation, proper informed consent procedures, adherence to protocol procedures, record of safety and efficacy parameters, adequate reporting and follow-up of adverse events, administration of concomitant medication, drug receipt/dispensing/return records, study medication administration information, and date of completion and reason.

Specific items required as source documents will be reviewed with the investigator prior to the study. Findings from this review of CRFs and source documents will be outlined in a Site Visit Report and discussed with the investigator. The sponsor expects that, during monitoring visits, the investigator (and as appropriate the study coordinator) will be available, the source documents will be available, and a suitable environment will be provided for review of study-related documents.

Data Monitoring Committee
This study will use a Data Monitoring Committee (DMC). The DMC will review accrual information, and safety data such as listing and nature of adverse events. An independent statistician will provide the DMC with, safety data listing, data summary and appropriate analysis for review at the completion of the phase I study. The DMC will review the safety of the combination on a quarterly basis while any subject is still receiving study drug.

Use of Information and Publication
All information on indoximod, NewLink operations, patent application, manufacturing process and basic scientific data supplied by the sponsor to the investigator and not previously published is considered confidential and remains the sole property of NewLink Genetics and the PI. The investigator agrees to use this information only to accomplish this study and will not use it for other purposes without the sponsor's written consent. The investigator understands that the information developed in the clinical study will be used by NewLink in connection with the continued development of indoximod and thus may be disclosed as required to other clinical investigators or government regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

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

15.3 Human Subjects Protection

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

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

Participation of Children
No children will participate in this study.

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

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

There are no new anticipated severe adverse side effects to the treatment approach technique employed in this study. Theoretical risks may include the induction of unanticipated autoimmune disease and/or liver, kidney, lung, heart and CNS damage and/or coagulopathy and bleeding as a result of excessive activation of the complement system. Expected risks and discomforts to the patients are minimal and will be those of needle sticks for phlebotomy. Patients will be treated as deemed medically appropriate for any immediate or delayed adverse event related to the treatment.

Blood and tissue specimens collected in the course of this research project may be banked and used in the future to investigate new scientific questions related to this study.

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

Recruitment Strategy
Patients, their physicians or family members may contact the clinical sites directly. Information about the clinical trial can be obtained at clinicaltrials.gov. Given the number of patients with metastatic pancreas cancer and the limited therapy available, we believe enrollment for this trial will be completed in less than 2 years.

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

16.0 STATISTICAL METHODS

16.1.1 General Considerations

Descriptive statistical methods will be used to summarize data from this study. Unless stated otherwise, the term descriptive statistics refers to number of patients (n), mean, median, standard deviation (SD), minimum and maximum for continuous data and frequencies and percentages for categorical data.

A formal detailed statistical analysis plan (SAP) will be created prior to the review of any data. All data collected during the study will be included in data listings. Unless otherwise noted, the data will be sorted first by dose level, patient number, and then by date within each patient number.

All statistical analyses will be conducted with the SAS® software package version 9.2 or higher.

16.1.2 Determination of Sample Size

Phase 1 component: The Phase 1 component of the trial will be conducted to assess the safety of indoximod and to identify the RLT and RP2D of indoximod in combination with gemcitabine plus nab-paclitaxel in patients with metastatic pancreas cancer.

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 [11], 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)[12].

16.2 Analysis Populations

16.2.1 Phase 1 Component Analysis Populations

There will be 1 analysis population defined for the Phase 1 component, the safety population.

The Safety Population will consist of all patients receiving at least 1 dose of indoximod.

16.2.2 Phase 2 Component Analysis Populations

There will be 3 analysis populations defined for the Phase 2 component, 1 safety population and 2 efficacy evaluation populations

The Safety Population will consist of all patients receiving at least 1 dose of indoximod. This includes both the Phase 2 cohort and the biopsy expansion cohort.

The Efficacy Evaluable (EE) Population will consist of all patients 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. 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.

The Evaluable for Non-Target Disease Response (ENDR) Population will include patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least 1 cycle of therapy, and have had their disease re-evaluated through radiographic imaging. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

16.3 Primary and Secondary Endpoints

16.3.1 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 4.2.1 as 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. The RP2D will be determined by the identified MTD, the highest dose at which ≤ 1 out of 6 patients experiences an RLT, and include an assessment of toxicities that occur at later time points. Dose Escalation Rules are defined in Section 4.2.2.

Analysis of Phase 1 component primary endpoints will be performed on the Safety Population.

16.3.2 Phase 2 Component Primary Efficacy Endpoint

The primary efficacy endpoint for the Phase 2 component is 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 data cutoff for final efficacy analysis, 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 for estimation of summary statistics.

Analysis of Phase 2 component primary endpoints will be performed on the EE Population.

16.3.3 Phase 2 Component Secondary Endpoints

Secondary endpoints for the Phase 2 component include:

- Progression Free Survival (PFS)
- [redacted]

- To determine the response rate, duration of response, and duration of overall CR of patients treated with gemcitabine and nab-paclitaxel with indoximod.

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

For all patients, PFS will be calculated from the date of enrollment to the time of CT scan documenting progression (or other unambiguous indicator of disease development), or date of death, whichever occurs first. Patients who have no documented progression and are still alive prior to the data cutoff for final efficacy analysis, or who dropout prior to study end, will be censored at the date of the last radiological evidence documenting absence of progression.

Response and disease progression will be evaluated using RECIST version 1.1, and measurement of effect is further defined in Section 14. Response rate is defined as the percentage of patients with either complete or partial response while on study. Time to progression will be calculated from the start of treatment to the time of documented radiological evidence of disease recurrence or progression.

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. The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented. Stable disease is measured from the start of the treatment until the criteria for progression are met.

Analysis of Phase 2 component secondary endpoints will be performed on the EE Population. Additional exploratory analyses may be performed.

16.4 Safety Analysis

Additional safety analyses will be conducted using the Safety Population and will include summaries of adverse events (AEs), concomitant medications, vital signs, hematology and chemistry laboratory parameters, and 12-lead electrocardiogram, which will be described further in the Statistical Analysis Plan.

Adverse Events will be graded using CTCAE version 4 and coded using the Medical Dictionary for Regulatory Activities (MedDRA®) for purposes of summarization. All AEs occurring during the study will be included in by-patient data listings and tabulated. Events leading to death, SAEs, and events resulting in study discontinuation will be tabulated. Safety variables will be tabulated and presented by dose cohort. Exposure to study drug and reasons for discontinuation of study treatment will be tabulated.

Medical History will be coded using MedDRA, and will be included in by-patient data listings and tabulated. Concomitant medications will be coded using the World Health Organization

(WHO) Drug Dictionary. The use of concomitant medications will be included in by-patient data listings and tabulated.

17.0 REFERENCES

1. Beatty, G.L., et al., CD40 Agonists Alter Tumor Stroma and Show Efficacy Against Pancreatic Carcinoma in Mice and Humans. Science, 2011. 331(6024): p. 1612-1616.
2. Kraman, M., et al., Suppression of Antitumor Immunity by Stromal Cells Expressing Fibroblast Activation Protein–α. Science, 2010. 330(6005): p. 827-830.
3. Morse, M.A., J.R. Hall, and J.M. Plate, Countering tumor-induced immunosuppression during immunotherapy for pancreatic cancer. Expert Opinion on Biological Therapy, 2009. 9(3): p. 331-339.
4. Sarkhosh, K., et al., Temperature-sensitive polymer-conjugated IFN-gamma induces the expression of IDO mRNA and activity by fibroblasts populated in collagen gel (FPCG). J Cell Physiol, 2004. 201(1): p. 146-54.
5. Qian, F., et al., Efficacy of levo-1-methyl tryptophan and dextro-1-methyl tryptophan in reversing indoleamine-2,3-dioxygenase-mediated arrest of T-cell proliferation in human epithelial ovarian cancer. Cancer Res, 2009. 69(13): p. 5498-504.
6. Potula, R., et al., Inhibition of indoleamine 2,3-dioxygenase (IDO) enhances elimination of virus-infected macrophages in an animal model of HIV-1 encephalitis. Blood, 2005. 106(7): p. 2382-90.
7. Muller, A.J., et al., Inhibition of indoleamine 2,3-dioxygenase, an immunoregulatory target of the cancer suppression gene Bin1, potentiates cancer chemotherapy. Nat Med, 2005. 11(3): p. 312-9.
8. Metz, R., et al., Novel tryptophan catabolic enzyme IDO2 is the preferred biochemical target of the antitumor indoleamine 2,3-dioxygenase inhibitory compound D-1-methyl-tryptophan. Cancer Res, 2007. 67(15): p. 7082-7.
9. Conroy, T., et al., GEMCITABINE PLUS NAB-PACLITAXEL versus gemcitabine for metastatic pancreatic cancer. N Engl J Med, 1817. 364(19): p. 1817-25.
10. Horton, T.M., et al., Toxicity assessment of molecularly targeted drugs incorporated into multiagent chemotherapy regimens for pediatric acute lymphocytic leukemia (ALL): review from an international consensus conference. Pediatr Blood Cancer. 54(7): p. 872-8.
11. 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.
12. Hintze, J. (2013). PASS 12. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com.

18.0 APPENDICES

18.1 Appendix A: 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.

18.2 Appendix B. Study Medication Diary

Study Medication Diary **Subject Initials: ___ ___** **Subject #: NLG2104 - ___ ___ ___**
Cycle: _____ **Cycle Start Date: __ __ / __ __ __ / __ __ __ __** **Subjects planned daily dose: _____ mg**
# of capsules dispensed: ____ by: _____ on __ __ / __ __ __ / __ __ __ __
# of capsules returned: ____ to: _____ on __ __ / __ __ __ / __ __ __ __

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each Cycle.
2. You will take ____ capsules each day. **Take the capsules with water. Do not eat or drink anything other than water for 1 hour before or after taking the study medication.** (Do not take with antacids).
3. Record the date, the number of capsules you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please bring your pill bottle and this form to your physician at each return visit.

Date	Day	#Capsules	AM Dose (time HH:MM)	#Capsules	AM Dose (time HH:MM)	Comments

Subject Initials (Initialed by Subject): ___ ___ Date:__ __ / __ __ __ /_ __ __ __

To be completed by site staff upon return of study medication diary:

Total Number of Capsules taken this cycle: _____Percent of Compliance: _____

Comments on capsules taken, capsules not taken as planned, capsules lost, or other discrepancies: _____

Signature of Study Nurse or Study Designee:

Date:__ __ / __ __ __ /

18.3 Appendix C: Informed Consent Form Template

RESEARCH PATIENT INFORMATION AND CONSENT FORM

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

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

Participation

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

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

You are being asked to take part in this research study because you have been diagnosed with metastatic pancreatic cancer.

Why is this research being done?

The purpose of this study is to determine the effects, good and/or bad, of the chemotherapy regimen gemcitabine and nab-paclitaxel with the addition of indoximod (an experimental drug) to find out if the combination is possibly better than the gemcitabine and nab-paclitaxel regimen alone.

About the study drugs:

Indoximod treatment is experimental at this time whereas gemcitabine and nab-paclitaxel are intravenous drugs that are approved for commercial use as a prescribed drug by the US Food and Drug Administration (US FDA) for the treatment of metastatic pancreatic cancer.

The experimental drug indoximod is an oral medication that blocks an enzyme called IDO. Doctors think that tumors use IDO to escape attack by your body's immune system, so by blocking this IDO enzyme it may help your body attack the tumor cells more effectively. Indoximod given along with standard chemotherapy may increase the effectiveness of the chemotherapy regimen (gemcitabine plus nab-paclitaxel).

Should you take part in this study?

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

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

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

Why are you being asked to take part?

We are asking you to take part in this research study because you have metastatic pancreatic cancer (pancreatic cancer that has spread to other parts of your body).

How many people will participate in the study?

This study will have two parts, a dose-escalation phase (the first part of the study) and then later, a dose-expansion part (the second part of the study). In the first part of the study, up to 18 people will be asked to participate. In the second part, 80 additional people will be asked to participate across multiple institutions. After the second part has been fully enrolled, an additional 40 subjects will be asked to participate in an expansion study. Approximately <<XX>> patients will be enrolled at <<CLINICAL SITE>>>.

What will happen during this study?

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

- Medical history, including information about you and your cancer, previous treatments for your cancer and other medications you are taking or have taken. Certain medications are not allowed to be taken during the study treatment.

- Complete physical exam including vital signs (heart rate, temperature, breathing rate, blood pressure, height and weight)
- Performance Status (questions about your ability to perform everyday activities)
- Your tumor size will be measured by CT scans or MRI (as well as PET scans in some instances).
- Standard blood tests, using up to 6 teaspoons of blood, to measure your liver and kidney function, white blood cells, red blood cells and platelets, your blood sugar and blood electrolytes and if you are female and able to become pregnant, to confirm you are not pregnant. You will not be allowed to enter the study of you are pregnant or lactating.
- Research blood tests will be taken to monitor how your body will be affected by the drug. These initial tests will serve as a guide to see how your body reacts after you have received the study drug throughout the study.
- Additionally, 1 teaspoon of blood will be drawn and stored for later testing of an enzyme that is released in tumors, called IDO enzyme (this is an immune suppressing enzyme released by the tumor and indoximod seems to block this enzyme). This is an optional test that may help us better understand who will respond to study treatment with indoximod. You will sign a separate consent for this testing.

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

Treatment regimen

[redacted]

[redacted]

[redacted]

[redacted]

DOSE-EXPANSION PHASE:

[redacted]

[redacted]

EXAMPLE SCHEDULE

Preliminary Visit(s), Screening Process within 7-14 days prior to start of treatment • You will be asked to come to the hospital/clinic for a CT scan or MRI to assess a baseline evaluation of your disease. • Other procedures that will be done during this time: o Blood draw o Physical exam and recording of medical history o EKG
Day 1 – Gemcitabine/Nab-Paclitaxel Chemotherapy + Indoximod • Nab-Paclitaxel administered intravenously over 30-40 minutes • Gemcitabine administered intravenously over 30-60 minutes • Indoximod given orally (pills) – taken twice a day every day
Day 8 – Gemcitabine/Nab-Paclitaxel Chemotherapy + Indoximod • Nab-Paclitaxel administered intravenously over 30-40 minutes • Gemcitabine administered intravenously over 30-60 minutes • Indoximod continues – taken twice a day every day
Day 15 – Gemcitabine/Nab-Paclitaxel Chemotherapy + Indoximod • Nab-Paclitaxel administered intravenously over 30-40 minutes • Gemcitabine administered intravenously over 30-60 minutes • Indoximod continues – taken twice a day every day
Day 22 – Indoximod Only - REST WEEK from Chemotherapy • Indoximod continues – taken twice a day every day

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

It is unknown exactly how long you would stay on the study. You will receive the chemotherapy every 3 weeks with a week of rest (cycle). The indoximod treatment is given daily throughout the cycle. Treatment would continue until your disease stops responding to the treatment or you can no longer tolerate the study therapy. You are also free to stop participating at any time you decide to do so.

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

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

When will you be taken off study?

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

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

Will you be paid for taking part in this study?

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

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

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

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

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

Additionally, you and/or your insurance company will not be responsible for special blood tests to measure the drug levels.

<<<ADD SPECIFIC RESEARCH TESTS HERE>>>

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

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

- You might be able to get the indoximod from the manufacturer or your pharmacy, but you or your insurance company may have to pay for it.

- If there is no indoximod available at all, no one will be able to get more and the study would close.

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

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

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

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

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

Most Common Side Effects: (Likely to happen to 20% or more of patients)
- Nausea
- Fatigue or feeling tired

Common Side Effects: (Likely to happen to 10 – 19% of patients)
- Anorexia or loss or appetite
- Decrease in red blood cells (anemia)
- Diarrhea
- Vomiting

Less Common Side Effects: (Likely to happen to 5 to 10% of patients)
- Decrease in white blood cells (neutrophils and lymphocytes)
- Headache

- Rash
- Constipation
- Hair loss

Rare Side Effects**: (**Likely to happen to less than 5%)

- Dizziness
- Lung Infection
- Fever associated with low white blood cells (febrile neutropenia)
- Increase in blood potassium, glucose, and creatinine levels
- Multi-organ failure
- Sleeplessness (insomnia)
- Mouth sores (oral mucositis)
- Dehydration
- Ringing in ears, hearing loss
- Low blood levels of sodium
- Low blood pressure (hypotension)
- Redness, pain, numbness, and possible peeling of hands and feet
- Respiratory failure
- Inflammation of the colon (colitis)
- Inflammation of the joints (arthritis)
- Decrease in platelets
- Muscle weakness
- Inflammation of the liver (hepatitis)
- Soft tissue infections
- Increased bilirubin level in blood
- Low blood levels of glucose, phosphate, calcium, magnesium, and albumin
- Peripheral sensory neuropathy
- Shortness of breath
- Abdominal pain
- Itching skin
- Blurred vision
- Altered taste
- Inflammation of the inner lining of the lungs (pneumonitis)
- Accumulation of fluid in the abdomen (ascites)
- Increase in white blood cells
- Parkinsonism (tremor, rigidity, instability, slowness of movement, masked face, voice changes)

Autoimmune Events

Autoimmunity is a term that describes when your immune system begins to attack normal cells in your body. Two patients out of 48 in a completed indoximod study developed an autoimmune reaction in their pituitary gland called hypophysitis. Both of these patients received prior

experimental immune therapies which may have increased the risk of this occurring, but there is a distinct possibility that this may occur with indoximod alone.
One of the two hypophysitis patients were on low dose steroids and thyroid hormone as long as they were alive, and one of the patients was able to stop the steroids but remained on thyroid hormone for the rest of her life. To date, none of the patients who did not receive prior immune therapies have developed this side effect. The pituitary gland is considered the "master gland" which coordinates the function of your other glands such as your thyroid, adrenals, and gonads (ovaries/testicles). If it does not function properly (pituitary insufficiency) you may experience symptoms of

- Weakness
- Fatigue
- Loss of libido (lack of interest in sexual intercourse)
- You may need to take hormone replacement therapy to treat these or other symptoms.

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

- Weight loss
- Lack of appetite (anorexia)
- Weakness
- Nausea
- Vomiting
- Low blood pressure (hypotension).

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

GEMCITABINE (Gemzar®)

The following side effects are common (occurring in more than 30%) for patients taking gemcitabine:

- Flu-like symptoms (muscle pain, fever, headache, chills, fatigue)
- Fever (within 6-12 hours of first dose)
- Fatigue
- Nausea (mild)
- Vomiting
- Poor appetite
- Skin rash
- Low Blood Counts (your white and red blood cells and platelets may temporarily decrease. This can put you at increased risk for infection, anemia and/or bleeding.)

- Temporary increases in liver enzymes
- Blood or protein in the urine

These are less common side effects (occurring in 10 -29% of patients):

- Diarrhea
- Weakness
- Hair loss
- Mouth sores
- Difficulty sleeping
- Shortness of breath

There can be treatment delays or interruptions, if needed, to make the treatment safer or more tolerable if there are side effects.

NAB-PACLITAXEL (Abraxane®)

The following side effects are **Common** (occurring in more than 30%) for patients taking nab-paclitaxel:

- Low Blood Counts (Your white and red blood cells and platelets may temporarily decrease. This can put you at increased risk for infection, anemia and/or bleeding.)
- Hair loss
- Numbness, tingling, pain, or weakness in the hands or feet
- Tiredness
- Rash
- Nausea and vomiting
- Diarrhea
- Swelling in the hands or feet
- Fever
- Decreased appetite

Less Common (occurring in 20 -29% of patients):

- Dehydration

Uncommon (occurring in 10 to 19% of people)

- Muscle pain
- Joint pain
- Weakness
- Mouth sores and mouth pain
- Alteration in taste
- Headache
- Decrease in blood potassium levels
- Cough
- Nose bleeds
- Urinary Tract Infections
- Pain in arms or legs

- Depression

Rare but could be Serious (occurring in less than 10%)
- Infection
- Pneumonitis (inflammation of lung tissues)
- Hypersensitivity reactions including anaphylactic reactions (allergic reactions that are life threatening)
- Abnormal heart beat
- High blood pressure

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

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

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

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

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

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

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

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

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

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

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

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

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

Research-Related Injury

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

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

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

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

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

For the purposes of your participation in this study and the protection of your identity, your study doctor will assign you a unique code, such as a series of numbers and/or letters. The study doctor will record the study data collected from you in a report form that uses your assigned code, not your name. This is to protect your study data by making it anonymous for most study purposes.

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

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

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

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

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

Use and Sharing of Study Data that Identifies You

The use and sharing by your study doctor of study data that identifies you, such as your original medical records, are explained in a separate HIPAA Authorization. By signing that form, you

show that you give permission for the uses and sharing of this data as described in that document. You do not have to sign that form, but if you do not, you will not be allowed to participate in this study. To withdraw your HIPAA Authorization you will need to do so in writing as described in that document. There is a risk that your information will be given to others without your permission.

What if new information becomes available?

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

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

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

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

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

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

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

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

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

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

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

Clinical Trial Information in Public Database

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

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

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

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

Signature of Person Taking Part in Study Date

Printed Name of Person Taking Part in Study

Statement of Person Obtaining Informed Consent / Research Authorization

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

Signature of Person Obtaining Informed Consent / Research Authorization Date

Printed Name of Person Obtaining Informed Consent / Research Authorization

Statement of Investigator

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

Signature of Study Investigator Date

Printed Name of Study Investigator

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

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

This means we will take an additional 18 mL (about 3 teaspoons) of blood to be stored for subsequent (later) analysis related to the IDO enzyme. The IDO enzyme is an immune suppressing enzyme released by the tumor and indoximod seems to block this enzyme.

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

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

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

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

Please initial your choice below:

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

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

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

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

_____
Printed Name of Person Explaining Consent

_____ _____
Signature of Person Explaining Consent Date

Expansion Study Addendum

Why are you being asked to take part?

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

How many people will participate in the expansion study?

Forty (40) patients will be asked to participate across multiple institutions. Approximately <<XX>> patients will be enrolled at <<CLINICAL SITE>>>.

What will happen during the expansion study?

Study treatment in the Phase 2 expansion will follow the same treatment plan for Phase 2 already described in this consent form except for the addition of obtaining two tumor biopsies.

Your doctor will perform a core needle biopsy one time before you start study treatment and then again in approximately 8 weeks (at the end of Cycle 2).

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

How is a core needle biopsy done?

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

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

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

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

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

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

What are the risks of the Core Needle Biopsies?

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

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

Who will pay for the Core Needle Biopsies?

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

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

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

Signature of Person Taking Part in Study Date

Printed Name of Person Taking Part in Study

Signature of Person Explaining Consent Addendum Date

Printed Name of Person Explaining Consent Addendum