A Phase II, Open-label Pilot Study Evaluating the Safety and Activity of Nal-IRI in Combination with 5-FU and Oxaliplatin in Preoperative Treatment of Pancreatic Adenocarcinoma (NEO-Nal-IRI Study)

Protocol Number:	UF-STO-PANC-004 (SRMC identifier: UF-GI-008)
UF IRB #:	201800866
Coordinating Center:	University of Florida
Principal Investigator:	Thomas J. George, Jr., MD, FACP University of Florida 1600 SW Archer Road Gainesville, FL 32608 Telephone: (352) 273-8008 Fax: (352) 265-0735 Email: Thom.George@medicine.ufl.edu
Junior Principal Investigator:	Sherise Rogers, MD, MPH Email: Sherise.Rogers@medicine.ufl.edu
Statistician:	Ji-Hyun Lee, PhD Email: jihyun.lee@ufl.edu
Protocol Management:	UFHCC Project Management Office Email: PMO@cancer.ufl.edu
Clinical Phase:	Phase II
IND Status:	Exempt
Investigational Agent(s):	Nanoliposomal-Irinotecan (ONIVYDE®, Ipsen Biopharmaceuticals, Inc.)
NCT#	NCT03483038
Date of Original Protocol:	January 9, 2017
Date of Current Protocol:	March 14th, 2022
Version of Current Protocol:	6
PROTOCOL REVISION RECORD	**Version 5.3, dated 30JUL2021** Version 5.2, dated 21SEP2020 Version 5.1, dated 09SEP2020 Version 5.0, dated 03OCT2019

Version 4.0, dated 26JUN2019
Version 3.0, dated 07FEB2019
Version 2.0, dated 04SEP2018
Version 1.0, dated 09JAN2017

Keywords: Neoadjuvant, chemotherapy, pancreatic adenocarcinoma, ONIVYDE®, borderline resectable, resectable

TABLE OF CONTENTS Page

ABBREVIATIONS

AE	adverse event
ALT	alanine transaminase (also SGPT)
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate transaminase (also SGOT)
AUC	area under curve
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
ChemoRT	Chemoradiotherapy
CL	clearance
C_{max}	highest concentration determined in the measuring interval
CPT-11	unencapsulated irinotecan
CR	complete remission
CrCl	creatinine clearance
CRF	case report form
CRO	Clinical Research Office
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	clinical trials management system
CTV	clinical target volume
DISC	Data Integrity & Safety Committee
DNA	deoxyribonucleic acid
DPD	dihydrypyrimidine dehydrogenase
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment
FDG	fluorodeoxyglucose positron emission
5-FU	5-fluorouracil
FSH	follicle stimulating hormone
fx	fraction
GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factor
GTV	gross tumor volume
Gy	Gray
HRT	hormone replacement therapy
ICF	informed consent form
ICH	International Conference on Harmonization
IGRT	Image-guided radiation therapy

IMRT	Intensity-modulated radiation therapy
IRB	Institutional Review Board
IV	intravenous
kg	kilogram(s)
LV	leucovorin
LLOQ	lowest limit of quantification
MCV	mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
mITT	modified Intention-to-Treat
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
Nal-IRI	Nanoliposomal irinotecan
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSAE	non-serious adverse event
OAR	organs at risk
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PMO	Project Management Office
PET	positron emission tomography
PFS	progression free survival
PI	principal investigator
PK	pharmacokinetics
PR	partial remission
PS	performance status
PT	prothrombin time
PTT	partial thromboplastin time
PTV	planning target volume
Q2W	every two weeks
Q3W	every three weeks
RECIST	Response Evaluation Criteria In Solid Tumors
RT	Radiotherapy
SAE	serious adverse event
SBRT	stereotactic body radiation therapy
SC	subcutaneous
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase (also AST)
SGPT	serum glutamic pyruvate transaminase (also ALT)

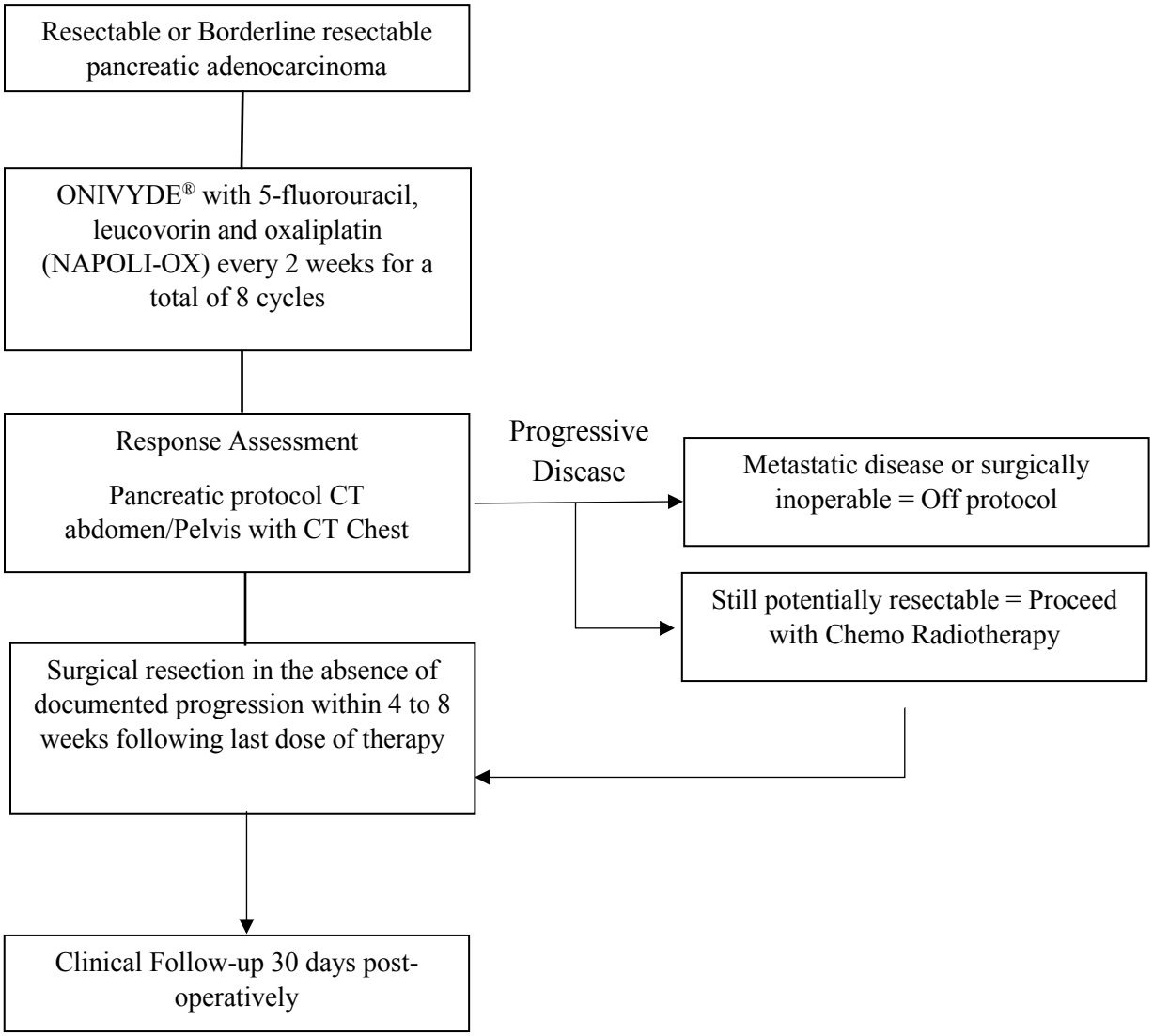
SMA	superior mesenteric artery
UF	University of Florida
UFHCC	University of Florida Health Cancer Center
ULN	upper limit of normal
US	United States
WHO	World Health Organization
WOCBP	women of childbearing potential

Protocol Signature Page

A Phase II, Open-label Pilot Study Evaluating the Safety and Activity of Nal-IRI in Combination with 5-FU and Oxaliplatin in Preoperative Treatment of Pancreatic Adenocarcinoma (NEO-Nal-IRI Study)

Study Principal Investigator:	_____ Signature of Investigator	_____ Date
	_____ Printed Name of Investigator	
	_____ Name of Facility	
	_____ Location of Facility (City/State)	
Local Principal Investigator:	_____ Signature of Investigator	_____ Date
	_____ Printed Name of Investigator	
	_____ Name of Facility	
	_____ Location of Facility (City/State)	
	By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.	

STUDY SCHEMA



NALIRIFOX Cycle Length = 2 weeks
Accrual Goal= 28 subjects

PROTOCOL SYNOPSIS

Title:	A Phase II, Open-label Pilot Study Evaluating the Safety and Activity of Nal-IRI in Combination with 5-FU and Oxaliplatin in Preoperative Treatment of Pancreatic Adenocarcinoma (NEO-Nal-IRI Study)
Funding Organization:	Ipsen Biopharmaceuticals, Inc.
Investigational Agent Supplier:	Ipsen Biopharmaceuticals, Inc.
Rationale:	Pancreatic cancer is the third leading cause of cancer deaths in US with modest survival even in early stage disease with the only chance for long-term survival is with complete resection of the cancer. Surgical resection is routinely followed by adjuvant chemotherapy, as it is widely believed that micro-metastatic disease is present even in early clinical stages of the disease. This strategy is associated with a proven reduction in the risk of recurrence of the cancer with documentation that two drug therapy is superior to one. Neoadjuvant (pre-operative) treatment offers many advantages in terms of earlier systemic treatment of micro-metastatic disease, limiting the toxicity of therapy to when patients are more likely to tolerate the side effects, and down staging of tumor to allow more patients to achieve complete surgical resection, which is thus far the best predictor of good long-term outcome. Recognizing that multi-agent combination chemotherapy confers the best disease control in the metastatic and adjuvant settings, this rationale has been previously demonstrated to also be feasible in the neoadjuvant space, particularly for patients with high-risk disease including resectable or borderline resectable cancers. A major challenge in treating patients with aggressive combination of neoadjuvant therapy relates to toxicity, recognizing that patients need to be capable of receiving full doses and all cycles of therapy to ensure optimal down staging and micrometastatic sterilization, yet still be capable of safely undergoing a major surgical resection. The most active therapy (inclusive of survival and response rates) in the metastatic setting is demonstrated by use of FOLFIRINOX therapy (5-fluorouracil, leucovorin, oxaliplatin and irinotecan), but it typically requires dose modifications, delays and growth factor support. Commonly, the irinotecan component of this polyagent therapy is reduced or dropped in clinical practice when toxicities develop, leading to several “modified” FOLFIRINOX regimens in use. The toxicity profile of irinotecan liposomal injection (ONIVYDE®) with 5-fluorouricil and leucovorin in the second line metastatic setting is very reasonable with the added benefit of

	improved drug delivery to tumor. In the neoadjuvant setting, where patient toxicity is paramount and tumor vasculature is undisrupted, the incorporation of ONIVYDE® could have an important anti-neoplastic effect by improved biologic drug delivery and improved full treatment compliance. Delivering a complete (4 month) course of systemic therapy with maintenance of patient health and minimization of post-op complications would represent a clinically significant step forward in the field of pancreatic cancer therapy. The current proposal aims to substitute irinotecan liposomal injection (ONIVYDE®) for traditional irinotecan in the standard FOLFIRINOX regimen and deliver the therapy in the neoadjuvant setting. The primary goal of this strategy is to rapidly establish perioperative safety with regards to surgical outcomes. Together, this study and the associated correlative studies will provide comprehensive, robust and efficient clinical and biologic data to support the further rational development of ONIVYDE®.
Objectives:	Primary: • To establish the safety and feasibility of ONIVYDE® in combination with 5-fluorouracil, leucovorin, and oxaliplatin (NALIRIFOX) in the neoadjuvant setting of resectable or borderline resectable pancreatic adenocarcinoma Secondary: • To determine the treatment completion rate of therapy defined by completion of all intended cycles • To determine the rate of complete surgical resection (R0) and other histopathologic downstaging • To determine radiographic objective response rate (ORR)of the primary tumor as measured by RECIST 1.1 criteria • To determine the biochemical response rate and pattern of response as measured by serial CA 19-9 levels • To determine the patient-reported quality of life during treatment as measured by the NCI validated FACT-G scale Exploratory: • To collect tissues and blood for post-hoc secondary exploratory biomarker, CTC, ctDNA, pharmacogenomic and tumor mutational profile assessments as well as potential PDX development. • Biospecimens will be collected and subsequently examined for microbiota content and any associations with patient and tumor characteristics, treatment outcomes and change over time.
Study Design:	This is a phase II, open label, single arm pilot trial.

Accrual Goal:	A total of 28 evaluable subjects.
Inclusion Criteria:	Individuals eligible for study participation must meet the following criteria: A. Written informed consent obtained from the subject and the ability for the subject to comply with all the study-related procedures. B. Both males and females ≥ eighteen years of age. C. A new clinical diagnosis of resectable or borderline resectable, previously untreated pancreatic adenocarcinoma confirmed by pathologic specimen evaluation D. No clinical evidence of metastatic disease, confirmed by CT of chest/abdomen and pelvis with IV contrast (or MRI of abdomen and pelvis with non-contrast chest CT, if IV contrast is contraindicated). E. Potentially resectable local disease, confirmed by CT of abdomen with IV contrast (MRI abdomen if CT/contrast is contraindicated). Radiographic confirmation of resectable or borderline resectable pancreatic cancer is verified by documented consensus discussion of the GI Multidisciplinary Tumor Board. The ultimate determination of whether a potential subject meets the criteria of "resectable or borderline resectable" lies in the consensus of the UF GI Multidisciplinary Tumor Board, or equivalent body (for external sites). F. Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1. G. Treated biliary obstruction (if applicable). H. Subjects with known or suspected Gilbert's disease must be formally tested for UGT1A1*28 with results available to study team prior to treatment initiation. I. Adequate organ function; as defined by: i. Hematologic- - ANC > 1,500 cells/µl without the use of hematopoietic growth factors; and - Platelet count > 100,000 cells/µl; and - Hemoglobin > 9 g/dL (blood transfusions are permitted for patients with hemoglobin levels below 9 g/dL) ii. Hepatic-

	- Serum total bilirubin within 1.5 ULN for the institution, with a trend downwards (biliary drainage is allowed for biliary obstruction), - AST and ALT less than or equal to 2.5 x ULN iii. Renal- - Serum creatinine of less than or equal to 1.5 x ULN iv. Cardiac- - Normal ECG or ECG without any clinically significant findings as defined by the treating physician J. Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy throughout the study and for at least 7 months after the last dose of study drug to minimize the risk of pregnancy. Prior to study enrollment, women of childbearing potential must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. WOCBP include any woman who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or who is not post-menopausal. Post-menopause is defined as: • Amenorrhea that has lasted for ≥ 12 consecutive months without another cause, or • For women with irregular menstrual periods who are taking hormone replacement therapy (HRT), a documented serum follicle-stimulating hormone (FSH) level of greater than 35 mIU/mL. K. Males with female partners of child-bearing potential must agree to use physician-approved contraceptive methods (*e.g.*, abstinence, condoms, vasectomy) throughout the study and should avoid conceiving children for 4 months following the last dose of study drug.
Exclusion Criteria:	Subjects with any of the following will not be eligible for study participation: A. A medical history of prior anti-cancer treatment for pancreatic cancer.

	B. Locally advanced unresectable disease (see the criteria for resectability from inclusion criteria) or evidence of metastatic disease. C. Any other invasive malignancy within the past three years. D. Presence of any known contraindications to or hypersensitivities to the investigational products. E. Use of strong CYP3A4 inhibitors or inducers, which cannot be discontinued prior to study entry. F. A non-surgical candidate. G. Subject is unable to understand, provide consent or comply with study requirements, treatments or instructions in the opinion of the treating physician. H. Uncontrolled diarrhea, active infection, known interstitial lung disease or other medical condition that precludes safe administration of this combination therapy consistent with manufacturer recommendations. I. Unwilling/unable to comply with birth control requirements while on study. J. Females or males of childbearing potential who are **unwilling or unable** to use an acceptable method to avoid pregnancy for the entire study period and for at least 7 months for females and 4 months for males after the last dose of study drug. K. Females who are pregnant or breastfeeding. L. History of any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of protocol therapy or that might affect the interpretation of the results of the study or that puts the subject at high risk for treatment complications, in the opinion of the treating physician. M. Prisoners or subjects who are involuntarily incarcerated. N. Subjects who are compulsorily detained for treatment of either a psychiatric or physical illness. O. Subjects demonstrating an inability to comply with the study and/or follow-up procedures. P. Known dihydrypyrimidine (DPD) deficiency
Efficacy Assessments:	4 to 8 weeks after completion of neoadjuvant chemotherapy subjects will undergo surgical resection. The primary endpoint is the complication rate for evaluable patients who complete surgery, and

	this will be compared to expected complication rate. Pre-operative imaging will be compared to the baseline studies to assess radiographic response and continued surgical resectability potential. RECIST Radiographic criteria and clinical evaluations will be used to determine radiographic response and resectability. Surgical resection rates will be calculated and pathologic downstaging will be determined. Biochemical response rates will be calculated by serial CA19-9 levels and characterized as those with normalization of CA19-9 during therapy, reduction without normalization or no reduction with assessment of the temporal nature of these changes and correlation to surgical resection rates. Treatment completion rate will be calculated for all patients and is defined as the completion of all intended treatment cycles. Statistical analyses will be conducted by the study biostatistician using SAS v9.1 (SAS institute, Cary, NC)
Statistical Considerations:	For this prospective phase II pilot study, the sample size justification is based on the primary endpoint, the complication rate for evaluable patients who complete surgery. A sample size of 25 patients achieves ~80% to detect a reduction of 20% in the 30-day post-operative complication rate (from 30% to 10%), using a one-sided exact test with a significance level of 0.05. Assuming 10% drop-out rate, we will accrue a total of 28 patients for this study. The study expects a 20-month accrual period with an additional follow-up of 7 months after the last patient is enrolled. Subjects failing to proceed to surgery will be replaced, but all will support the secondary analyses. The sample size calculation is conducted by PASS 16.
Estimated Enrollment Period:	20 months
Estimated Study Duration:	27 months

1. BACKGROUND

1.1 Pancreatic Cancer Therapy

Pancreatic cancer is the third leading cause of cancer deaths in US with modest survival even in early stage disease[1]. It is poised to become the second leading cause of cancer deaths by 2030 [2]. The only chance for long-term survival is with complete resection of the cancer, but few are candidates for this approach with outcomes still being far from acceptable in this curative setting. Surgical resection is routinely followed by adjuvant chemotherapy, as it is widely believed that micro-metastatic disease is present even in early clinical stages of the disease. This strategy is associated with a proven reduction in the risk of recurrence of the cancer with documentation that two drug therapy is superior to one[3]. Neoadjuvant (pre-operative) treatment offers advantages in terms of earlier systemic treatment of micro-metastatic disease, limiting the

toxicity of therapy to when patients are more likely to tolerate the side effects, and down staging of tumor to allow more patients to achieve complete surgical resection, which is thus far the best predictor of good long-term outcome[4] . Recognizing that multi-agent combination chemotherapy confers the best disease control in the metastatic and adjuvant settings, this rationale has been previously demonstrated to also be feasible in the neoadjuvant space, particularly for patients with high risk disease including borderline resectable cancers[5]. Our program has previously demonstrated success in investigator-initiated protocol development, enrollment and analysis associated with novel neoadjuvant pancreatic adenocarcinoma clinical trials[6] . In the setting of borderline resectable and LAPC, high-volume academic institutions and national professional guidelines support a neoadjuvant therapy approach with multi-agent chemotherapy.[7] The development and favorable outcome with contemporary cytotoxic combination therapy in metastatic setting with FOLFIRINOX (5-Fluorouracil, Oxaliplatin, Irinotecan) with high response rates in metastatic setting had led to increased utilization of this particular regimen in the neoadjuvant setting. The use of FOLFIRINOX chemotherapy in the neoadjuvant setting has been explored in several non-randomized studies with promising safety profile, surgical outcomes and long term results, but at the cost of significant toxicity.[8,9]

A major challenge in treating patients with aggressive combination neoadjuvant therapy relates to toxicity, recognizing that patients need to be capable of receiving full doses and cycles of therapy to ensure optimal down staging and micrometastatic sterilization, yet still be capable of safely undergoing a major surgical resection. The most active therapy (inclusive of survival and response rates) in the metastatic setting is demonstrated by use of FOLFIRINOX therapy (5-fluorouracil, leucovorin, oxaliplatin and irinotecan), but it typically requires routine dose modifications, delays and growth factor support[10]. Commonly, the irinotecan component of this polyagent therapy is reduced or dropped in clinical practice when toxicities develop, leading to several “modified” FOLFIRINOX regimens in use. When used in the neoadjuvant setting, FOLFIRINOX regimens consistently require dose modifications (65%), but still demonstrate meaningful clinical down staging and surgically negative margins (70% R0 resection rate)[11]. However, toxicity limits the number of pre-operative cycles that can be delivered and post-operative complications are not trivial. Even at high to very high volume centers, 30-day post-operative mortality secondary to pancreatic resection is in the range of 3.8-7.5%[12]. In addition to this, clinically significant complications including delayed gastric emptying (15-17%), bile leak (1-2%), and pancreatic fistula (2-22%) may require either prolonged hospitalization or readmission[13-14]. With the addition of FOLFORINOX, even at modified doses, this complication rate is as high as 27-35%[15-18]. Such post-operative complications limit the ability to provide further adjuvant systemic therapy or radiotherapy.

1.2 Nanoliposomal Irinotecan

nal-IRI is irinotecan (also known as CPT-11) encapsulated in a liposome drug delivery system (liposomal irinotecan; nal-IRI). The active ingredient of the nal-IRI injection, irinotecan, is a member of the topoisomerase I inhibitor class of drugs and is a semi-synthetic and water soluble analog of the naturally-occurring alkaloid, camptothecin. Topoisomerase I inhibitors work to arrest uncontrolled cell growth by preventing the unwinding of DNA and therefore preventing replication. The pharmacology of irinotecan is complex, with extensive metabolic conversions involved in the activation, inactivation, and elimination of the drug[19-21]. Irinotecan is a prodrug that is converted by nonspecific carboxylesterases into a 100-1000 fold more active metabolite,

SN-38[22] . SN-38 is cleared via glucuronidation, for which major pharmacogenetic differences have been shown, and biliary excretion. These drug properties contribute to the marked differences in efficacy and toxicity observed in clinical studies with irinotecan[23, 24] .

Drug carrier technologies represent a rational strategy to improve the PK and biodistribution of irinotecan while protecting it from premature metabolism. nal-IRI employs a novel intraliposomal drug stabilization technology for encapsulation of irinotecan into long-circulating liposome-based nanoparticles with high drug load and high in vivo stability. The stable nanoliposome formulation of irinotecan has several attributes that may provide an improved therapeutic index. The controlled and sustained release should improve activity of this schedule-dependent drug by increasing duration of exposure of tumor tissue to drug, an attribute that allows it to be present in a higher proportion of cells during the more sensitive S-phase of the cell cycle. The improved PK, high intravascular drug retention in the liposomes, and EPR effect may potentially result in site-specific drug delivery to solid tumors. Stromal targeting results from the subsequent depot effect, where liposomes accumulating in tumor associated macrophages release the active drug and convert it locally to the substantially more cytotoxic SN-38. The preferentially local bioactivation should result in reduced exposure to potential sites of toxicity and increased exposure to neighboring cancer cells within the tumor.

The toxicity profile of irinotecan liposomal injection (ONIVYDE®) with 5-fluorouricil and leucovorin in the second line metastatic setting is very reasonable with the added benefit of improved drug delivery to tumor[25]. In the neoadjuvant setting, where patient toxicity is paramount and tumor vasculature is undisrupted, the incorporation of ONIVYDE® could have an important anti-neoplastic effect by improved biologic drug delivery and improved full treatment compliance. Delivering a complete (4 month) course of systemic therapy with maintenance of patient health and minimization of post-op complications would represent a clinically significant step forward in the field of pancreatic cancer therapy.

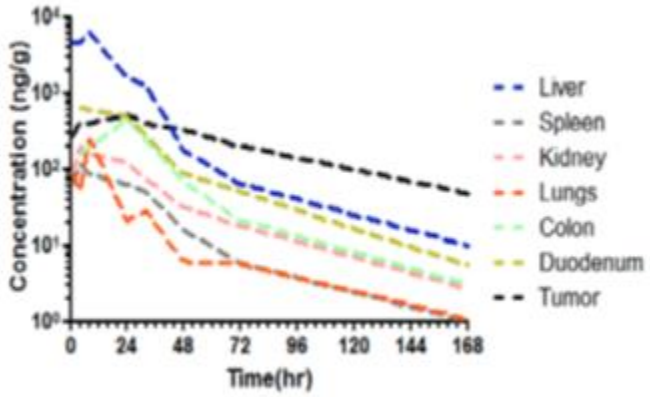
This protocol aims to substitute irinotecan liposomal injection (ONIVYDE®) for traditional irinotecan in the standard FOLFIRINOX regimen and deliver the therapy in the neoadjuvant setting. The primary goal of this strategy is to rapidly establish perioperative safety with regards to surgical outcomes. The doses and schedule will be those established by the safety run-in/Arm 1 of the currently enrolling randomized phase II front-line study in metastatic pancreatic cancer (NCT02551991). Recent safety data from that study supports the incorporation of ONIVYDE in this combination for previously untreated patients with metastatic pancreatic cancer[36]. This study will also help establish a benchmark for radiographic response rate, pathologic down staging and treatment compliance. Potential post-hoc correlative analyses include, but are not limited to, assessment of pancreatic cancer circulating tumor cells associated with treatment response, development of patient-derived cell lines and xenografts from refractory tumor removed at the time of surgical resection to determine pathways of resistance and microenvironmental immunosuppression, comprehensive mutational profiling of pancreatic adenocarcinoma tissue and pharmacologic precision medicine program assessments of novel pharmacogenomic profiles (e.g., additional haplotypes of UGT1A1, as well as UGT1A7, ABCG2/B1/C2, and SLCO1B1) associated with irinotecan-associated GI toxicity and myelosuppression[26-28]. Taken together, this study will support continued development of this novel combination regimen in the adjuvant, perioperative or metastatic setting.

1.3 Overview of Non-Clinical Studies

nal-IRI has been shown in preclinical settings to have a broad spectrum of activity in a wide range of solid tumors including colon, pancreatic, gastric, cervical, non-small cell lung, small cell lung, ovarian, thyroid, and breast cancers, as well as glioma, Ewing's sarcoma, and neuroblastoma, often with a high degree of anti-tumor activity against resistant or difficult to treat cancer models[29-31,] . nal-IRI has also shown potent antitumor activity, including durable tumor regressions, and was markedly superior to the equivalent dose of free drug in a bioluminescent-based orthotopic xenograft pancreatic model[32].

The PK properties of nal-IRI were evaluated in an HT-29 colon cancer subcutaneous xenograft model[29]. Both irinotecan and SN-38 were cleared very rapidly (within 8 hours) from the plasma following non-liposomal irinotecan administration; however, nal-IRI clearance was demonstrated to be considerably slower and remained in circulation for over 50 hours. SN-38 plasma exposure was also greater though C-max levels were reduced following nal-IRI administration, suggesting the advantage of the irinotecan liposomal formulation in prolonging exposure and half-life via the ability of the lipid bilayer to protect the conversion of prodrug CPT-11 to SN-38. Further, both irinotecan and SN-38 accumulated in tissues for extended time (at least 1 week after nal-IRI administration), yet there were relatively higher levels of prolonged accumulation in the tumor compared to normal tissue, where the metabolites are at very low levels after 48 hours (Figure B). Activation of irinotecan to SN-38 by the liver is the primary path for SN-38 tumoral accumulation when non-liposomal irinotecan is administered. In contrast, these data suggest that accumulation of nal-IRI in the tumor and subsequent liposome breakdown and local conversion of irinotecan to SN-38 is responsible for the enhanced tumor exposure of SN-38 when nal-IRI is administered. These preclinical data demonstrating longer retention time in tumor lesions with nal-IRI administration compared to non-liposomal irinotecan administration formed the basis for clinical development.

Figure B. Tissue Distribution of nal-IRI in an HT-296 Xenograft Study[12]



Levels of SN-38 in various tissues following a single nal-IRI (20 mg/kg) dose are shown. Prolonged accumulation of SN-38 (~168 h) seen in tumor compared to other organs (~48 h).

1.4 Overview of Clinical Studies

nal-IRI has been studied in patients with solid tumors, including cervical cancer, gastric cancer, pancreatic cancer, and colorectal cancer (see Table A). An overview of disease areas currently being studied is presented in Table B; additional study details can be found at ClinicalTrials.gov.

Table A. Summary of Published Clinical Studies with nal-IRI

Study	**PEP0201**	**PEP0202**	**PEP0203[32]**	**PEP0206[33]**	**PEP0208[31]**	**NAPOLI-1[25]**	**Colorectal[34]**
Tumor Type	Solid tumors	Cervical	Solid Tumors	Gastric	Pancreas	Pancreas	Colorectal
Phase	1	1	1	1	2	3	2
Study Design	Open label, dose escalation	Open label, dose escalation	Open label, dose escalation	Open label, 3-arm study comparing nal-IRI, docetaxel, and irinotecan (44 pts/arm)	Open label, single arm	Randomized comparison of nal-IRI and nal-IRI+5-FU/LV vs common control (5-FU/LV)	Comparison of nal-IRI + 5-FU/LV + bevacizumab versus FOLFIRI + bevacizumab
Dosing Frequency	Q3W	Q3W	Q3W	Q3W	Q3W	Q3W (mono arm) Q2W (combo arm)	Q2W
Dose Level, mg/m^2*	60 (n=1) 120 (n=6) 180 (n=4)	60 (n = 3) 80 (n = 3	60 (n=3) 80 (n=6) 100 (n=5) 120 (n=2)	120	120	120 (mono arm) 80 (combo arm)	80
Combination and Dose	No	Cisplatin 60 mg	5-FU/LV 2000/500 mg/m^2	No	No	5-FU/LV 2000/200 mg/m^2	5-FU/LV 2400/400 mg/m^2 + bevacizumab 5 mg/kg
Key Result	MTD identified as 120 mg/m^2	Study terminated	MTD identified as 80 mg/m^2	Similar safety profile across irinotecan and nal-IRI arms; 6 responses in nal-IRI arm met primary endpoint	Median surival = 5.2 months	Combination arm achieved median OS 6.1 months, 1.9-month improvement over control arm (HR=0.57; P=0.0009)	

*The doses of nal-IRI in publications written before October 2015 were expressed as the irinotecan hydrochloride trihydrate. nal-IRI dosing according to the prescribing information is expressed as the irinotecan free base. Therefore, the published expression of the 80 mg/m^2 dose based on irinotecan hydrochloride trihydrate is equivalent to a 69.3 mg/m^2 dose based on irinotecan free base. This was rounded to 70 mg/m^2 to minimize any potential dosing errors. Similarly, the nal-IRI monotherapy arm (120 mg/m^2 irinotecan hydrochloride trihydrate) is equivalent to 100 mg/m^2 of irinotecan free base.

Table B. Other Clinical Studies with nal-IRI

Study	Tumor Type	Phase	Study Design	Dosing Frequency	Dose Level, mg/m^2		Combination	Status
NCT02551991	Pancreas		Open label comparison of nal-IRI + 5-FU/LV + oxaliplatin or nal-IRI + 5-FU/LV vs nab-paclitaxel + gemcitabine	Q2W	70		Oxaliplatin	Enrolling
N/A	Glioma	1	Open label, dose escalation	Q3W	Heterozygous* 60 (n=3) 90 (n=6) 120 (n=3) 150 (n=6)	Wild Type* 120 (n=6) 180 (n=7) 240 (n=3)	None	Enrollment completed; MTD identified for heterozygous=150 mg/m^2 and MTD identified for wild-type=120 mg/m^2
NCT02640365	Colorectal	1b	Open label, dose escalation of nal-IRI + irinotecan (Group A; noncolorectal) or nal-IRI + 5-FU/LV + irinotecan + bevacizumab (Group B; colorectal)	Q2W	60 or 80 mg*		Irinotecan, bevacizumab	Enrolling
NCT01770353	Solid tumors	1	Open label, ferumoxytol prior to first dose	Q2W	80*		None	
NCT02022644	Pancreas	2	Open label, dose escalation using convection-enhanced delivery for direct tumoral injection	Single dose	Dose* 20 40 60 80	Tumor Volume 1-4 cm^3 1-4 cm^3 2-5 cm^3 2-6 cm^3	None	
NCT02013336	Pediatric solid tumor	1	Open label, dose escalation	Q3W	60 (n=3)* 90 (n=3)* 120 (n=3)* 150*		Cyclophosphamide	

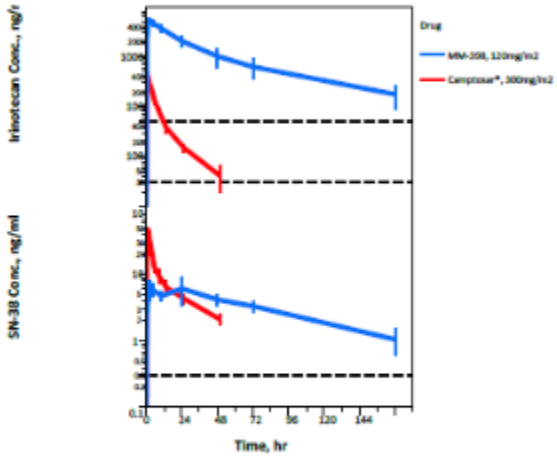
					180* 210*		
NCT02631733	Solid tumors	1	Open label, dose escalation of velaparib	Q2W	70	Velaparib	
NCT02231723	Pancreas	1	Open label, dose-escalation study of BBI608 + Gemcitabine and nab-Paclitaxel or mFOLFIRINOX or, FOLFIRI or nal-IRI+5-FU/LV	Q2W	70	BBI-608 (Napabucasin)	

*The doses of nal-IRI in publications and protocols written before October 2015 were expressed as the irinotecan hydrochloride trihydrate. nal-IRI dosing according to the prescribing information is expressed as the irinotecan free base. Therefore, the published expression of the 80 mg/m^2 dose based on irinotecan hydrochloride trihydrate is equivalent to a 69.3 mg/m^2 dose based on irinotecan free base. This was rounded to 70 mg/m^2 to minimize any potential dosing errors.

1.4.1 Nal-IRI Pharmacokinetics in Humans

The PK profile of single agent nal-IRI has been investigated in several studies, in which plasma levels of total irinotecan, SN-38 and encapsulated irinotecan were measured. In a single phase II clinical study, direct comparison of the PK of irinotecan and SN-38 in patients administered nal-IRI or conventional (i.e., free) irinotecan was evaluated[33, 35]. Compared to the administration of conventional irinotecan 300 mg/m^2 Q3W, administration of nal-IRI 120 mg/m^2 Q3W resulted in higher exposure of total irinotecan (C_{max}: 13.4-fold, $AUC_{0-\infty}$: 46.2-fold, $t_{1/2}$: 2.0-fold), and higher SN-38 $t_{1/2}$ (3-fold) and marginally higher $AUC_{0-\infty}$ (1.4-fold), however, SN-38 C_{max} was reduced by 5.3-fold (Figure C). In other PK studies of single agent nal-IRI, similar findings were observed when compared to standard doses of conventional irinotecan. Based on population PK analysis, no significant association was observed between the PK parameters of total irinotecan and SN-38 following nal-IRI monotherapy and when co-administered with 5-FU/LV. This result is consistent with the lack of drug interaction noted between irinotecan and 5-FU[33]. A summary table of PK parameters from 95 patients who received 60-180 mg/m^2 nal-IRI is found below (see Table C).

Figure C: Mean Plasma Concentrations of Total Irinotecan and SN-38 Following the Administration of Either MM-398 (120mg/m^2) or Camptosar® (300mg/m^2) in Study PEP0206



Gastric cancer patients received either nal-IRI (MM-398) at a dose of 120 mg/m^2 (blue line) or non-liposomal irinotecan (Camptosar®) at a dose of 300 mg/m^2 (red line) every 3 weeks. Total irinotecan (top) and its active metabolite, SN-38 (bottom) were measured during Cycle 1. Error bars indicate 95% confidence interval. Dotted lines indicate lower limit of quantification (LLOQ); total irinotecan measurements consist of two LLOQ values because of two different irinotecan assay was used to measure low and high range of concentrations. The concentrations less than LLOQ values were set to the corresponding LLOQ. [Data on file, Merrimack Pharmaceuticals; Ma 2015]

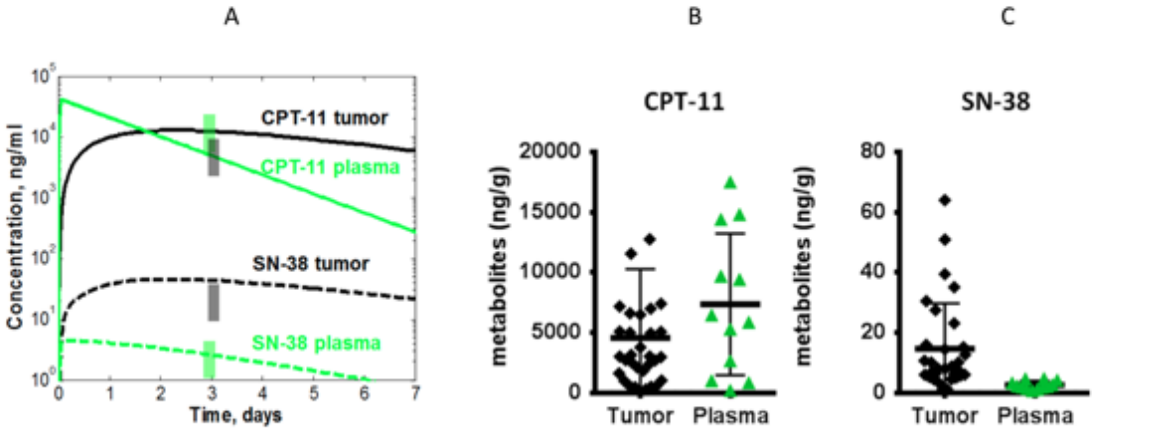
Table C. Summary Statistics of nal-IRI PK Parameters across Multiple PK Studies

PK Parameters	Dose, mg/m^2	Analytes					
		Total Irinotecan			SN-38		
		N	Median	%IQR	N	Median	%IQR
C_{max}, µg/mL or ng/mL	60	4	28.8	86	4	3.8	226
	80	25	38.0	36	25	4.7	89
	90	6	53.6	37	6	7.5	89
	100	11	41.9	41	11	6.2	79
	120	45	59.4	32	45	7.2	57
	180	4	102.4	87	4	11.8	89
$T_{1/2}$	60	4	22.0	87	3†	145.1	233
	80	23†	26.85	110	13†	49.3	103
	90	6	14.8	97	6	35.7	53
	100	11	21.6	192	10†	62.3	37
	120	45	15.6	198	40†	57.4	67
	180	4	22.8	86	4	50.2	122
$AUC_{0-\infty}$, h·µg/mL or h·ng/mL	60	4	352	489	3†	813	249
	80	23†	1030	169	13†	587	69
	90	6	1481	1123	6	506	102
	100	11	919	256	10†	453	99
	120	45	1258	192	40†	574	64
	180	4	2076	90	4	1069	183
Vd, L/m^2	60	4	3.0	87	NA		
	80	23†	2.2	55			
	90	6	1.5	40			
	100	11	2.2	24			
	120	45	1.9	52			
	180	4	2.1	30			

†$T_{1/2}$ and $AUC_{0-\infty}$ were not calculated for a subset of patients due to insufficient number of samples in the terminal phase. NA= not available. C_{max} are in µg/ml for total irinotecan and ng/ml for SN-38; AUC are in h µg/ml for total irinotecan and h ng/ml for SN-38. [Data on File, Merrimack Pharmaceuticals, Inc.]

The above PK results obtained from patients treated with either nal-IRI or non-liposomal irinotecan confirmed the preclinical observation that nal-IRI extended plasma PK of both CPT-11 and SN-38 compared to treatment with non-liposomal irinotecan. Further, a Phase I clinical study of nal-IRI monotherapy (NCT01770353) investigated tumor levels of both CPT-11 and SN-38 following treatment with nal-IRI using post-treatment biopsies. Based on model predictions, SN-38 levels in tumor were expected to be higher than in plasma, suggesting local conversion of CPT-11 to SN-38 in the tumor microenvironment with nal-IRI (Figure D – Item A). Predictions were confirmed by measuring levels of CPT-11 and SN-38 in tumor biopsy samples collected from patients 72 hours post-dose, demonstrating 5-fold higher levels of SN-38 in the tumor than the plasma (Figure D – Item B and C). Collectively the evidence suggests that the prolonged systemic exposure to CPT-11 and SN-38 leads to prolonged levels of SN-38 in tumor tissue, which in turn leads to prolonged DNA damage to tumor cells, suggesting an advantage of nal-IRI compared to conventional irinotecan.

Figure D: Clinical Evidence for Local Activation and Accumulation of SN-38 in Tumor Tissue



A) The mechanistic tumor PK model of nal-IRI predicted higher SN-38 levels in tumor compared to plasma. The range of actual data, collected from a Phase I study of patients (n=12) with advanced solid tumors, is indicated by the gray (tumor) or green (plasma) vertical bars.
B) CPT-11 levels
C) SN-38 levels, as measured from patient tumor (black) and plasma (green) samples collected 72h post-nal-IRI infusion. [Ramanathan 2014]

1.4.2 Nal-IRI Safety in Humans

It has been shown in animal and human PK studies that once irinotecan is released from the nal-IRI liposomes, the conversion of irinotecan to SN-38 is similar to that of the unencapsulated irinotecan. The safety of nal-IRI, therefore, may be indirectly compared with the safety of irinotecan, primarily based on a qualitative comparison of adverse reactions, as reported in the Camptosar US label for irinotecan[32]. The comparison is qualitative, as both irinotecan and nal-IRI have been used in different doses and schedules as monotherapy and combination therapy with other chemotherapeutic agents; therefore, quantitative comparisons are difficult. The most common adverse reactions of irinotecan and nal-IRI are similar and are mainly gastrointestinal events and myelosuppression. The common adverse reactions (>30%) observed in clinical studies with irinotecan in combination with other agents are: nausea, vomiting, abdominal pain, diarrhea, constipation, anorexia, mucositis, neutropenia, leukopenia (including lymphocytopenia), anemia, thrombocytopenia, asthenia, pain, fever, infection, abnormal bilirubin, and alopecia. The common adverse reactions (>30%) observed in single agent irinotecan therapy in clinical studies are: nausea, vomiting, abdominal pain, diarrhea, constipation, anorexia, neutropenia, leukopenia (including lymphocytopenia), anemia, asthenia, fever, body weight decreasing, and alopecia[32]. With respect to liposomal irinotecan, nal-IRI, when used in combination with 5-FU and leucovorin, the most common adverse reactions (≥20%) observed in clinical trials considered to be related are: diarrhea, nausea, vomiting, decreased appetite, neutropenia, fatigue, anemia, stomatitis and pyrexia. The overall safety profile of nal-IRI is presented in detail in the related Investigator Brochure. Additionally, Table D summarizes the most common ≥Grade 3 adverse events with ≥2% incidence compared with the control arm from the NAPOLI-1 trial comparing nal-IRI + 5-FU/LV (at a dose of 70 mg/m^2 given on an every-2-week schedule), or nal-IRI monotherapy (at a dose of 100 mg/m^2 given on

an every-3-week schedule), with 5-FU/LV alone (given weekly for 4 weeks followed by 2 weeks of rest) in the same population of patients who had received prior gemcitabine therapy.

In the phase II NALIRIFOX study (NCT02551991)[38], the MTD (liposomal irinotecan 50 mg/m^2 [free-base equivalent], oxaliplatin 60 mg/m^2, 5-fluorouracil 2400 mg/m^2, leucovorin 400 mg/m^2 every 2 weeks) was based on dose-limiting toxicities and cumulative safety data in four dose-exploration cohorts. The MTD was received by 32 of 56 patients, seven during dose exploration and 25 during dose expansion (median age 58.0 years [range, 39-76], 28 [87.5%] with metastatic disease at diagnosis [29 at study entry], and one receiving study treatment at data cutoff [26 February 2020]). Of these patients, 22 of 32 had grade ≥3 treatment-related TEAEs, most commonly neutropenia (31.3%), febrile neutropenia (12.5%) and hypokalaemia (12.5%); ten had serious treatment-related TEAEs; and three died from TEAEs considered unrelated to treatment. Median PFS and OS were 9.2 (95% CI: 7.69-11.96) and 12.6 (8.74-18.69) months, respectively.

NOTE: nal-IRI dosing according to the prescribing information is expressed as the irinotecan free base. The doses of nal-IRI in publications written before October 2015 were expressed as the irinotecan hydrochloride trihydrate. Converting a dose based on irinotecan hydrochloride trihydrate to a dose based on irinotecan free base is accomplished by substituting the Molecular Weight of irinotecan hydrochloride trihydrate (677.19 g/mole) with the Molecular Weight of irinotecan free base (586.68 g/mole), which results in a conversion factor of 0.866. Therefore, the published expression of the 80 mg/m^2 dose based on irinotecan hydrochloride trihydrate is equivalent to a 69.3 mg/m^2 dose based on irinotecan free base. This was rounded to 70 mg/m^2 to minimize any potential dosing errors. Similarly, the ONIVYDE® monotherapy arm (120 mg/m^2 irinotecan hydrochloride trihydrate) is equivalent to 100 mg/m^2 of irinotecan free base. Information published prior to October 2015 included the background sections of this protocol uses the trihydrate doses (80 mg/m^2 and 120 mg/m^2).

Table D: Most Common Grade ≥3 Adverse Events Observed in Nal-IRI Containing Arms Occurring at ≥5% Overall with ≥2% Incidence Versus 5-FU/LV

	Nal-IRI+5-FU/LV (n=117)		Nal-IRI (n=147)		5-FU/LV (n=134)	
Adverse Event, %	Any Grade	Grades 3/4	Any Grade	Grades 3/4	Any Grade	Grades 3/4
Diarrhea	59.0	12.8	70.1	21.1	26.1	4.5
Vomiting	52.1	11.1	54.4	13.6	26.1	3.0
Nausea	51.3	7.7	60.5	5.4	34.3	3.0
Decreased appetite	44.4	4.3	49.0	18.8	32.1	2.2
Fatigue	40.2	13.7	36.7	6.1	27.6	3.7
Neutropenia*	39.3	27.4	25.2	15.0	5.2	1.5
Anemia	37.6	9.4	32.7	10.9	23.1	6.7
Hypokalemia	2.0	3.4	21.8	11.6	9.0	2.2

*Includes agranulocytosis, febrile neutropenia, granulocytopenia, neutropenia, neutropenic sepsis, decreased neutrophil count, and pancytopenia[25].
5-FU/LV=5-fluorouracil/leucovorin.

1.5 Rationale for Regimen/Doses/Schedule

Pancreatic cancer is the third leading cause of cancer deaths in US with modest survival even in early stage disease[1]. It is poised to become the second leading cause of cancer deaths by 2030[2]. Long term survival for patients with this disease are still <10%. The only chance for long-term survival is with complete resection of the cancer, but few are candidates for this approach with outcomes still being far from acceptable even in this curative setting. Surgical resection is routinely followed by adjuvant chemotherapy, as it is widely believed that micro-metastatic disease is present even in early clinical stages of the disease. This strategy is associated with a proven reduction in the risk of recurrence of the cancer with documentation that two drug therapy is superior to one[3]. Neoadjuvant (pre-operative) treatment offers advantages in terms of earlier systemic treatment of micro-metastatic disease, limiting the toxicity of therapy to when patients are more likely to tolerate the side effects, and down staging of tumor to allow more patients to achieve complete surgical resection, which is thus far the best predictor of good long-term outcome[4]. Recognizing that multi-agent combination chemotherapy confers the best disease control in the metastatic and adjuvant settings, this rationale has been previously demonstrated to also be feasible in the neoadjuvant space, particularly for patients with high-risk disease including borderline resectable cancers[5]. Our program has previously demonstrated success in investigator-initiated protocol development, enrollment and analysis associated with novel neoadjuvant pancreatic adenocarcinoma clinical trials[6].

A major challenge in treating patients with aggressive combination like FOLFIRINOX in neoadjvuant setting is toxicity which commonly leads to dose modification of irinotecan component. The toxicity profile of irinotecan liposomal injection (ONIVYDE®) with 5 fluorouracil and leucovorin in second line metastatic setting is very reasonable[25]. In the current study, nal-IRI will be evaluated instead of conventional irinotecan to improve the safety, tolerability, and ultimately efficacy of the FOLFIRINOX regimen. By adding oxaliplatin to the NAPOLI-1 regimen that has proven efficacy in post-gemcitabine pancreatic cancer, the potential to increase DNA damage and potentiate efficacy exists. Further, due to the nal-IRI prolonged PK properties and sustained tumor exposure, it is thought that using nal-IRI instead of conventional irinotecan would improve upon the efficacy of FOLFIRINOX. The standard dose regimen of FOLFIRINOX which demonstrated efficacy is 85 mg/m2 oxaliplatin, 180 mg/m2 irinotecan, and fluorouracil at a dose of 400 mg/m2 administered by IV bolus followed by a continuous infusion of 2400 mg/m2. Yet due to toxicity, modified FOLFIRINOX regimens are often used (e.g. elimination of the 5-FU bolus and irinotecan dose reduction) with unknown effects on the efficacy and safety of modified schedules. . The combination of ONIVYDE® with 5-flurouracil and oxaliplatin is currently being studied in the phase 2 study in previously untreated metastatic pancreatic cancer[36]. In the current study, a modified triplet regimen is proposed, whereby no bolus of 5-FU will be administered based on currently ongoing phase 2 study of NALIRIFOX in previously untreated metastatic pancreatic adenocarcinoma. The dose of oxaliplatin (60 mg/m2) in this combination regimen with the standard continuous infusion dose of 5-FU (excluding the bolus), and the every 2 week dose of nal-IRI was previously shown to be tolerable and efficacious in combination with 5-FU. Note that with nal-IRI dosing, the C_{max} of SN-38 is predicted to be lower than would be expected for standard dosing with non-liposomal irinotecan. Additionally, in a small Phase 2 study in colorectal cancer, data suggest that nal-IRI + 5-FU/LV

may have less toxicity than FOLFIRI[34]. Based on this data, toxicity of the nal-IRI-containing triplet regimen is not expected to be greater than that seen with FOLFIRINOX in metastatic setting and proposed study would help us determine safety and toxicity of this regimen in neoadjuvant setting.

2. OBJECTIVES

2.1 Primary

- To establish the safety and feasibility of ONIVYDE® in combination with 5-fluorouracil, leucovorin, and oxaliplatin (FOLNal-IRINOX) in the neoadjuvant setting of resectable or borderline resectable pancreatic adenocarcinoma
- Primary endpoint: 30-day post-op complication rate as measured by hospital readmission, death, second surgery or interventional procedure or major complications extending hospital stay.

2.2 Secondary

- To determine the treatment completion rate of therapy defined by completion of all intended cycles
- To determine the rate of complete surgical resection (R0) and other histopathologic downstaging
- To determine radiographic objective response rate (ORR) of the primary tumor as measured by RECIST 1.1 criteria
- To determine the biochemical response rate and pattern of response as measured by serial CA 19-9 levels
- To determine the patient-reported quality of life during treatment as measured by the NCI validated FACT-G scale

2.3 Exploratory

- To collect tissues and blood for post-hoc secondary exploratory biomarker, CTC, ctDNA, pharmacogenomic and tumor mutational profile assessments as well as potential PDX development.
- Biospecimens will be collected and subsequently examined for microbiota content and any associations with patient and tumor characteristics, treatment outcomes and change over time.

3. STUDY DESIGN

3.1 Study Overview

This is an open-label, single arm pilot trial of ONIVYDE® with 5-fluorouracil, leucovorin and oxaliplatin (NALIRIFOX) in the neoadjuvant setting of resectable or borderline resectable pancreatic adenocarcinoma. A total of 28 subjects are planned. Each subject will be administered the outlined study drug regimen every two weeks as outlined in Table 3.1. Each subject will receive a total of eight treatments. Evaluations will be taken Day 1 of each cycle, within four weeks prior to planned surgery, and four to six weeks post-operatively.

Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be entered into the study.

The following treatment regimens will be used:

Table 3.1: Study Treatment Regimen (FOLFNal-IRINOX)

Agent	Dose	Route/Duration	Schedule
ONIVYDE®	50 mg/m^2 [starting dose is 36 mg/m^2 (Dose Level -1) for subjects who are homozygous for UGT1A1*28]	IV over 90 minutes	1 every 14 days
Oxaliplatin	60 mg/m^2	IV over 120 minutes	1 every 14 days
Leucovorin	400 mg/m^2	IV over 120 minutes	1 every 14 days
5-fluorouracil infusion	2400 mg/m^2	IV continuous infusion for 46 hours	1 every 14 days
Administer sequentially as written, except oxaliplatin and leucovorin, which may be administered concurrently in separate bag using a Y-line. In the event that oxaliplatin is discontinued, leucovorin can be administered alone and the administration duration may be shorted to fifteen minutes.			

Total duration of active subject participation will be approximately 7-8 months. After the post-surgical visit, subjects will be followed for survival approximately every 6 months for 5 years.

4. SELECTION OF SUBJECTS

Subjects with a diagnosis of pancreatic adenocarcinoma who meet the following inclusion and exclusion criteria will be eligible for participation in this study.

4.1 Number of Subjects

A total of 28 evaluable subjects are to be enrolled.

4.2 Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for study participation:

A. Written informed consent obtained from the subject and the ability for the subject to comply with all the study-related procedures.
B. Both males and females ≥ eighteen years of age.
C. A new clinical diagnosis of borderline resectable, or resectable, previously untreated pancreatic adenocarcinoma confirmed by pathologic specimen.
D. No clinical evidence of metastatic disease, confirmed by CT of chest/abdomen and pelvis with IV contrast (or MRI of pancreas with non-contrast chest CT, if IV contrast is contraindicated).
E. Potentially resectable local disease, confirmed by CT of the abdomen with IV contrast (MRI abdomen if CT/contrast is contraindicated) which radiographically confirmation of resectable or borderline resectable pancreatic cancer verified by documented consensus discussion of the GI Multidisciplinary Tumor Board and guided by the published expert consensus criteria for resectable or borderline resectable. The ultimate determination of whether a potential subject meets the criteria of "resectable or borderline resectable" lies in the consensus of the UF GI Multidisciplinary Tumor Board, or equivalent body (for external sites).
F. Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1.
G. Treated biliary obstruction (if applicable)
H. Subjects with known or suspected Gilbert's disease must be formally tested for UGT1A1*28 with results available to study team prior to treatment initiation
I. Adequate organ function; as defined by:
   i. Hematologic-
      - ANC > 1,500 cells/µl without the use of hematopoietic growth factors; and
      - Platelet count > 100,000 cells/µl; and
      - Hemoglobin > 9 g/dL (blood transfusions are permitted for patients with hemoglobin levels below 9 g/dL)
   ii. Hepatic-
      - Serum total bilirubin within 1.5 ULN for the institution, with a trend downwards (biliary drainage is allowed for biliary obstruction),
      - AST and ALT less than or equal to 2.5 x ULN

iii. Renal-
- Serum creatinine less than or equal to 1.5 x ULN

iv. Cardiac-
- Normal ECG or ECG without any clinically significant findings as defined by the treating physician

J. Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy throughout the study and for at least 7 months after the last dose of study drug to minimize the risk of pregnancy. Prior to study enrollment, women of childbearing potential must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy.

WOCBP include any woman who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or who is not post-menopausal. Post-menopause is defined as:

- Amenorrhea that has lasted for ≥ 12 consecutive months without another cause, or
- For women with irregular menstrual periods who are taking hormone replacement therapy (HRT), a documented serum follicle-stimulating hormone (FSH) level of greater than 35 mIU/mL.

K. Males with female partners of child-bearing potential must agree to use physician-approved contraceptive methods (*e.g.*, abstinence, condoms, vasectomy) throughout the study and should avoid conceiving children for 4 months following the last dose of study drug.

4.3 Exclusion Criteria

Subjects with any of the following will not be eligible for study participation:

A. A medical history of prior anti-cancer treatment for pancreatic cancer.
B. Locally advanced unresectable disease (see the criteria for resectability from inclusion criteria) or evidence of metastatic disease.
C. Any other invasive malignancy within the past three years.
D. Presence of any known contraindications to or hypersensitivities to the investigational products.
E. Use of strong CYP3A4 inhibitors or inducers which cannot be discontinued prior to study entry.
F. A non-surgical candidate.
G. Subject is unable to understand, provide consent or comply with study requirements, treatments or instructions in the opinion of the treating physician.

H. Uncontrolled diarrhea, active infection, known interstitial lung disease or other medical condition that precludes safe administration of this combination therapy consistent with manufacturer recommendations.

I. Unwilling/unable to comply with birth control requirements while on study.

J. Females or males of childbearing potential who are **unwilling or unable** to use an acceptable method to avoid pregnancy for the entire study period and for at least 7 months for females and 4 months for males after the last dose of study drug.

K. Females who are pregnant or breastfeeding.

L. History of any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of protocol therapy or that might affect the interpretation of the results of the study or that puts the subject at high risk for treatment complications, in the opinion of the treating physician.

M. Prisoners or subjects who are involuntarily incarcerated.

N. Subjects who are compulsorily detained for treatment of either a psychiatric or physical illness.

O. Subjects demonstrating an inability to comply with the study and/or follow-up procedures.

P. Known dihydrypyrimidine (DPD) deficiency

4.4 Inclusion of Women and Minorities

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

5. REGISTRATION PROCEDURES

All study participants must be registered with the UF Clinical Trial Management System (OnCore) prior to participation in this trial. This is not registration into the trial. The participating site must fax or email the completed study specific eligibility checklist and registration forms, supporting documents and signed informed consent to the Coordinating Center. Unsigned or incomplete forms will be returned to the site. Once documents are received, the designated Research Coordinator will review them to confirm eligibility and to complete the registration process. If eligibility cannot be confirmed, the research coordinator will query the site for clarification or additional documents as needed. Subjects failing to meet all study eligibility requirements will not be registered and will be unable to participate in the trial.

6. STUDY PROCEDURES

Please see the Schedule of Events located in Appendix A.

6.1 Screening Evaluations

Written informed consent must be obtained prior to performing any study-specific evaluations or tests. Tests or evaluations performed as standard of care within the specified screening period, but prior to informed consent, may be accepted for this study and need not be repeated.

The following pre-treatment measurements will be obtained within 28 days prior to the initiation of therapy:

a. A medical history and physical exam, including vital signs, will be obtained from each subject.
b. Vital Signs – Temperature, resting pulse, blood pressure and respiratory rate
c. Height, weight and ECOG performance will be obtained from each subject.
d. Blood and urine samples will be obtained for the following laboratory studies:
   - CBC with differential count
   - Comprehensive metabolic panel
   - CA 19-9
   - Urinalysis
   - Urine pregnancy test (females of potential child-bearing status only). This test must be done within 7 days of treatment.
e. ECG (document any abnormalities)
f. CT of chest/abdomen and pelvis with IV contrast (or MRI of abdomen/pelvis with non-contrast chest CT, if IV contrast is contraindicated).
g. Submission of diagnostic tumor specimen

6.2 On-Treatment Evaluations (Day 1 of Cycles 1 to 8) +/- 3 days

On-Treatment evaluations must be obtained prior to treatment provision.

a. Height, weight and ECOG performance status will be obtained from each subject.
b. An interim medical history and physical exam, including vital signs, symptoms evaluation for toxicity and adverse effect assessment will be obtained from each subject.
c. Blood samples for a CBC with differential count, comprehensive metabolic panel, and CA 19-9 will be obtained.
d. Research blood samples
e. A urine or serum pregnancy test will be obtained for all females of childbearing potential at the start of each cycle during study treatment,
f. ECG (only on Day 1 of Cycles 1-8) (as medically indicated)
g. FACT-G, quality of life assessment (only on Day 1 of Cycles 1, 5, and 8).
h. Microbiota sample collection (only at Day 1 of Cycles 1 and 5). Stool collection may be performed at home and mailed or brought to clinic, or obtained in clinic. Urine and oral samples will be collected in clinic.

6.3 Pre-surgical Evaluation (within 4 weeks prior to surgery)

Pre-surgical evaluations should be within four to eight weeks following the last dose of chemotherapy.

a. Height, weight and ECOG performance status will be obtained from each subject.
b. An interim medical history and physical exam, including vital signs, will be obtained from each subject.
c. Blood samples for a CBC with differential count, comprehensive metabolic panel, and CA 19-9 will be obtained.
d. Research blood samples
e. CT of chest/abdomen and pelvis with IV contrast (or MRI of abdomen/pelvis with non-contrast chest CT, if IV contrast is contraindicated) should be performed following, but no more than 4 weeks after the administration of the last cycle of neoadjuvant chemotherapy.
f. Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 will be utilized to assess tumor response
g. ECG (as medically indicated)
h. FACT-G, quality of life assessment.
i. Microbiota sample collection (after completion of chemotherapy **and** after completion of radiotherapy if performed). Stool collection may be performed at home and mailed or brought to clinic, or obtained in clinic. Urine and oral samples will be collected in clinic.

6.4 Follow up Evaluations (4-6 weeks post-op) – End of Treatment Evaluation

a. Height, weight and ECOG performance status will be obtained from each subject.
b. An interim medical history and physical exam, including vital signs, will be obtained from each subject.
c. Blood samples for a CBC with differential count, comprehensive metabolic panel, and CA 19-9 will be obtained.
d. Documentation of the pathology report findings with submission of surgical specimen samples will be obtained.
e. Research blood samples
f. Submission of surgical pathologic tumor specimen
g. FACT-G, quality of life assessment.
h. Microbiota sample collection (at post-surgical/EOT visit). Stool collection may be performed at home and mailed or brought to clinic, or obtained in clinic. Urine and oral samples will be collected in clinic.

6.5 Survival Follow up

Survival follow-up every 6 months for 5 years and documentation of any recurrence.

6.6 Efficacy Assessments

6.6.1 Tumor Response

Tumor response will be assessed using RECIST (version 1.1) criteria. Reference Appendix C for guidelines.

6.6.2 Primary Efficacy Assessment

Determine the activity of ONIVYDE® plus leucovorin, and oxaliplatin (NALIRIFOX) in subjects with pancreatic adenocarcinoma.

6.6.3 Secondary Efficacy Assessments

Determine radiographic response rate by RECIST (Version 1.1) criteria, the rate of surgical resection, the biochemical response rate and pattern measured by CA 19.9 serum levels, and quality of life of subject receiving protocol therapy. All radiographic images and responses will be reviewed and confirmed by a third party investigator-independent radiographic review.

Quality of life measurements will be collected and recorded by subjects with subsequent analysis performed on all subjects. Specifically, the FACT-G (Functional Assessment of Cancer Therapy – General, Version 4.0) will be employed as a previously validated subject self-reporting tool in oncology patients. Reference Appendix D for FACT-G questionnaire.

Additional exploratory tissue and serum correlative analyses in protocol participants is further detailed in Section 9.2.

7. STUDY TREATMENT

All subjects entering the screening phase will receive a unique subject number. This number will be used to identify the subject throughout the study. Subjects withdrawn from the study will retain their subject number.

7.1 Treatment Schedule/Administration

Refer to Table 3.1 for the protocol treatment regimen.

Overall treatment plan

- ONIVYDE® with 5-fluorouracil, leucovorin and oxaliplatin (NALIRIFOX) at the recommended for phase II doses determined from NCT02551991-IV dosing every 2 weeks x 8 total treatments (4 months)
- Surgical resection in the absence of documented progression within 4-8 weeks following last dose of therapy. Clinical response assessment following last cycle of NALIRIFOX.
- Optional chemoradiotherapy with evidence of local disease progression or as otherwise defined in Section 7.2.4
- Optimal supportive care and growth factor support per recommendations from NCT02551991
- Clinical follow-up 4-6 weeks post-operatively (EOT visit)
- Survival follow-up every 6 months for 5 years and documentation of any recurrence.

7.2 Specific Supportive Care

7.2.1 Dose Calculations

Mosteller/Dubois formula would be used for body surface area calculator according to the institution guidelines. Actual body weight would be used for the BSA calculation which would be obtained within 72 hours prior to Day 1 of each cycle. Formula used for BSA calculation should be consistent throughout the treatment.

CrCl would be calculated using MDRD equation:

GFR (ml/min/1.73 m^2) = 175 x $(S_{Cr})^{-1.154}$ x $(Age)^{-0.203}$ x (0.742, if female) x (1.212, if African American)

7.2.2 Concomitant Therapy

Relevant medical history should be obtained at screening and include prior medications and treatment history. All medications taken within 4 weeks prior to screening, regardless of indication, should be recorded. However, routine pre-treatment supportive care medications do not need to captured.

Any therapy or medication (except study drugs), administered from screening until the post-op visit (or pre-op visit if the subject does not proceed with surgery), is considered a concomitant therapy or medication. However, if a course of a new anti-cancer therapy is initiated prior to that follow-up period visit, a record of concomitant medications will no longer be performed. Medications administered as a routine part of the resection surgery and associated hospitalization will not be recorded. If the use of any concomitant treatments (medications or procedures) becomes necessary, the treatment must be recorded, including the name of the drug or treatment, dose, route, date, indication for use, expected duration, and frequency of treatment. Assessment and documentation of concomitant medications will be done at each visit. (See section 7.2.4 for prohibited concomitant medication.) Guidelines for treating certain medical conditions with concomitant medication is discussed in section 7.2.3.

7.2.3 Allowed Concomitant Therapy

See protocol-specific supportive care information in Section 7.2. All other supportive measures consistent with optimal patient care will be given throughout the study.

> **Nausea**: Dexamethasone and 5HT3 blocker will be prescribed as premedication and anti-emetics will be prescribed and changed as clinically warranted during study period.
>
> **Diarrhea**: Acute diarrhea and abdominal cramps, developing during or within 24 hours after nal-IRI administration, may occur as part of a cholinergic syndrome. The syndrome can be treated with atropine. Prophylactic or therapeutic administration of atropine, according to institutional standards, should be considered in patients experiencing

cholinergic symptoms during the study. Diarrhea can be debilitating and on rare occasions is potentially life-threatening. Diarrhea should be managed according to institutional guidelines or according to ASCO guidelines[37]. In general, for grade 3 or 4 diarrhea, nal-IRI should be withheld. Loperamide should be initiated for late-onset diarrhea of any severity. Intravenous or subcutaneous atropine 0.25 to 1 mg should be administered (unless clinically contraindicated) for early-onset diarrhea of any severity.

Neutropenia: Use of G-CSF or Peg-G-CSF is permitted to treated neutropenia and neutropenic fever, however prophylactic use of G-CSF is permitted for high risk patients as per treating physician's discretion and if subject has already experienced neutropenic fever or an episode of grade 3 or 4 neutropenia. Please refer to Section 7.3.3 for neutropenia adverse event guidelines. If needed, either G-CSF 5mcg/kg/dose subcutaneous on Days 4-10 of each cycle or PegG-GCF 6 mg subcutaneous on Day 4 of each cycle are acceptable as per treating physician discretion.

Infusional Hypersensitivity: Platinum hypersensitivity can cause dyspnea, bronchospasm, itching, and hypoxia. Appropriate treatment includes supplemental oxygen, steroids, antihistaminic, bronchodilators or vasopressors as per treating physician's discretion.

Pharyngo-laryngeal Dysesthesias: Oxaliplatin induced pharyngo-laryngeal dysesthesia, which can be triggered by cold, is generally treated with anxiolytics. If pharyngo-laryngeal dysesthesia occurs during infusion, treat based on severity:

Grade 1 – prolong infusion to 6 hours

Grades 2 or 3- Stop infusion, administer benzodiazepines, reassure subject, and restart infusion at the discretion of treating physician.

7.2.4 Radiotherapy

External beam radiotherapy is only allowable following completion of neoadjuvant chemotherapy and study drug treatment based upon repeat imaging and clinical assessments at the pre-operative time point with either of the following scenarios:

1) Evidence of local disease progression that is resulting in uncontrolled pain, obstruction or other clinically relevant complication suggestive of conversion to a locally advanced clinical stage.
2) Radiographic evidence at the time of surgical planning of local disease persistence that, in the opinion of the treating surgeon and with consensus of the multidisciplinary tumor board, jeopardizes the ability to attain a margin negative surgical outcome.

The schedule of radiotherapy in this protocol should conform to the following parameters:

Radiation planning and dosing:

- Supine with arms up in VacLoc immobilization.

Segmentation, Contours and Dose Specifications:

- CTV1 Includes: Primary Tumor (GTV), primary lymphatics and region at risk. This includes the SMA origin with 7 – 15 mm margin, SMA and SMV vessels adjacent to the pancreatic head, regional lymphatics (including the porta hepatic, gastro-hepatic, celiac and superior mesenteric nodes).
- CTV2 Includes: Primary Tumor (GTV) plus enlarged lymph nodes with 7 – 15 mm margin. PTV Expansions are 10 mm depending on motion and physics dosimetry protocol.
- Organs at Risk segmentation (OAR): Small bowel, large bowel, duodenum, stomach, liver, kidneys, and spinal cord.

IMRT / IGRT Radiotherapy Prescription:
CTV1: 45 - 50.4 Gy at 1.8 Gy/Fx to >95% PTV
CTV2: (GTV Boost) Final Dose of 50.4 – 54 Gy at 1.8 Gy/Fx to >95% PTV

Concomitant infusional 5-FU or daily capecitabine, per NCCN guidelines and institutional practice, is strongly recommended.

Alternative radiotherapy dosing with short course or SBRT, or proton therapy, may be considered upon review of the case, at the discretion of the PI and with consultation of radiotherapy sub-investigators.

In any situation requiring radiotherapy, surgery should still be planned 4-8 weeks after the last dose of chemoradiotherapy or radiotherapy. Please note additional consideration for pre-surgical imaging assessments in the Scheduled of Events (Appendix A), as an additional assessment may be required after completion of radiotherapy.

Otherwise, radiotherapy use is prohibited during study treatment. Patients may undergo post-operative radiotherapy after completing the EOT assessment if surgical resection resulted in a positive margin or other feature that justifies this modality. If a patient has radiographic progression of disease that renders them inoperable or they develop metastatic disease during the course of study treatment, these patients will be removed from study and can be treated per institutional practice.

7.2.5 Prohibited Concomitant Therapy

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol

- Investigational agents other than the study drug in this trial
- Radiation therapy
- The following drugs are noted in the irinotecan prescribing information as interacting with irinotecan: St. John's Wart, CYP3A4 inducing anticonvulsants (phenytoin, phenobarbital, and carbamazepine), ketoconazole, itraconazole, troleandomycin, erythromycin, diltiazem and verapamil. Treatment with these agents and any others that interact with irinotecan, 5-FU, or oxaliplatin, or should be avoided.

Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (e.g. Flu - Mist®) are live attenuated vaccines, and are not allowed.

7.3 Dose Modifications

The National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events Version 4 (CTCAE) will be used to grade toxicity (http://evs.nci.nih.gov/ftp1/CTCAE/About.html). All dose reductions for all arms should be based on the worst preceding toxicity. If a subject's dose is reduced during the study due to toxicity, it should remain reduced for the duration of the study; dose re-escalation to an earlier dose is not permitted.

Treatment should be delayed to allow sufficient time for recovery to levels, and upon recovery, treatment should be administered according to the guidelines in the tables below.

If the subject had febrile neutropenia, the ANC must have resolved to ≥ 1500/mm3 and the subject must have recovered from infection. For Grade 3 or 4 non-hematological toxicities, treatment should be delayed until they resolve to Grade 1 or baseline. Guidelines for dose adjustments of each individual treatment within the regimen are found in the tables below for hematologic toxicities (section 7.3.3), and for non-hematological toxicities (section 7.3.2), In case a patient experiences an infusion reaction, either institutional guidelines or the guidelines provided for infusion reaction management (see Section 6.4) should be followed.

Oxaliplatin may be discontinued if allergic reaction occurs or other toxicity that precludes safe continuation of oxaliplatin, even at lower doses. Subjects may continue to receive irinotecan liposome injection + 5-FU/LV at the discretion of the investigator and continue in the study.

In general, treatment holds may not exceed beyond 14 days without patient removal from this trial unless the situation is discussed and approved by the PI due to circumstances that do not jeopardize the integrity of the trial data or patient safety.

7.3.1 Dose Modification Table

Agent	Dose level 0 (starting dose)	Dose Level -1	Dose level -2
Oxaliplatin	60 mg/m^2	50 mg/ m^2	40 mg/ m^2
ONIVYDE®	50 mg/m^2	42 mg/m^2	36 mg/m^2
ONIVYDE® in UGT1A1*28 homozygous		36 mg/m^2	29 mg/m^2
5-Fluorouracil infusion	2400 mg/m^2	1920 mg/m^2	1600 mg/m^2

7.3.2 Non- Hematologic Toxicity

Toxicity – NCI Grade (v.4)	Suggested Dose Modification
Gastrointestinal **Diarrhea** Grade 1/2	No Dose modification Initiate/optimize supportive care
Grade 3/4	Optimize supportive care and hold treatment until ≤ Grade 1 • 1st occurrence - Reduce ONIVYDE® to Dose Level -1 • 2nd occurrence - Reduce infusion 5-FU to Dose Level -1 and test for UGT1A1*28 • 3rd occurrence - Reduce ONIVYDE® to Dose Level -2 • 4th occurrence - Reduce infusion 5-FU to Dose Level -2 • 5th occurrence - Discontinue ONIVYDE®
Hepatic **Total bilirubin, AST, or Alk Phos** Grade 3	Hold treatment until ≤ Grade 2 – provide/replace biliary stent if needed or other workup • 1st occurrence – Resume at previous dose • 2nd occurrence - Reduce Oxaliplatin to Dose Level -1 • 3rd occurrence - Reduce ONIVYDE® to Dose Level -1 • 4th occurrence – Discontinue ONIVYDE®
Grade 4	Discontinue protocol therapy unless resolution of non-study associated etiology (i.e., biliary stent migration) • 1st occurrence – Resume at previous dose • 2nd occurrence - Discontinue offending agent
Interstitial Lung Disease or Pulmonary Fibrosis Any Grade	Hypersensitivity reaction can be secondary to Oxaliplatin or ONIVYDE® and it will be treated based on severity and as per treating physician's discretion.
Hypersensitivity reaction Any Grade	Hypersensitivity reaction can be secondary to Oxaliplatin or ONIVYDE® and it will be treated based on severity and as per treating physician's discretion.

Toxicity – NCI Grade (v.4)	Suggested Dose Modification
	Guidelines provided in section 7.4.1.
Other Clinically Significant Non-Hematologic Toxicities*	
Grade 3	Hold treatment until AE resolves to ≤ Grade 1. • 1st occurrence – Reduce the suspected offending agent to Dose Level -1 • 2nd occurrence – Reduce the suspected offending agent to Dose Level -2 • 3rd occurrence – Discontinue the suspected offending agent
Grade 4	Hold treatment until AE resolves to ≤ Grade 1. • Reduce the suspected offending agent to Dose Level -1 • 2nd occurrence – Discontinue the suspected offending agent
* Determination of "clinically significant" Aes and "offending drug" is at the discretion of the treating physician. In all situations where toxicity justifies discontinuation of an agent, only the individual offending agent should be eliminated from the regimen and continuation of treatment otherwise per protocol is recommended.	

7.3.3 Hematologic Toxicity

Toxicity – NCI Grade (v.4)	Suggested Dose Modification
Hematologic Neutrophils/ granulocytes Grade 3,4 or Severe Neutropenia	Hold treatment and check weekly until ANC ≥ 1500/mm^3. • 1st Occurrence – Reduce ONIVYDE® to Dose Level -1 • 2nd occurrence – Reduce 5-FU infusion to Dose Level -1 • 3rd occurrence - Reduce Oxaliplatin to Dose Level -1 • 4th occurrence - Reduce ONIVYDE® to Dose Level -2 • 5th occurrence - Discontinue ONIVYDE Either GCSF or Peg-GCSF is permitted when appropriate
Thrombocytopenia Grade 2 (1st Event)	Hold treatment and check weekly until platelets are ≥ 75,000/mm^3. Resume treatment at same dose level.
Grade 2 (2nd Event) or Grade 3, 4	Hold treatment and check weekly until platelets are ≥ 75,000/mm^3. • Upon recovery - Reduce Oxaliplatin to Dose Level -1 • 2nd occurrence – Reduce ONIVYDE® to Dose Level -1 • 3rd occurrence - Reduce Oxaliplatin to dose level -2 • 4th occurrence – Reduce 5-FU to dose level -1 • 5th occurrence - Discontinue Oxaliplatin • 6th occurrence - Discontinue ONIVYDE®

Other hematologic toxicities do not require dose modification. However, red blood cell transfusion should be considered for hemoglobin < 8 g/dL or significant symptoms of anemia. In all situations where toxicity justifies discontinuation of an agent, only the individual offending agent should be eliminated from the regimen and continuation of treatment otherwise per protocol is recommended after discussion with the PI.

7.4 Management of Infusion Reactions

The guidelines described in this section can be followed in case of infusion reactions to any study treatment given per protocol (e.g. nal-IRI, oxaliplatin etc.). Infusion reactions will be defined according to the National Cancer Institute CTCAE (Version 4.03) definitions of an allergic reaction or anaphylaxis as defined below.

7.4.1 Allergic Reaction

Allergic reaction (i.e., a disorder characterized by an adverse local or general response from exposure to an allergen):

Grade 1: Transient flushing or rash, drug fever <38° C (<100.4°F); intervention not indicated.
Grade 2: Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for ≤ 24 hours.
Grade 3: Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates).
Grade 4: Life-threatening consequences; urgent intervention indicated.

7.4.2 Anaphylaxis

Anaphylaxis (i.e., a disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing hypersensitivity immune response), presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death:

Grade 1: Not applicable.
Grade 2: Not applicable.
Grade 3: Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension.
Grade 4: Life-threatening consequences; urgent intervention indicated.

7.4.3 Infusion Reaction Guidelines

Institutional policies or the following treatment guidelines shall be used for the management of infusion reactions.

Grade 1:
- Slow infusion rate of offending agent by 50%.
- Monitor patient every 15 minutes for worsening of condition.
- Future infusions may be administered at a reduced rate (e.g. over 120 minutes for nal-IRI), at the discretion of the Investigator.

Grade 2:
- Stop infusion of offending agent.
- Administer diphenhydramine hydrochloride 50 mg IV, acetaminophen 650 mg orally, and oxygen.
- Resume infusion at 50% of the prior rate once infusion reaction has resolved.
- Monitor subject every 15 minutes for worsening of condition.
- For all subsequent infusions, pre-medicate with diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV, and acetaminophen 650 mg orally.
- Future infusions may be administered at a reduced rate (e.g. over 120 minutes for nal-IRI), at the discretion of the Investigator.

Grade 3:
- Stop infusion and disconnect infusion tubing from patient.
- Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV, bronchodilators for bronchospasm, and other medications or oxygen as medically necessary.
- No further treatment will be permitted during this visit.

Grade 4:
- Stop the infusion and disconnect infusion tubing from subject.
- Administer epinephrine, bronchodilators or oxygen as indicated for bronchospasm.
- Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV and other medications as medically necessary.
- Consider hospital admission for observation.
- No further treatment will be permitted during this visit.

For subjects who experience a > grade 1 infusion reaction, pre-medication with a combination of diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV, and acetaminophen 650 mg orally or per institutional guidelines may be provided as part of subsequent treatments.

7.5 Supportive Care Guidelines

Subjects should receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics, antidiarrheals, analgesics, etc., when appropriate. Supportive care, especially pain control, will be optimized in all subjects. Guidance is provided for management of common side effects of ONIVYDE® in order to maximize opportunity for benefit. Investigators

are strongly urged to discuss with Medical Monitor and/or the Principal Investigator prior to discontinuing study treatment for reasons other than radiographic PD.

7.6 Other Considerations

Other toxicities requiring special attention include:

QTc prolongation that occurs in the setting of diarrhea induced electrolyte imbalance should be treated with appropriate electrolyte repletion. Once the underlying abnormality is corrected and the ECG abnormalities have reversed, treatment may continue under careful monitoring and with appropriate dose modification for diarrhea as described above.

8. TREATMENT DISCONTINUATION

8.1 Removal of Subjects From Study

Subjects who discontinue participation in the clinical study on their own or subjects who are withdrawn by the investigator, for reasons other than completion of treatment, disease progression or toxicity, will be defined as premature withdrawals. Subjects who are not initiated on study drug, but sign informed consent and undergo at least some of the screening procedures will be considered screening failures. A record of these patients will be maintained by the study site. Subjects who are treated with at least one full course of NALIRIFOX will contribute to the intention-to-treat analyses. Any subjects that do not complete surgery will be replaced, but all patients will contribute to the intention-to-treat design of the study and relevant endpoints.

8.2 Criteria For Study Treatment Discontinuation

A subject will be discontinued from protocol therapy under the following circumstances:

- Any anti-cancer therapy or medication (except study drugs), administered from screening until the completion of the EOT visit.
- Any adverse event which, in the Investigator's opinion, requires termination of the study medication.
- Disease progression, unless at the discretion of the principal investigator (in collaboration with any co-sponsors or collaborators) continued treatment with study drug is appropriate.
- Substantial non-compliance (>25% of missed doses accounting for delays and dose modifications per protocol or instructions from research team staff for Aes), with the requirements of the study.
- The patient presents with a beta-HCG test consistent with pregnancy. Pregnancy will be reported along the same timelines as a serious adverse event.
- The patient uses illicit drugs or other substances that may, in the opinion of the Investigator, have a reasonable chance of contributing to toxicity or otherwise interfering with results.

- The development of a second malignancy that requires treatment, which would interfere with this study.
- The patient is lost to follow-up.
- Interruption in study drugs administration for greater than 14 days (see Dose Modification section).
- Development of an intercurrent illness or situation which would, in the judgment of the investigator, affect assessments of clinical status and study endpoints to a significant degree.

The Investigator will make every reasonable effort to keep each patient in the study unless it is in the patient's best interests to discontinue participation. If a patient is removed from the study or declines further participation, all EOT evaluations should be performed if the patient is willing and able to be assessed. The EOT visit should occur on the date of the visit that the patient was removed from study or within the next 30 days. A description of the reason(s) for withdrawal from the study must be recorded on the case report form (CRF). The Investigator should also ensure that all patients are followed up for survival status after the Final Study Visit.

Relevant visit data should be entered on the CRF and any unused study medication will be accounted for and returned for all patients participating in the study, even for a brief period of time. Patients who discontinue following entry will have relevant information completed and recorded on the CRF. All patients who discontinue because of adverse events or clinically significant laboratory abnormalities should be followed up until they recover or stabilize, and the subsequent outcome will be recorded. If any patient should die during the trial or within 30 days of stopping study treatment, the Investigator will inform the UF Health Data Integrity and Safety Committee.

8.3 Replacement of Subjects

Subjects will be replaced if they have not received any doses of study drug prior to their discontinuing participation in the protocol for any reason. Subjects will also be replaced if they do not complete surgery as listed in section 8.1. Subjects will be replaced if they initiate a different, new course of anti-cancer therapy (aside from radiotherapy as described in the protocol, section 7.2) in the interval between the last dose of Onivyde and surgery.

9. BIOLOGICAL SPECIMENS AND CORRELATIVES

9.1 Source of Specimens

Blood, serum, and plasma will be collected at different time points for study evaluations. All specimens collected as part of this study will be labeled with a study-specific ID number distinct from their personal information. A master code key that links specimen ID with patient identifiers will be maintained in a restricted section of OnCore available only to the PI or approved study team delegates. A new biopsy is obtained for diagnostic reasons, the biopsy must be performed from a tumor site that is not the only site of measurable disease. For subjects with only one site of measurable disease, biopsies from that site will be allowed if CT imaging performed after biopsy

still shows measurable disease and/or the biopsy is not expected to impact the measurability of the lesion.

9.2 Correlative Studies

Tissues and blood samples will be collected as exploratory analyses which may include but are not limited to biomarker, pharmacogenomic, CTC enumeration, cell-free DNA, and tumor mutational profile assessments in an attempt to characterize individual treatment responses and correlate with pathologic/radiographic response. It is also planned to utilize specimens for potential PDX implantation with supplemental correlative analyses to determine mechanism of response or resistance. Subject tissue and blood samples collected during this study may also be used for additional analyses proposed and conducted by the PI and study team that cannot currently be anticipated. De-identified subject blood and tissue samples will be sent to Tempus to the following research location for testing: 600 W Chicago Ave. Ste 510, Chicago, IL 60654.

Collection of biospecimens will allow these and/or other analyses to take place in a preplanned, but post-hoc manner. Only genetic tests that are obtained by the treating physician as part of routine clinical care will be disclosed to the patient by the treating physician. No genetic test results from the correlative analyses in this study will be disclosed. Any molecular tests performed as part of routine clinical care in a CLIA-approved laboratory should be made available through the ordering physician and are not the responsibility of the study, even if that information is subsequently collected and analyzed as part of the study.
Each subject will be asked to provide stool, oral and urine microbiome samples at a minimum of 4 time points (unless they receive radiotherapy per protocol, in which case, 5 time points), as noted in sections 6.2 and 6.3. Processing, storage and analyses will be conducted through the UFHCC Microbiome Biorepository. Biospecimens will be collected and subsequently examined for microbiota content and any associations with patient and tumor characteristics, treatment outcomes and change over time.

9.3 Preparation, Shipment and Storage of Specimens

All blood and tissue samples will be labeled with the subject's unique study number and physically stored at the Clinical and Translational Science Institute (CTSI) Biorepository at the University of Florida. Processing, storage and analyses of microbiota specimens (stool, oral, and urine) will be conducted through the UFHCC Microbiome Biorepository. During the life of the study, these biospecimens remain available only to the study team and only those exploratory analyses listed in Section 9.2 will be considered, unless added through a protocol amendment. For analyses that require research collaborations outside of UF, only de-identified specimens will be shared. Samples will be stored for the life of the study and will then be destroyed or transferred to a UFHCC Biospecimen bank (UFHCC Biobank; IRB201901513) for general research use if subjects agree to enroll in the separate banking study.

At study enrollment, all subjects will be given the option to provide permission for their blood, tumor tissue, and microbiota samples to be collected and stored for long-term use (i.e., beyond the life of this study). Thus, future research on remaining biospecimens after the study-specific analyses have been completed can only be considered by subjects providing their additional consent on an IRB-approved consent form for optional biobanking. Future specific use of those biomaterials will require secondary IRB approval. At the closure of this treatment trial, any biospecimens remaining from subjects who have provided consent for long-term storage/use will be destroyed or transferred to the UFHCC Biobank. For subjects who consent to the treatment study, but decline secondary long-term storage, their biomaterials will be destroyed at the completion of the treatment trial and will not be transferred.

10. STUDY DRUG INFORMATION

10.1 Study Drug Name

Irinotecan liposomal [MM-398] (ONIVYDE®, Ipsen Biopharmaceuticals)

10.1.1 Identification

Nal-IRI (irinotecan liposome injection, also known MM-398) is irinotecan in the form of the sucrosofate salt, encapsulated in liposomes for intravenous infusion. Nal-IRI is developed by Ipsen Biopharmaceuticals for intravenous administration in the management of patients with metastatic adenocarcinoma of the pancreas. Nal-IRI is irinotecan in the form of the sucrosofate salt, encapsulated in liposomes for intravenous infusion. It will be supplied in sterile, single-use vials containing 10 mL of nal-IRI at a concentration of 4.3 mg/mL. nal-IRI must be stored refrigerated at 2 to 8°C, with protection from light.

10.1.2 Packaging and Labeling of Nal-IRI

Twenty vials of nal-IRI will be packaged in a cardboard container. The individual vials, as well as the outside of the cardboard container, will be labeled in accordance with local regulatory requirements.

10.1.3 Drug Supply

The manufacturer (or designee) will ship Study Drug to the investigational sites. The initial study drug shipment will be shipped after site activation (i.e., all required regulatory documentation has been received by the Sponsor and a contract has been executed). Subsequent study drug shipments will be made after site request for resupply.

10.1.4 Storage, Handling and Dispensing

Nal-IRI must be stored refrigerated at 2 to 8 °C, with protection from light. Light protection is not required during infusion. Nal-IRI must not be frozen. Responsible individuals should inspect

vial contents for particulate matter before and after they withdraw the drug product from a vial into a syringe. They must contact the manufacturer or its designee if they notice a problem with the study drug.

Nal-IRI must be diluted prior to administration.

- Withdraw the calculated volume of ONIVYDE® from the vial. Dilute ONIVYDE® in 500 mL 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP and mix diluted solution by gentle inversion.
- Allow diluted solution to come to room temperature prior to administration.

The diluted solution is physically and chemically stable for 4 hours at room temperature (15–25°C), but it is preferred to be stored at refrigerated temperatures (2–8°C), and protected from light. The diluted solution must not be frozen. Because of possible microbial contamination during dilution, it is advisable to use the diluted solution within 24 hours if refrigerated (2–8°C), and within 4 hours if kept at room temperature (15–25°C).

The Investigator (or assigned designee, i.e., study pharmacist) will dispense the proper diluted solution to the subject to satisfy dosing requirements for this trial.

10.1.5 Administration of Nal-IRI

- Infuse diluted solution intravenously over 90 minutes. Do not use in-line filters. Any unused portion is to be discarded.

10.1.6 Drug Ordering and Accountability

The investigator and investigational site staff are responsible for maintaining an accurate inventory and accounting of study drug. A record of all vials of study drug received and administered should be maintained on an investigational drug inventory form provided by the sponsor / site. The following information will be recorded:

Date and quantity of study drug received

Date and quantity of study drug dispensed from the pharmacy per patient

Date and quantity of study drug administered to each patient

Date and quantity of study drug destroyed (if prepared and dispensed, but not administered for any reason, the study drug may not be returned to inventory)

Date and quantity of study drug returned to sponsor, if applicable

Each shipment of study drug will contain an invoice describing the amount of drug shipped to the investigational site. The information on the invoice will be verified against the actual amount of drug received.

The study pharmacist will reconcile the information on the investigational drug inventory form with the actual amount of study drug remaining at each site on a routine basis. At the conclusion of the study, the study pharmacist will either package and ship all unused vials of study drug back to Ipsen Biopharmaceuticals, Inc. or destruction or document the destruction, in accordance

with local regulations and institutional policy. Following use, empty vials of study drug may be destroyed according to local regulatory and environmental requirements. A record of any such destruction will be placed in the investigator's regulatory file.

10.1.7 Contraindications

Avoid the use of strong CYP3A4 inducers if possible; substitute non-enzyme–inducing therapies at least 2 weeks prior to initiation of nal-IRI. Avoid the use of strong CYP3A4 or UGT1A1 inhibitors, if possible; discontinue strong CYP3A4 inhibitors at least 1 week prior to starting therapy.

The following drugs are noted in the irinotecan prescribing information as interacting with irinotecan: St. John's Wort, CYP3A4 inducing anticonvulsants (phenytoin, phenobarbital, and carbamazepine), ketoconazole, itraconazole, troleandomycin, erythromycin, diltiazem and verapamil. Treatment with these agents and any others that interact with irinotecan or 5-FU should be avoided.

Because 5-FU interacts with warfarin, caution should be exercised if concomitant use is necessary. Refer to the s package inserts of 5-FU and leucovorin for any other drug interactions.

10.1.8 Adverse Event Profile

Diarrhea

Irinotecan can induce both early and late forms of diarrhea that appear to be mediated by different mechanisms. Early diarrhea (occurring during or shortly after infusion of irinotecan) is cholinergic in nature. It is usually transient and only infrequently severe. It may be accompanied by symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyper-peristalsis that can cause abdominal cramping. For patients who experienced early cholinergic symptoms during the previous cycle of nal-IRI, prophylactic administration of atropine will be given at the discretion of the investigator. Late diarrhea (generally occurring more than 24 hours after administration of irinotecan) can be life threatening since it may be prolonged and may lead to dehydration, electrolyte imbalance, or sepsis. Late diarrhea should be treated promptly with loperamide, and octreotide should be considered if diarrhea persists after loperamide, as described in Section 5.6.1 (Therapy for Diarrhea). Loss of fluids and electrolytes associated with persistent or severe diarrhea can result in life threatening dehydration, renal insufficiency, and electrolyte imbalances, and may contribute to cardiovascular morbidity. The risk of infectious complications is increased, which can lead to sepsis in patients with chemotherapy-induced neutropenia. Patients with diarrhea should be carefully monitored, given fluid and electrolyte replacement if they become dehydrated, and given antibiotic support if they develop ileus, fever, or severe neutropenia.

Neutropenia

Deaths due to sepsis following severe neutropenia have been reported in patients treated with irinotecan and nal-IRI. Neutropenic complications should be managed promptly with antibiotic support. G-CSF may be used to manage neutropenia at the investigator's discretion or per institutional policy.

Hypersensitivity
Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have been observed with irinotecan, however, have not been observed with nal-IRI to date. This could be due to the limited cumulative patient exposure to date of nal-IRI, or the use of appropriate premedication and early recognition and treatment of expected adverse events. There is insufficient evidence to know whether these known adverse reactions of irinotecan are also associated with nal-IRI. Suspected drugs should be withheld immediately and aggressive therapy should be given if hypersensitivity reactions occur.

Colitis/Ileus
Cases of colitis complicated by ulceration, bleeding, ileus, and infection have been observed. Patients experiencing ileus should receive prompt antibiotic support.

Thromboembolism
Thromboembolic events have been observed in patients receiving irinotecan-containing regimens; the specific cause of these events has not been determined.

Pregnancy
The pregnancy category of irinotecan is D. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with irinotecan. If a pregnancy is reported, treatment should be discontinued. The patient should be withdrawn from the study, and the pregnancy should be followed until the outcome becomes known.

Patients at Particular Risk
In clinical trials of the weekly schedule of irinotecan, it has been noted that patients with modestly elevated baseline serum total bilirubin levels (1.0 to 2.0 mg/dL) have had a significantly greater likelihood of experiencing first-cycle grade 3 or 4 neutropenia than those with bilirubin levels that were less than 1.0 mg/dL (50.0% [19/38] versus 17.7% [47/226]; $p<0.001$). Patients with abnormal glucuronidation of bilirubin, such as those with Gilbert's syndrome, may also be at greater risk of myelosuppression when receiving therapy with irinotecan.

Acute Infusion Associated Reactions

Acute infusion-associated reactions characterized by flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness of chest or throat, and hypotension have been reported in a small number of patients treated with liposome drugs. In most patients, these reactions generally resolve within 24 hours after the infusion is terminated. In some patients, the reaction resolves by slowing the rate of infusion. Most patients who experienced acute infusion reactions to liposome drugs are able to tolerate further infusions without complications.

Other Anticancer Therapies
Subjects will be treated with one or more of the following approved therapies:

• 5-FU
• Leucovorin
• oxaliplatin

Description of Combination Therapies
A description of each anticancer therapy to be used in combination with nal-IRI is described below. Please also refer to the package inserts for more details.

Storage and Handling of Combination Therapies
Refer to the country specific package inserts for details on storage and handling for 5-FU and leucovorin, and oxaliplatin,

Packaging and Labeling of Combination Therapies
Commercially available 5-FU and leucovorin (l + d racemic form, or the levoleucovorin l form) and oxaliplatin will be administered in accordance with the specific treatment regimen and package inserts.

Potential Toxicities of Combination Therapies

Potential Toxicities with 5-FU
Stomatitis and esophagopharyngitis (which may lead to sloughing and ulceration), diarrhea, anorexia, nausea, emesis and leukopenia are commonly seen with treatment; alopecia and dermatitis, in the form of pruritic rash usually appearing on the extremities, may also be seen (see US package insert). Common adverse events (≥20 %) that were observed with nal- IRI in combination with 5-FU/LV in clinical trials considered to be related were: diarrhea, nausea, vomiting, decreased appetite, neutropenia, fatigue, anemia, stomatitis and pyrexia.

Potential Toxicities with Oxaliplatin
The following adverse events are relatively common (≥ 40%) with oxaliplatin treatment in combination with 5-FU/LV and are to be expected with the nal-IRI-containing regimen: peripheral sensory neuropathy, neutropenia, thrombocytopenia, anemia, nausea, increases in transaminases and alkaline phosphatase, diarrhea, fatigue, emesis, and stomatitis. In a phase 3 study of the FOLFIRINOX regimen (5-FU/LV + irinotecan + oxaliplatin), the most common (> 5%) Grade 3-4 adverse events were: neutropenia, fatigue, vomiting, diarrhea, thrombocytopenia, sensory neuropathy, anemia, elevated alanine aminotransferase (ALT) level, thromboembolism, and febrile neutropenia[10], Grade ¾ hypersensitivity reactions, including anaphylactic reactions, have been observed in 2-3% of colon cancer patients receiving oxaliplatin; see package insert for more information.

11. ADVERSE EVENTS

11.1 Definitions

11.1.1 Adverse Event

The term "adverse event" (AE) includes any sign, symptom, syndrome, or illness that appears or worsens in a subject during the period of observation in the clinical study and that may impair the wellbeing of the subject. The term also covers laboratory findings or results of other diagnostic procedures that are considered to be clinically significant (*e.g.*, that requires unscheduled diagnostic procedures or treatment measures, or result in withdrawal from the study). An AE is therefore any unfavorable and unintended symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product.

The adverse event may be:

- A new illness/condition;
- Worsening of a sign or symptom of the condition under treatment, or of a concomitant illness/condition;
- An effect of the study drug; or
- A combination of 2 or more of these factors.

No causal relationship with the study drug or with the clinical study itself is implied by the use of the term "adverse event."

The Investigator will probe, via discussion with the subject, for the occurrence of Aes during each subject visit and record the information in the site's source documents. Aes will be recorded in the subject CRF. Aes will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

Surgical procedures themselves are not adverse events; they are therapeutic measures for conditions that require surgery. The condition(s) for which the surgery is required may be an adverse event. Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures are not adverse events.

When a clear diagnosis is available that explains the abnormal objective findings, this diagnosis will be recorded as an adverse event and not the abnormal objective findings (*e.g.*, viral hepatitis will be recorded as the adverse event and not the transaminase elevation). If a definitive diagnosis is not available, then the sign(s) (*e.g.*, clinically significant elevation of transaminase levels) or symptom(s) (*e.g.*, abdominal pain) will be recorded as the adverse event.

Adverse events fall into the categories "serious" and "non-serious."

11.1.2 Serious Adverse Event

A serious adverse event is one that at any dose of the study drug or at any time during the period of observation:

- Results in death
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below for exceptions)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event, defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed above. Examples of such events include but are not limited to intensive treatment in an emergency department or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization. "Medically important" should be marked only if no other serious criteria are met.

An "unexpected SAE" is any SAE for which the nature, specificity or severity is not consistent with the currently known adverse event profile of the investigational agent(s).

NOTE: The following hospitalizations are not considered SAEs in UFHCC clinical studies:

- a visit to the emergency room or other hospital department lasting less than 24 hours that does not result in admission (unless considered an "important medical event" or a life-threatening event)
- elective surgery planned before signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- medical/surgical admission for purpose other than remedying ill health state that was planned before study entry. Appropriate documentation is required in these cases.
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative).

Clarification of the difference in meaning between "severe" and "serious"

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). Any grade ≥ 3 adverse event per CTCAE is generally considered severe AE. This is not the same as "serious," which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

11.1.3 Non-Serious Adverse Event

A non-serious adverse event is any adverse event not meeting any of the serious adverse event

criteria.

11.2 Period of Observation

Following the subject's written consent to participate in the study, all SAEs must be collected, including those thought to be associated with protocol-specified procedures. Collection of all SAEs must continue until the post-op visit (or pre-op visit if the subject does not proceed with surgery). If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., protocol-specified resection surgery). SAEs not related to a later protocol-specified procedure will not be collected beyond 30 days post last dose of study treatment. The investigator should notify the DISC of any SAE occurring after this time period that is believed to be related to the investigational product or protocol-specified procedure.

The investigator will begin collecting non-serious adverse event (NSAE) information once administration of the investigational product is initiated. This NSAE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects. Treated subjects, including those who were prematurely discontinued from the study, will be followed for any adverse events that occur during the study until the post-op visit (or pre-op visit if the subject does not proceed with surgery). However, after 30 days post last dose of study treatment, only unexpected AEs related to a protocol-specified procedure (e.g. resection surgery and associated hospitalization) will be reported. If another course of anti-cancer therapy is initiated prior to the that follow-up period visit, collection of adverse events will no longer be performed, with the exception of events that may be possibly, probably, or definitely related to the investigational agent or are clinically significant.

11.3 Documenting / Reporting of Adverse Events by Investigator

All adverse events collected per section 11 must be fully recorded in the subject's case record form.

Documentation must be supported by an entry in the subject's file. A laboratory test abnormality considered clinically relevant, e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an adverse event. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product, action taken and outcome.

Every attempt should be made to describe the adverse event in terms of a diagnosis that encompasses the component signs and symptoms. If only nonspecific signs or symptoms are present, then these should be recorded as separate diagnoses on the pages of the case report form.

All subjects who have adverse events, whether considered associated with the use of study drug or not, must be monitored to determine the outcome. The clinical course of the adverse event will be followed according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the Principal Investigator considers it medically justifiable to terminate follow-up. Should the adverse event result in death, a full

pathologist's report should be supplied, if possible.

11.3.1 Assessment of Causal Relationship of Study Drug

The Investigator will provide an assessment of the potential causal relationship between adverse events and study medication by determining whether or not there is a reasonable possibility that the event was caused by the study medication. The relationship or association of the adverse event to the study medication will be characterized as not related, probably not related, possibly related, probably related, or related:

Not Related: There is not a temporal relationship to the study drug administration or the adverse event is clearly due only to the progression of the underlying disease state, intercurrent illness, concomitant medication, concurrent therapy or other known cause.

Probably Not Related: There is little or no chance that the study drug administration caused the adverse event; the event is most likely due to another competing cause, including intercurrent illness, progression or expression of the disease state, or a reaction to a concomitant medication or concurrent therapy appearing to explain the reported adverse event.

Possibly Related: The association of the adverse event with the study drug administration is unknown; however, the adverse event is not reasonably attributed to any other condition.

Probably Related: When a reasonable temporal relationship exists between the adverse event and the study drug administration; significant symptoms abate upon discontinuation of the study drug and there is a reasonable explanation based on known characteristics of the study drug and there is no clear association with preexisting disease or therapy, intercurrent illness, concurrent therapy or other factor(s).

Related: When the adverse event is a known side effect of the study drug or there is a temporal relationship to the administration of the study drug; or the adverse event reappears upon re-administration of the study drug (rechallenge); or the significant symptoms of the adverse event abate upon discontinuation of the study drug (dechallenge).

11.3.2 Intensity of Adverse Events

The intensity of adverse changes in physical signs or symptoms will be graded according to the CTCAE version 4. For all other adverse events not described in the CTCAE, the intensity will be assessed by the Investigator using the following categories:

Mild (Grade 1) – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.

Moderate (Grade 2) – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required.

Severe (Grade 3) – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible.

Life-threatening (Grade 4) – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.

Death (Grade 5) – the event resulted in death.

11.3.3 Action Taken with Study Drug

The action the Investigator took with study drug as a result of the event should be recorded as one of the following:

None – No action was taken with regard to the study drug as a result of the adverse event.

Interrupted – Study drug was stopped due to the adverse event, but was later resumed at the same dose.

Dose decreased – The dose of study drug was decreased as a result of the adverse event.

Permanently discontinued – The subject was withdrawn from the study due to the adverse event.

Only one item should be chosen. If multiple actions apply, the following "worst case" scenario hierarchy should be used to determine the preferred entry:

Discontinued > dose decreased > therapy interrupted.

11.3.4 Definition of Outcome

The outcome of the AE should be recorded as one of the following:

Resolved without sequelae – The subject fully recovered from the adverse event with no observable residual effects.

Resolved with sequelae – The subject recovered from the adverse event with observable residual effects.

Not resolved – The adverse event was present at the time of last observation.

Death – The subject died as a result of the adverse event.

11.4 Immediately Reportable Events

11.4.1 Serious Adverse Events

Serious adverse events (SAE's) must be documented and reported to the UFHCC DISC Safety Team **within 5 days** of learning of the event. The SAE Report and any email correspondence must be kept within the study files at the study site. The site investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

Follow-up information will be submitted to the UFHCC CRO stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable), and whether the participant continued or withdrew from study participation

The UFHCC Project Management Office (PMO) must also be notified of the SAE **within 24 hours** of knowledge of the event by email at pmo@cancer.ufl.edu.

Ipsen Biopharmaceuticals Reporting Requirements

SAEs must be reported to Ipsen Biopharmaceuticals **within 24 hours** of knowledge of the event using the contact information below:

Ipsen Biopharmaceuticals SAE Reporting Contact Information
Via email: drugsafety.USA@ipsen.com or fax: 855-631-0644 or phone: 855-463-5127

11.4.2 Other Events Requiring Immediate Reporting

All pregnancies, regardless of outcome, must be reported to the UFHCC DISC, including pregnancies that occur in the female partner of a male study subject. All pregnancies must be followed to outcome.

Although overdose (dose variance of >25%) and cancer are not always serious by regulatory definition, these events should also be reported to the DISC in an expedited manner. In case the overdose did not result in any adverse event, the Investigator should report this as "overdose, no adverse event" on the SAE form and provide the intended amount, as well as the actual amount, of drug administered. In the event of overdose or exaggerated response, appropriate supportive measures should be employed. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

Pregnancies and overdoses should be documented and reported per the SAE reporting guidelines in section 11.4.1 above.

11.5 IND Safety Reports Unrelated to this Trial

IND safety reports not occurring on this trial but involving the study intervention (outside SAEs) received from outside sources will be forwarded to participating sites for submission to their Institutional Review Boards per their guidelines.

12. STATISTICAL METHODS

The sections below provide an overview of the statistical considerations and analyses.

12.1 Sample Size Determination

For this prospective phase II pilot study, the sample size justification is based on the primary endpoint, the complication rate for evaluable patients who complete surgery. A sample size of 25 patients achieves ~80% to detect a reduction of 20% in the 30-day post-operative complication rate (from 30%[16, 18] to 10%), using a one-sided exact test with a significance level of 0.05. Assuming 10% drop-out rate, we will accrue a total of 28 patients for this study. The study expects a 20-month accrual period with an additional follow-up of 7 months after the last patient is enrolled. The sample size calculation is conducted by PASS 16.

12.2 Analysis of Primary Endpoint

The primary analysis will use the modified Intention-to-Treat (mITT) population consisting of subjects who are enrolled and received any dose of study medication. The mITT population will be included in summary tables of subject demographics and disease characteristics, and in analysis of efficacy. Subjects who did not progress to surgery (for any reason) or are lost to follow-up will be censored at the day of their last objective tumor assessment and will be unevaluable for the primary endpoint. Subjects failing to proceed to surgery will be replaced, but all will support the secondary endpoints including feasibility, safety and correlative biologic analyses.

Post-operative complications will be measured at the EOT visit 4-6 weeks after surgery. Complications occurring within 30 days after surgery and contributing to the primary endpoint are defined as hospital re-admission, death, second surgery or interventional procedure or major complications extending hospital stay. The proportion and its exact 90% confidence interval of 30-day post-operative complication rate will be calculated. Statistical analyses will be conducted using SAS v9.4 (SAS institute, Cary, NC).

12.3 Analysis of Secondary Endpoints

Secondary endpoints will also be analyzed in a similarly descriptive manner. Treatment completion rate is defined by the administration of all eight intended cycles of neoadjuvant chemotherapy. The surgical complete resection rate (R0) will be determined from review of the pathology reports and inclusive of pathologic nodal status and TNM staging (AJCC 8th Edition). Pre-operative imaging will be compared to the baseline studies to assess radiographic response, in those who have RECIST measurable disease at baseline. The radiographic objective response rate (RR) is equal to the proportion of patients achieving a best overall response of partial or complete response (CR + PR), according to RECIST from the start of the treatment until disease progression/recurrence. Clinical benefit rate is equal to the objective RR plus the proportion of patients attaining stable disease (CR + PR + SD). Patients with initially measurable disease who do not have a tumor response assessment for any reason will be considered non-responders and will be included in the denominator when calculating the response rate. Biochemical response rate is measured as

the difference between baseline and maximal nadir of serum CA19-9 level. Proportion and exact 95% CI based on binomial distribution will be estimated for each of the secondary endpoints described above. Subjects will further be characterized as those with normalization of CA19-9 during therapy, reduction without normalization or no reduction with assessment of the temporal nature of these changes and correlation to surgical resection rates. Secondary and exploratory endpoints may be characterized between those with resectable vs. borderline resectable disease at study entry, but without any planned formal analyses between these two subsets. Mean and 95% CI, assuming a normal distribution, median (range) will be estimated for quality of life (QOL) parameters using the FACT-G validated patient reported outcome instrument.

12.4 Analysis of Exploratory Endpoints

Exploratory biomarkers and molecular assay results will be analyzed post-hoc. These assessments are dependent upon funding support for determination including, but not limited to CTC enumeration and correlation with pathologic/radiographic response, pharmacogenomic determination of any relationship with toxicity/safety, tumor mutational profile assessments correlating with response vs. non-response as well as PDX development with supplemental correlative analyses to determine mechanisms of response and resistance.

12.5 Analysis of Safety Data

Safety analyses will be performed on all patients who receive any dose of study medication. Adverse events that occur more than 30 days after the administration of the last dose of treatment will not be included. Safety evaluation will be performed based on the actual therapy received. The safety and tolerability of study drug is determined by reported Aes, physical examinations, laboratory tests, and ECGs. All patients will be assessed regularly for potential occurrence of Aes from the time that treatment starts until 30 days after the last dose of study therapy or 30 days post-operatively, whichever is longer. Aes will be summarized with the incidence and percentage of patients with at least one occurrence of a preferred term (according to the most severe NCI-CTCAE Version 4.0 grade) will be included. The number of Aes reported will also be summarized. Causality (relationship to study drug) will be summarized separately. Duration of AE will be determined and included in listings along with action taken and outcome. Laboratory results will be classified according to NCI-CTCAE, Version 4.0. Incidence of laboratory abnormalities will be summarized; laboratory results not corresponding to an NCI-CTCAE Version 4.0 term will not be graded. Laboratory toxicity shifts from baseline to worst grade will also be provided. The results from physical examination and vital sign measurement will be tabulated. Descriptive statistics will be provided as appropriate.

12.6 Enhanced AE Safety Monitoring

When accrual is greater than 10 subjects, if at any time, 5 of the initial 10 treated subjects or 50% or more of all treated subjects have experienced a non-hematologic grade >= 3,4, 5 adverse event considered at least possibly related to treatment (possible, probable, or

definite), accrual will be temporarily suspended to this study for a review by the PI and the Data Integrity and Safety Committee. Grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related" will be reviewed and monitored, to assess for the emergence of a previously unrecognized treatment-related adverse event.

13. DATA AND SAFETY MONITORING

13.1 Data Integrity and Safety Committee

This protocol will be reviewed and monitored by the University of Florida Health Cancer Center (UFHCC) DISC in accordance with their policies and procedures. They will review and monitor study progress, toxicity, safety and other data from this trial. Questions about subject safety or protocol performance will be addressed with the sponsor-investigator, statistician and study team members. Should any major concerns arise; the DISC will offer recommendations regarding whether or not to suspend the trial.

UFHCC DISC data and safety monitoring activities include:

- Review of clinical trial conducted for progress and safety
- Review of all adverse events requiring expedited reporting as defined in the protocol
- Review of reports generated by data quality control review process
- Notification of the sponsor-investigator of recommended action
- Notification of sites coordinated by the UFHCC of adverse events requiring expedited reporting and subsequent committee recommendations for study modifications

13.2 Monitoring

UFHCC monitors will utilize on-site and/or remote monitoring periodically during the trial to determine whether sites are complying with the protocol. Source documents will be reviewed for verification of agreement with data as submitted via the data collection system. The site investigator/institution guarantee access to source documents by UFHCC or its designee and appropriate regulatory agencies.

The trial site may also be subject to quality assurance audit by any collaborating sponsors or their designee as well as inspection by appropriate regulatory agencies.

It is important for the site investigator and their relevant personnel to be available during the monitoring visits and possible audits and for sufficient time to be devoted to the process.

13.3 Principal Investigator Responsibilities

As part of the responsibilities assumed by conducting this study, the Principal Investigator (PI) agrees to maintain and have available for monitoring adequate case records (accurate source documents and CRFs) for the subjects treated under this protocol.

The PI will be primarily responsible for monitoring of adverse events, protocol violations, and other immediate protocol issues. The study coordinator will collect information on subjects

enrolled through the use of electronic or paper adverse event (AE) forms, CRFs, and Informed Consent forms.

14. EMERGENCY PROCEDURES

14.1 Emergency Contact

In emergency situations, the treating physician should contact the Principal Investigator by telephone at the number listed on the title page of the protocol.

14.2 Emergency Identification of Investigational Products

This is a non-blinded, non-randomized study. Thus, there will be no need for unmasking procedures, and the identification of the investigational product can be made by simple inquiry to the investigational pharmacy.

14.3 Emergency Treatment

During and following a subject's participation in the study, the treating physician and/or institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the study.

15. ADMINISTRATIVE, ETHICAL, AND REGULATORY CONSIDERATIONS

15.1 Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Principal Investigator and Co-Investigators abide by Good Clinical Practice (GCP), as described in International Conference on Harmonization (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki.

The study will be conducted in compliance with the protocol. The protocol, any amendments, and the subject informed consent will receive Institutional Review Board (IRB) approval before initiation of the study.

The Principal Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

All potential serious breaches must be reported immediately to the UFHCC DISC and IRB of record, if applicable. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

15.2 Institutional Review Board

Before study initiation, the investigator must have written and dated approval from the IRB for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects. The investigator should also provide the IRB with a copy of the Investigator Brochure or product labeling, information to be provided to subjects, and any updates. The investigator should provide the IRB with reports, updates, and other information (e.g., amendments, and administrative letters) according to regulatory requirements or institution procedures.

15.3 Delegation of Investigator Responsibilities

The Principal Investigator will ensure that all persons assisting with the study are adequately informed about the protocol, any amendments to the protocol, the study treatments, and their study-related duties and functions. The Principal Investigator will maintain a list of Co-Investigators and other appropriately qualified persons to whom he has delegated significant study-related duties.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks. This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure; debarment). Systems with procedures that ensure the quality of every aspect of the study will be implemented.

15.4 Subject Information and Informed Consent

Before being enrolled in this clinical trial, the subject must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to him or her. An informed consent document that includes both information about the study and the consent form will be prepared and given to the subject. This document will contain all ICH, GCP, and locally required regulatory elements. The document must be in a language understandable to the subject and must specify the person who obtained informed consent.

After reading the informed consent document, the subject must give consent in writing. The written informed consent will be obtained prior to conducting any study-related procedures or tests. The subject's consent must be confirmed at the time of consent by the personally dated signature of the person conducting the informed consent discussions. A copy of the signed consent document must be given to the subject.

The PI will retain the original signed consent document. The PI will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

15.5 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

Subjects will be told that the IRB, UF Health DISC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection law.

15.6 Protocol Amendments

Once the study has started, amendments should be made only in exceptional cases. Protocol amendments cannot be implemented without prior written IRB approval except as necessary to eliminate immediate safety hazards to subjects. A protocol amendment intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the IRB and CRO are notified within five business days. All amendments will be submitted to the IRB and written verification that the amendment was submitted and subsequently approved is to be obtained.

15.7 Case Report Forms

The Principal Investigator and/or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account.
An electronic case report form (eCRF) is required and must be completed for each included subject. The completed dataset is the sole property of UFHCC and should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from UFHCC.

15.8 Record Retention

Study documentation includes all eCRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study

with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

UF Health Cancer Center requires that all study documentation be maintained for at least 6 years from the date of final study publication. No study records may be destroyed without prior authorization from UF.

15.9 Sub-Site Management and Communication Plan

On a weekly basis for the duration that the site has subjects on study treatment, the UFHCC Project Management Office will be in communication with each sub-site to receive updates on study and subject status. Communication will be in the form of e-mail, phone, and weekly study meetings that include at least one representative from each site. Adverse events and regulatory status approvals / updates will be standing agenda items at these meetings. Once all site subjects are completed with the treatment phase of the study (ie., in the 5 year survival follow up phase), meeting frequency may be decreased.

De-identified site data, as well as site study team records, will be reviewed (at a minimum) approximately every 12-16 weeks (at a minimum) to ensure accuracy and up-to-date certifications / local approvals are on file. All local approval documentation by IRB or otherwise must be provided to UFHCC and contained in the site's regulatory files.

Protocol amendments with red-lined, clean versions and a summary of changes will be provided to sites for IRB submission. Consent form (ICF) amendments will be provided in the study's model consent and will contain tracked changes. Updates to the local ICF must be approved by UFHCC PMO prior to submission to the local IRB. Other document updates such as to the Investigator Brochure and lab manual must be submitted to the local IRB as per their guidelines.

Activated secondary sites are expected to submit modifications to their local IRBs, per local guidelines within 4 weeks of receipt unless otherwise noted. All approval documentation must be forwarded to UFHCC PMO within 2 weeks of approval. If the IRB of record for a sub-site is UF-IRB-01, UFHCC PMO will submit updates on the site's behalf with input from the sub-site(s). Approval will be provided via email to the sub-site(s) as soon as possible when obtained. The University of Florida IRB requires that all events meeting the definition of unanticipated problem or serious noncompliance be reported as outlined.

Documentation of participating site's IRB approval of annual continuing reviews, protocol amendments, SAE reports, and protocol deviations, regulatory violations and unanticipated events must be kept on file at UFHCC PMO.

16. REFERENCES

1. American Cancer Society. http://www.cancer.org. Accessed June 24, 2017.
2. Rahib, Lola, et al. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer research 74.11 (2014): 2913-2921.
3. Neoptolemos, J.P., Palmer, D.H., Ghaneh, P., Psarelli, E.E., Valle, J.W., Halloran, C.M., Faluyi, O., O'Reilly, D.A., Cunningham, D., Wadsley, J. and Darby, S., 2017. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. The Lancet, 389(10073), pp.1011-1024.
4. Gillen, S., Schuster, T., Zum Büschenfelde, C. M., Friess, H., & Kleeff, J. (2010). Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. PloS med, 7(4), e1000267.
5. Desai NV, et al. Cancer Med. 2015 Aug;4(8):1224-39.
6. Sliesoraitis S et al. J Clin Oncol 32, 2014 (suppl; abstr e15201); NCT01470417.
7. National Comprehensive Cancer Network. (2017, September 11). NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf.
8. Parekh, H.D., Starr, J., and George, T.J., (2017). The multidisciplinary approach to localized pancreatic adenocarcinoma. Current Treatment Options in Oncology, 18 (12), 73.
9. Marthey, L., Sa-Cunha, A., Blanc, J.F., Gauthier, M., Cueff, A., Francois, E., et al. FOLFIRINOX for locally advanced pancreatic adenocarcinoma: results of an AGEO multicenter prospective observational cohort. (2015). Annals of Surgical Oncology, 22 (1), 295-301.
10. Conroy, Thierry, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. New England Journal of Medicine 364.19 (2011): 1817-1825.
11. Rombouts S, et al. J Clin Oncol 34, 2016 (suppl; abstr 4115).
12. Birkmeyer JD, et al. NEJM, 2002;346(15):1128.
13. Traverso, L. William, and Yasushi Hashimoto. Delayed gastric emptying: the state of the highest level of evidence. Journal of hepato-biliary-pancreatic surgery 15.3 (2008): 262-269.
14. Lai, Eric CH, Stephanie HY Lau, and Wan Yee Lau. Measures to prevent pancreatic fistula after pancreatoduodenectomy: a comprehensive review." Archives of Surgery 144.11 (2009): 1074-1080.
15. Blazer, Marlo, et al. Neoadjuvant modified (m) FOLFIRINOX for locally advanced unresectable (LAPC) and borderline resectable (BRPC) adenocarcinoma of the pancreas. Annals of surgical oncology 22.4 (2015): 1153-1159.
16. Hosein, Peter J., et al. A retrospective study of neoadjuvant FOLFIRINOX in unresectable or borderline-resectable locally advanced pancreatic adenocarcinoma. BMC cancer 12.1 (2012): 199.

17. Ferrone, Cristina R., et al. Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer. Annals of surgery 261.1 (2015): 12.
18. Kim, S.S., Nakakura, E.K., Wang, Z.J., Kim, G.E., Corvera, C.U., Harris, H.W., Kirkwood, K.S., Hirose, R., Tempero, M.A. and Ko, A.H., 2016. Preoperative FOLFIRINOX for borderline resectable pancreatic cancer: Is radiation necessary in the modern era of chemotherapy?. Journal of surgical oncology, 114(5), pp.587-596.
19. F. Innocenti, D. L. Kroetz, E. Schuetz, M. E. Dolan, J. Ramírez, M. Relling, P. Chen, S. Das, G. L. Rosner, and M. J. Ratain, "Comprehensive pharmacogenetic analysis of irinotecan neutropenia and pharmacokinetics.," J. Clin. Oncol., vol. 27, no. 16, pp. 2604–14, Jun. 2009.
20. F. Bellanti, B. Kågedal, and O. Della Pasqua, "Do pharmacokinetic polymorphisms explain treatment failure in high-risk patients with neuroblastoma?," Eur. J. Clin. Pharmacol., vol. 67 Suppl 1, pp. 87–107, May 2011.
21. R. H. J. Mathijssen, R. J. van Alphen, J. Verweij, W. J. Loos, K. Nooter, G. Stoter, and A. Sparreboom, "Clinical pharmacokinetics and metabolism of irinotecan (CPT-11).," Clin. Cancer Res., vol. 7, no. 8, pp. 2182–94, Aug. 2001.
22. Y. Kawato, M. Aonuma, Y. Hirota, H. Kuga, and K. Sato, "Intracellular roles of SN-38, a metabolite of the camptothecin derivative CPT-11, in the antitumor effect of CPT-11.," Cancer Res., vol. 51, no. 16, pp. 4187–91, Aug. 1991.
23. Wang-Gillam, Andrea, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. The Lancet 387.10018 (2016): 545-557.
24. Sheng, Weian, et al. Capture, release and culture of circulating tumor cells from pancreatic cancer patients using an enhanced mixing chip. Lab on a Chip 14.1 (2014): 89-98.
25. Wang-Gillam, Andrea, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. The Lancet 387.10018 (2016): 545-557.
26. Sheng, Weian, et al. Capture, release and culture of circulating tumor cells from pancreatic cancer patients using an enhanced mixing chip. Lab on a Chip 14.1 (2014): 89-98.
27. George TJ, et al. J Gastrointest Cancer. 2014 Dec; 45 Suppl 1:222-5, 2.
28. Pham K, et al. Am J Pathol. 2016, 3.
29. A. V Kalra, J. Kim, S. G. Klinz, N. Paz, J. Cain, D. C. Drummond, U. B. Nielsen, and J. B. Fitzgerald, Preclinical activity of nanoliposomal irinotecan is governed by tumor deposition and intratumor pro-drug conversion., Cancer Res., Oct. 2014.
30. D. C. Drummond, C. O. Noble, Z. Guo, K. Hong, J. W. Park, and D. B. Kirpotin, "Development of a highly active nanoliposomal irinotecan using a novel intraliposomal stabilization strategy.," Cancer Res., vol. 66, no. 6, pp. 3271–7, Mar. 2006.
31. M. H. Kang, J. Wang, M. R. Makena, J. Lee, N. Paz, C. P. Hall, M. M. Song, R. I. Calderon, R. E. Cruz, A. Hindle, W. Ko, J. Fitzgerald, D. C. Drummond, T. J. Triche, and C. P. Reynolds, "Activity of MM-398 , nanoliposomal irinotecan (nal-IRI), in Ewings

family tumor xenografts is associated with high exposure of tumor to drug and high SLFN11 expression," Clin. Cancer Res., no. 184, 2014.

32. C.-S. Tsai, J. W. Park, and L.-T. Chen, "Nanovector-based therapies in advanced pancreatic cancer.," J. Gastrointest. Oncol., vol. 2, no. 3, pp. 185–94, Sep. 2011.
33. Roy, A.C., Park, S.R., Cunningham, D., Kang, Y.K., Chao, Y., Chen, L.T., Rees, C., Lim, H.Y., Tabernero, J., Ramos, F.J. and Kujundzic, M., 2013. A randomized phase II study of PEP02 (MM-398), irinotecan or docetaxel as a second-line therapy in patients with locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma. Annals of oncology, 24(6), pp.1567-1573.
34. Chibaudel, Benoist, Thierry Andre, Jean Baptiste Bachet, Dominique Auby, Jérôme Desramé, Gael Deplanque, Cedric Lecaille et al. "FOLFOX-aflibercept followed by maintenance therapy with fluoropyrimidine-aflibercept as first-line therapy in patients with metastatic colorectal cancer: A GERCOR single-arm phase II study (VELVET)." (2015): 3567-3567.
35. "CAMPTOSAR® (Irinotecan) Injection, intravenous infusion U.S. Package Insert," 2014. [Online]. Available: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020571s048lbl.pdf.
36. Andrew Peter Dean, Zev A. Wainberg, Ramesh K. Ramanathan, Patrick McKay Boland, Kabir Mody, Bin Zhang, Bruce Belanger, Floris A de Jong, Stephan Braun. A phase ½, open-label dose-escalation study of liposomal irinotecan (nal-IRI) plus 5 fluorouracil/leucovorin (5-FU/LV) and oxaliplatin (OX) in patients with previously untreated metastatic pancreatic cancer (mPAC). *J Clin Oncol* 36, 2018 (suppl; abstr 4111)
37. Benson III, A.B., Ajani, J.A., Catalano, R.B., Engelking, C., Kornblau, S.M., Martenson Jr, J.A., McCallum, R., Mitchell, E.P., O'dorisio, T.M., Vokes, E.E. and Wadler, S., 2004. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. Journal of Clinical Oncology, 22(14), pp.2918-2926.
38. Wainberg ZA, Bekaii-Saab T, Boland PM, Dayyani F, Macarulla T, Mody K, Belanger B, Maxwell F, Moore Y, Thiagalingam A, Wang T, Zhang B, Dean A. First-line liposomal irinotecan with oxaliplatin, 5-fluorouracil and leucovorin (NALIRIFOX) in pancreatic ductal adenocarcinoma: A phase I/II study. Eur J Cancer. 2021 Jul; 151:14-24. doi: 10.1016/j.ejca.2021.03.028. Epub 2021 May 4. PMID: 33957442.

17. APPENDICES

(Page intentionally left black. Please proceed to the following page.)

Appendix A: SCHEDULE OF EVENTS

Visit: / Procedure:	SCREENING (Day -28 to one day prior to Cycle 1/ Day 1)[3]	ON-TREATMENT (Cycle 1/ Day 1) +/- 3 days	ON-TREATMENT (Cycles 2-8/ Day 1) +/- 3 days	PRE-SURGICAL[7] (within 4 weeks prior to surgery)	FOLLOW-UP/SURVIVAL[9] (within 4-6 weeks post-op)
Informed Consent	X				
Medical History	X				
Interim Medical History		X	X	X	X
Physical Exam	X	X	X	X	X
Vital Signs[1]	X	X	X	X	X
Height	X	X	X	X	X
Weight	X	X	X	X	X
ECOG Performance Status	X	X	X	X	X
FACT-G		X	X[6]	X	X
CMP	X	X	X	X	X
CBC w/Diff	X	X	X	X	X
CA 19-9	X	X	X	X	X
Urinalysis	X				
Pregnancy Test (Urine)[3,4]	X	X	X		
Diagnostic Imaging Scan/TA[2,5,7]	X			X[7]	
Microbiome Samples[11]		X[11]	X[11]	X[11]	X[11]
ECG	X[12]	X[12]	X[12]	X[12]	
Administration of Study Drug		X	X		
Concomitant Medication Review	X	X	X	X[10]	X[10]
Adverse Event Review		X	X	X[10]	X[10]
Tumor specimen[8]	X				X
Research blood collection		X	X	X	X

1) Vital signs include temperature, resting pulse, blood pressure, and respiratory rate.
2) CBC/diff=complete blood count and white blood cell differential; CMP=12 item complete metabolic profile (sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, alkaline phosphatase, AST, ALT, total bilirubin, albumin); TA= Tumor assessment
3) Screening studies are repeated if there are more than 28 days prior to the initiation of study treatment; with the exception of the urine pregnancy test, which must be completed within seven days of study treatment initiation.
4) Pregnancy test on Day 1 of Cycles 1-8 can be either serum or urine.
5) TA= Tumor assessment by RECIST. Diagnostic CT scan and/or MRI scan.
6) FACT-G collected only on Day 1 of Cycles 1, 5, and 8.
7) Pre-surgical imaging should be obtained within 4 weeks of administering last planned cycle (8) of chemotherapy. In the event radiotherapy (RT) is used in the interim between chemotherapy and surgery, an additional pre-surgical imaging assessment may be required after RT is completed.

8) Submission of initial tumor specimen (FFPE) obtained prior to enrollment as part of diagnostic workup, as well as tumor tissue at the time of surgical resection, are both required for this study. In the event a FFPE block is not available at study entry, slides or cytology specimens may be acceptance with permission from the study PI.
9) Subjects will be followed for overall survival approximately every 6 months for 5 years after this visit.
10) Adverse Events and Concomitant Medications are to be collected in accordance with sections 11.2 and 7.2.2 of this protocol, respectively.
11) Microbiome samples will be collected up to 5 timepoints: enrollment, after 4 cycles, at completion of chemotherapy, after completion of radiation if applicable, and at post-surgical EOT. There will be no reportable protocol deviation for microbiome specimens not collected or collected outside of collection window. Such variance poses no risk to patient safety or primary study endpoints.
12) ECGs will be done at baseline and as medically indicated

Appendix B: 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

Appendix C: RECIST GUIDELINES (VERSION 1.1)

Response and progression will be evaluated in this study using the international criteria proposed by the New Response Evaluation Criteria in Solid Tumors (RECIST): Revised RECIST Guideline (version 1.1).

Measurability of Tumor at Baseline
Tumor lesions/lymph nodes will be categorized at baseline as measurable or non-measurable. Measurable disease is defined by the presence of at least 1 measurable lesion.

Measurable
Tumor lesions: Measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (slice thickness ≤5 mm)
- 10 mm caliper measurement by clinical exam (non-measurable lesions if cannot be accurately measured with calipers)
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan thickness recommended to be ≤5 mm).

Non-measurable
All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitis involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measureable by reproducible imaging techniques.

Special Considerations for Lesion Measurability
Bone Lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft t issue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI, can be considered measurable lesions if the soft tissue component meets the definition of measurability.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable)
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability. If non-cystic lesions are presented in the same patients, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated at a previously irradiated area, or in an area subjected to other loco-regional therapy, are non-measurable unless there has been demonstrated progression in the lesion.

Baseline Documentation of Target and Non-Target Lesion

Target Lesions

When more than 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Non-nodal target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and can be reproduced in repeated measurements. Measurable lymph nodes are target lesions if they meet the criteria of a short axis of ≥15 mm by CT scan. All measurements are to be recorded in the CRF in millimeters (or decimal fractions of centimeters [cm]).

Non-target Lesions

All other lesions (or sites of disease) are identified as non-target lesions (chosen based on the representativeness of involved organs and the ability to be reproduced in repeated measurements) and should be recorded at baseline. Measurement of these lesions are not required but should be followed as 'present,' 'absent,' or in rare cases 'unequivocal progression.' In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the CRF (for example, multiple liver metastases recorded as 1 liver lesion).
Lymph nodes with short axis ≥10 mm but <15 mm should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and are not recorded or followed.

Specifications by Methods of Measurement

All measurements should be recorded in metric notation, using a ruler or calipers if clinically assessed. 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. Imaging-based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessed by clinical exam.

An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. If prior to enrollment it is known a patient is not able to undergo CT scans with intravenous contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast

CT or MRI (with or without intravenous contrast) should be used to evaluate the patient at baseline and follow-up should be guided by the tumor type under investigation and the anatomic location of the disease.

Clinical Lesions: Clinical lesions will be considered measurable only when they are superficial and ≥10 mm diameter as assessed using calipers (for example, skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion is recommended. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray when progression is an important endpoint. Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT and MRI: CT scan is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤5 mm. When CT scan have slice thickness >5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (for example, for body scans). If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Ultrasound: Ultrasound should not be used to measure lesion size. 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.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

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

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete response (CR) in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (for example, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease (SD) in order to differentiate between response (or SD) and progressive disease (PD).

PET scan (FDG-PET, PET CT): PET is not recommended for lesion assessment. If a new lesion is found by PET, another assessment must be done by CT, unless the PET CT is of diagnostic quality. If CT is done to confirm the results of the earlier PET scan, the date of progression must be reported as the earlier date of the PET scan.

Bone Scan: If lesions measured by bone scan are reported at baseline, it is necessary to repeat the bone scan when trying to identify a complete response (CR) or partial response (PR) in target disease or when progression in bone is suspected.

Response Criteria

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. Tumor marker results must have normalized.

Partial Response (PR): At least a 30% decrease in the sum of diameter 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 (including the baseline sum if that is the smallest). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1 or more new lesions is also considered progression.
For equivocal findings of progression (for example, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

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

Not Evaluable (NE): When an incomplete radiologic assessment of target lesions is performed or there is a change in the method of measurement from baseline that impacts the ability to make a reliable evaluation of response.

Evaluation of Non-target Lesions

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

Non-CR/ non-PD: Persistence of 1 or more non-target lesions and/or maintenance of tumor marker level above the normal limits.

Progressive Disease: Unequivocal progression of existing non-target lesions. The appearance of 1 or more new lesions is also considered progression.

Not Evaluable: When a change in method of measurement from baseline occurs and impacts the ability to make a reliable evaluation of response.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the earliest of objective progression or start of new anticancer therapy, taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. The best overall response will be calculated via an algorithm using the assessment responses provided by the investigator over the course of the trial.

Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs. (When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point.) Table 17.2.1 provides a summary of the overall response status calculation at each time point for patients who have *measurable disease* at baseline.

Table 17.2.1- Time Point Response: Patients with Target or Measureable Disease

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all Evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease

Table 17.2.2 is to be used when patients have *non-measureable* disease only.

Table 17.2.2- Time Point Response: Patients with Non-Target or Non-Measureable Disease

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluable	No	NE
Unequivocal	Yes or No	PD
Any	Yes	PD

Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease; SD = stable disease.

[a] non-CR/non-PD is preferred over SD for non-target disease due to SD being increasingly used as an endpoint for assessment in trials; to assign this category when no lesions can be measured is not advised.

Frequency of Tumor Re-Evaluation

A baseline tumor evaluation must be performed within 4 weeks before patient begins study treatment. Frequency of tumor re-evaluation while on and adapted to treatment should be protocol-specific and adapted to the type and schedule of treatment. Normally, all target and non-target sites are evaluated at each assessment using the same method. However, bone scans may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.

Duration of Response

Duration of Overall Response
The duration of overall response is measured from the time measurement criteria are first met for CR or PR (whichever is first recorded) until the first date that disease is recurrent or objective progression is observed (taking as reference for PD the smallest measurements recorded on study).

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

Duration of Stable Disease
Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for objective progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, that is the reference for calculation of PD).

Appendix D: FACT-G (VERSION 4):

FACT-G (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-G (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Appendix E: SUMMARY OF CHANGES FROM PROTOCOL VERSION 4.0 TO VERSION 5.0

Version 4.0	**Version 5.0**
Eligibility was limited to subjects with borderline resectable carcinoma only	Updates were made throughout to include resectable subjects, in addition to borderline resectable subjects. Affected sections include protocol synopsis, 2.1, 3.1, 4.2, and 12.3. Additionally, minor administrative edits were made to the cover page, protocol signature page, and to clarify that OnCore is UF's Clinical Trial Management System in section 5.
Below text in 12.1 was replaced: For this prospective phase 2 pilot study, a total of 28 evaluable patients will be needed to achieve the primary endpoint. Evaluable patients are defined as those who complete surgery. This is based on the assumption of a 66% reduction (HR 0.34) in the 30-day post-operative complication rate from 30% (historical data) to 10% (expected). (alpha = 0.05; beta = 0.20), using a one-sided exact test of binomial proportion. The study assumes a 20-month accrual period with an additional follow-up of 7 months after the last patient is enrolled. This pilot phase II study and this sample size, while not definitive, will allow determination of safety, feasibility, compliance, toxicity, and generation of robust clinicopathologic outcome assessment to serve as a benchmark control for subsequent comparative studies.	**Section 12.1 now reads:** For this prospective phase II pilot study, the sample size justification is based on the primary endpoint, the complication rate for evaluable patients who complete surgery. A sample size of 25 patients achieves ~80% to detect a reduction of 20% in the 30-day post-operative complication rate (from 30% to 10%), using a one-sided exact test with a significance level of 0.05. Assuming 10% drop-out rate, we will accrue a total of 28 patients for this study. The study expects a 20-month accrual period with an additional follow-up of 7 months after the last patient is enrolled. The sample size calculation is conducted by PASS 16. **Note:** The Sample Size Considerations section of the synopsis was also updated to reflect this change.
Below text in Section 12.2 was removed: Statistical analyses will be conducted by the study biostatistician using SAS v9.1 (SAS institute, Cary, NC).	**Below text in Section 12.2 was added:** The proportion and its exact 95% confidence interval of 30-day post-operative complication rate will be calculated. Statistical analyses will be conducted using SAS v9.4 (SAS institute, Cary, NC).

Below text in 12.3 was replaced:	**Section 12.3 now reads:**
The number of patients achieving a response will be divided by the total of patients treated to yield the proportion responding. Exact confidence bounds (95% CI) will be calculated. Proportion and exact confidence boundaries (95% CI) will be estimated for toxicity and compliance with therapy. Similar calculations will be performed for the biochemical response rate measured as the difference between baseline and maximal nadir of serum CA19-9 level. Subjects will further be characterized as those with normalization of CA19-9 during therapy, reduction without normalization or no reduction with assessment of the temporal nature of these changes and correlation to surgical resection rates. Secondary and exploratory endpoints may be characterized between those with resectable vs. borderline resectable disease at study entry, but without any planned formal analyses between these two subsets. Mean and 95% confidence interval will be estimated for quality of life (QOL) parameters using the FACT-G validated patient reported outcome instrument**.**	Biochemical response rate is measured as the difference between baseline and maximal nadir of serum CA19-9 level. Proportion and exact 95% CI based on binomial distribution will be estimated for each of the secondary endpoints described above. Subjects will further be characterized as those with normalization of CA19-9 during therapy, reduction without normalization or no reduction with assessment of the temporal nature of these changes and correlation to surgical resection rates. Secondary and exploratory endpoints may be characterized between those with resectable vs. borderline resectable disease at study entry, but without any planned formal analyses between these two subsets. Mean and 95% CI, assuming a normal distribution, median (range) will be estimated for quality of life (QOL) parameters using the FACT-G validated patient reported outcome instrument.

Appendix F: SUMMARY OF CHANGES FROM PROTOCOL VERSION 5.0 TO VERSION 5.1

Version 5.0	**Version 5.1**
Clarifications throughout	• Updated the chemotherapy regimen name from "FOLNal-IRINOX" to "NAPOLI-OX" to be in better alignment with the nomenclature that the rest of the field is moving towards. This will help keep the study results relevant when published. • Survival follow up was required in previous versions, but this version notes these visits throughout to be more clear about when study participation ends (and be consistent with the ICF).
Eligibility Criteria Inclusion criteria E included guidelines for determining "borderline resectable" or "resectable."	The ultimate determination of whether a potential subject meets the criteria of "resectable or borderline resectable" lies in the consensus of the UF GI Multidisciplinary Tumor Board, or equivalent body (if applicable for external sites). The Inclusion Criteria E as previously written contained current guidance for this determination, but this guidance is not comprehensive, is subject to change based on most up-to-date best practices, and is not at any point intended to supercede the consensus decision of "resectable or borderline resectable" as documented by the tumor board. Language was updated to clarify.
Section 7.2.4 Radiotherapy	Section 7.2.4 now explicitly allows proton therapy upon review of the case and at the discretion of the PI. The section also clarifies the update to the schedule of events which notes that, in the event radiotherapy (RT) is used in the interim between chemotherapy and surgery, an additional pre-surgical imaging assessment may be required after RT is completed.
Section 12.6 absent	**Section 12.6 now reads:** 12.6 Enhanced AE Safety Monitoring When accrual is greater than 10 subjects, if at any time, 5 of the initial 10 treated subjects or 50% or more of all treated subjects have experienced a non-hematologic grade >= 3, 4, 5 adverse event considered at least possibly related to treatment (possible, probable, or definite), accrual will be temporarily suspended to this study

	for a review by the PI and the Data Integrity and Safety Committee. We will review Grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related," to assess for the emergence of a previously unrecognized treatment-related adverse event.
Section 15.9 absent	**Section 15.9 now reads:** On a weekly basis for the duration that the site has subjects on study treatment, the UFHCC Project Management Office will be in communication with each sub-site to receive updates on study and subject status. Communication will be in the form of e-mail, phone, and weekly study meetings that include at least one representative from each site. Adverse events and regulatory status approvals / updates will be standing agenda items at these meetings. Once all site subjects are completed with the treatment phase of the study (ie, in the 5 year survival follow up phase), meeting frequency may be decreased. De-identified site data, as well as site study team records, will be reviewed (at a minimum) approximately every 12-16 weeks (at a minimum) to ensure accuracy and up-to-date certifications / local approvals are on file. All local approval documentation by IRB or otherwise must be provided to UFHCC and contained in the site's regulatory files. Protocol amendments with red-lined, clean versions and a summary of changes will be provided to sites for IRB submission. Consent form (ICF) amendments will be provided in the study's model consent and will contain tracked changes. Updates to the local ICF must be approved by UFHCC PMO prior to submission to the local IRB. Other document updates such as to the Investigator Brochure and lab manual must be submitted to the local IRB as per their guidelines. Activated secondary sites are expected to submit modifications to their local IRBs, per local guidelines within 4 weeks of receipt unless otherwise noted. All approval documentation must be forwarded to UFHCC PMO within 2 weeks of approval. If the IRB of record for a sub-site is UF-IRB-01, UFHCC PMO will submit updates on the site's behalf with input from the sub-site(s). Approval will be provided via email to the sub-site(s) as soon as possible when obtained. The University of Florida IRB requires that all events meeting the definition of unanticipated problem or serious noncompliance be reported as outlined.

	Documentation of participating site's IRB approval of annual continuing reviews, protocol amendments, SAE reports, and protocol deviations, regulatory violations and unanticipated events must be kept on file at UFHCC PMO.
Appendix A: Schedule of Events	Update footnote to clarify that "In the event radiotherapy (RT) is used in the interim between chemotherapy and surgery, an additional pre-surgical imaging assessment may be required after RT is completed."

Appendix G: SUMMARY OF CHANGES FROM PROTOCOL VERSION 5.1 TO VERSION 5.2

Version 5.1	**Version 5.2**
Updated name of chemotherapy regimen	• Updated the chemotherapy regimen name from "FOLNal-IRINOX" to "NAPOLI-OX" to NALIRIFOX as indicated by the sponsor (Ipsen)
Section 12.1	• Added references for the estimation of 30% post-operative complication rate based on historical data
Section 12.2	• Corrected 95% to 90%, to specify that the 30-day post-operative complication rate and its **90%** exact confidence interval (CI) will be calculated.

Appendix H: SUMMARY OF CHANGES FROM PROTOCOL VERSION 5.2 TO VERSION 5.3

Version 5.2	**Version 5.3**
Cover Page	• Added NCT #
Protocol Synopsis **4.1 Inclusion Criteria**	• Updated inclusion criteria to include bilirubin 1.5 ULN, with values trending down
Protocol Synopsis **Section 2.3**	• Added microbiota samples as an exploratory objective
Sections 6.2, 6.3, 9.2, 9.3	• Added Microbiota collection information
Section 7.2.2	• Added routine pre-treatment Supportive Care meds need not be captured
Section 8.3	• Updated replacement of subjects criteria to include anti-cancer therapy addition.
Section 9.2	• Added Tempus as a research location for sending de-identified samples for analysis.
Section 10	• Updated Ipsen name to Ipsen Biopharmaceuticals
Appendix A Footnote 8	• Added FFPE block study entry guidelines
Appendix A Footnote 10	• Added AE and Concomitant Medications collection clarifications after end of treatment.
Appendix A Footnote 11	• Added microbiome collection timepoints.

Appendix I: SUMMARY OF CHANGES FROM PROTOCOL VERSION 5.3 TO VERSION 6

Version 5.3	**Version 6**
Title Page	• Added Dr. Sherise Rogers as Junior PI
Protocol Synopsis, Section 4.2, 4.3	• Updated reproductive risk contraceptive timeline based on IBv15
Section 1.4 Table B	• Deleted NCT02785068 study
Section 1.4.2	• Added results of NCT 02551991 study
Section 6.1, 6.2, 6.3, Appendix A	• Updated so ECGs past baseline/screening will only be performed if medically indicated, and to document any abnormalities at the screening ECG
Sections 6.4, 9.2, Appendix A Footnote 11	• Added Microbiota collection information
Section 7.2.2, 11.2, 11.3, Appendix A Footnote 10	• Updated collection of Concomitant Medications and Adverse Events after 30 days post last dose to capture complications of surgery
Section 7.3	• Added language that Oxaliplatin may be discontinued while subject remains on study
Section 16	• Added reference #38 for NCT 02551991 study
Appendix A Footnote 2	• Removed uric acid, added albumin