MELVIN AND BREN SIMON CANCER CENTER

INDIANA UNIVERSITY

A Phase II Study of Neoadjuvant FOLFIRINOX in Patients with Resectable Pancreatic Ductal Adenocarcinoma with Tissue Collection

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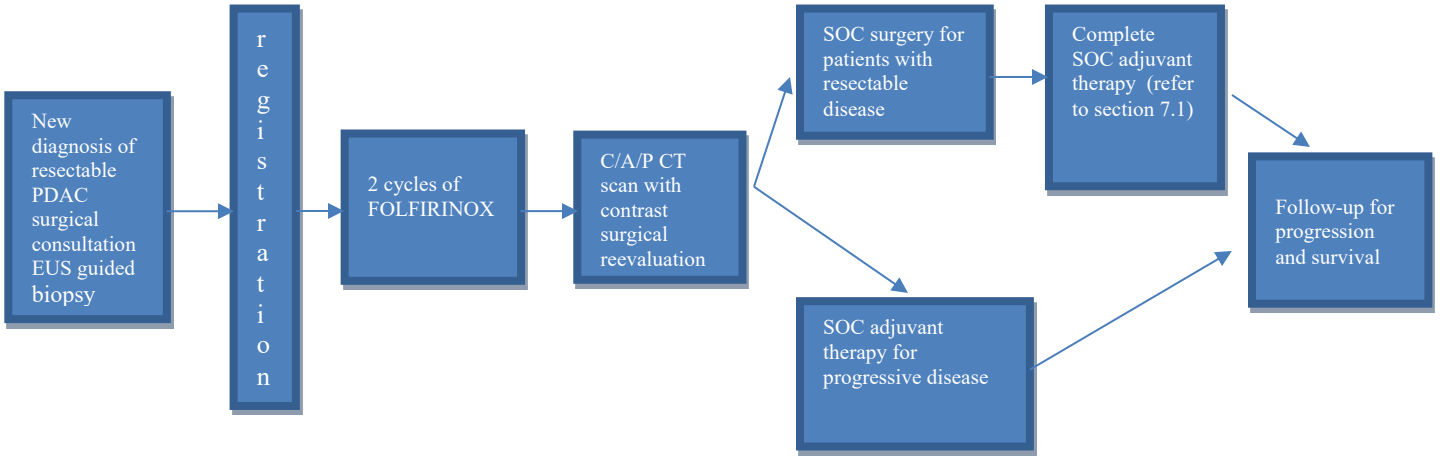
LIST OF ABBREVIATIONS

Abbreviations	Full Text
5-FU	5-Fluorouracil
ATIII	antithrombin III
AE	Adverse Event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANA	antinuclear antigen
AST	Aspartate aminotransferase
BP	Blood pressure
CA19-9	Carbohydrate antigen 19-9
CR	Complete response
CRO	Clinical research office
CRT	Combined chemoradiation
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTSI	Clinical and Translational Sciences Institute
DCR	Disease control rate
DFS	Disease free survival
DSMC	Data Safety Monitoring Committee
DSMB	Data Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
EUS	Endoscopic ultrasound
FAACT	Functional Assessment of Anorexia/Cachexia Therapy
FDP	fibrogen degradation products
FNA	Fine needle aspirate
FOLFIRINOX	5-FU, leucovorin, irinotecan and oxaliplatin
G-CSF	Prophylactic filgrastim
GGT	Gamma-Glutamyl Transferase
HFSR	Hand Food Skin Reaction
HIPAA	Health Insurance Portability and Accountability Act
HUS	Hemolytic uremic syndrome
IRB	Institutional Review Board
IV	Intravenous
ITT	Intention to treat
IUSCC	Indiana University Simon Cancer Center
LAPC	locally advanced pancreatic cancer
Mg	Milligram
mOS	Mean overall survival
MRI	Magnetic resonance imaging

MRN	Medical record number
N	Nausea
NCI	National Cancer Institute
NE	Not evaluable
NGS	Next generation sequencing
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PAC	Protocol Accrual Committee
PD	Progressive disease
PDAC	Pancreatic Ductal Adenocarcinoma
PFS	Progression free survival
PG-SGA	Scored Patient-Generated Subjective Global Assessment
PO	Oral
PR	Partial response
PRN	As needed
RECIST	Response Evaluation Criteria in Solid Tumors
RF	rheumatoid factor
RR	Response rate
SAE	Serious Adverse Event
SBRT	stereotactic body radiotherapy
SD	Stable disease
TTP	thrombitic thrombycytopenic purpura
ULN	Upper limit of normal
V	Vomitting
VOD	veno-occlusive disease
VWF	vonWillebrand's factor
WOCBP	Women of childbearing potential

SCHEMA



1. BACKGROUND & RATIONALE

Pancreatic Ductal Adenocarcinoma (PDAC) is the 4th leading cause of cancer related mortality in the USA. Approximately 45,000 Americans will be diagnosed with this disease annually and the majority of these patients will succumb to their disease. The incidence of PDAC has been on the rise for unknown reasons. Five year overall survival remains poor at 5% despite aggressive surgical interventions and adjuvant therapy (1). Fifteen to twenty percent of patients are diagnosed with locally resectable disease at the time of their initial presentation. There is no consensus regarding how to approach these patients, but a number of centers including Indiana University proceed with surgical resection first followed by adjuvant chemotherapy or chemoradiotherapy. Adjuvant therapy includes gemcitabine or 5-FU, based on improvement in disease free survival (DFS) and overall survival (OS) in patients receiving active therapy compared to observation alone (2). Even in patients who undergo Whipple surgery and adjuvant therapy, prognosis remains unfavorable with median overall survival (mOS) of less than 2 years (3). As such, new approaches are needed.

Long before gemcitabine was established as an option for adjuvant therapy; it was approved in the metastatic setting based on clinical benefit in patients who had symptomatic advanced disease (4). Over the last 2 decades, several combinations of gemcitabine based chemotherapy have failed to improve outcome in patients with metastatic disease. Recently, both FOLFIRINOX (5-FU, leucovorin, irinotecan and oxaliplatin) and nab-paclitaxel/gemcitabine were proven superior to gemcitabine alone in patients with metastatic pancreatic cancer leading to improvement in response rate (RR), progression free survival (PFS) and OS (5, 6).

1.1 Rationale for neoadjuvant therapy in PDAC

Several lines of evidence support a neoadjuvant approach in the treatment of patients with pancreatic cancer (7). This is based on the rationale that 70-80 % of patients who undergo resection with curative intent still experience relapse shortly after their recovery; perhaps neoadjuvant therapy might spare these patients with an aggressive biology a surgery that may not alter the course of their disease (8). Additionally, neoadjuvant chemotherapy provides the opportunity to evaluate response to therapy "*in vivo*", and spares patients with poor biology a

large and potentially morbid operation. Prior to FOLFIRINOX (RR: 31%) and nab-paclitaxel/gemcitabine (RR: 23%), the response rate to gemcitabine as a single agent was reported to be in a range of 6-7 %, which was unlikely to result in a meaningful R0 resection rate. Additionally, up to one-third of patients who undergo surgical resection may not recover well enough to undergo adjuvant therapy; therefore, ensuring adequate treatment in the form of neoadjuvant therapy theoretically results in better delivery of therapy.

1.2 Neoadjuvant therapy in PDAC: (Gemcitabine and 5-FU +/- XRT)

In earlier studies to evaluate the safety and efficacy of combined chemoradiation (CRT) in the neoadjuvant setting, 28 patients with resectable PDAC received concurrent 5FU based CRT (9). All 28 patients completed treatment and 9 required hospitalization due to gastrointestinal toxicity. Further studies evaluating this combination aimed at improving the resection rate, R0 resection and evaluating OS (10, 11). Studies revealed that patients who completed their preoperative therapy and underwent resection experienced longer survival compared to patients who had surgery first (12), or who did not undergo resection due to progression or decline in functional status (13, 14). A retrospective study using 5FU and cisplatin in combination with radiotherapy concluded that local control was achieved in preoperative chemoradiation with no significant difference in OS between the two groups (15). Whether this is related to ineffective systemic therapy (cisplatin is ineffective in the treatment of pancreatic cancer) or local control (which does not correlate with overall survival) is unknown.

While cisplatin is not commonly used in the treatment algorithm for patients with pancreatic cancer, a randomized phase II study with preoperative gemcitabine alone versus gemcitabine/cisplatin concluded that the combination arm achieved higher R0 resection rate, higher node negative rate and improved DFS at one year (16).

1.3 Neoadjuvant therapy: (FOLFIRINOX and nab-paclitaxel)

Based on the higher response rate to FOLFIRINOX compared to gemcitabine, several clinical trials are evaluating FOLFIRINOX in a variety of settings (resectable, borderline resectable, and locally advanced unresectable) and in combinations with radiation therapy including intensity modulated radiotherapy (IMRT) and stereotactic body radiotherapy (SBRT). In a retrospective review of patients with locally advanced pancreatic cancer (LAPC), 19 received FOLFIRINOX. Five patients (28%) underwent R0 resection, and after a course of chemoradiotherapy, 3 more patients underwent R0 resection, improving the resectability rate to 44%. Another retrospective review using modified FOLFIRINOX in patients with non-metastatic (Stage II, III) PDAC resulted in a 30% response rate, 13.7 months of mPFS and 17.8 months of mOS (17). The incidence of grade 4 neutropenia, grade 3/4 diarrhea, and fatigue were 3%, 13%, and 13%, respectively. Twenty-one patients with borderline resectable and LAPC were treated with FOLFIRINOX. Six patients (29%) required dose reductions due to toxicity. Two patients (9%) were unable to tolerate treatment and three patients (14%) had disease progression on treatment. Seven patients (33%) underwent surgical resection following treatment with FOLFIRINOX alone, 2 (10%) of which were initially unresectable. Two patients underwent resection following FOLFIRINOX and SBRT. The R0 resection rate for patients treated with FOLFIRINOX + SBRT was 33% (55% borderline resectable, 10% unresectable). Five patients (24%) demonstrated a significant pathologic response.

Given the manageable toxicity of the nab-paclitaxel/gemcitabine regimen, studies evaluating its safety and efficacy have been conducted and other studies are ongoing. In a small study, 16 patients received nab-paclitaxel/gemcitabine for 3 weeks, with one week off schedule. Two

patients had progressive metastatic disease during treatment (18). Nine patients had resection; 8 with R0 resection. One patient had a pathologic complete response (CR) and 4 near CR. In a similar approach, 25 patients with localized PDAC received nab-paclitaxel/gemcitabine in a phase II study. Twenty patients had resection with 19/20 with R0 resection. Histologic down staging was evident in 30% of patients achieving G3/4 pathologic response (19). A phase II study is currently undergoing the evaluation of this combination based on risk stratification for resection incorporating IMRT for patients with higher risk of local recurrence (20).

At Indiana University, we have been administering FOLFIRINOX for patients with good performance status who have borderline resectable pancreatic cancer or LAPC with the intention of inducing tumor response to convert their disease into a resectable disease. We have documented 4 cases of complete pathologic responses (pCR) and 4 cases of near (CR), which is very unusual in pancreatic carcinoma (unpublished data). One of the aims of the current study is to collect pre-treatment tissues in order to identify molecular/genetic factors that predict drug sensitivity.

1.4 Study Rationale

Adjuvant treatment with gemcitabine or 5-FU improves DFS and mOS in patients with resectable pancreatic cancer with median improvement in OS of 2 months over observation alone. Further work is needed to identify patients who will benefit from surgery and spare the rest extensive surgery that may not alter the course of their disease. Incorporating the new combinations of chemotherapy (FOLFIRINOX and nab-paclitaxel/gemcitabine) into the treatment of early stage pancreatic cancer might improve the resectability rate, DFS and OS; however, only prospective clinical trials will tell. Collecting tissues to correlate benefit from therapy with molecular studies and explore mechanisms of resistance will be valuable.

This proposal differs from what has been previously published or investigated because it will be targeting only patients with resectable pancreatic cancer, and will have a tissue collection component which will provide a great opportunity for translational research. Our study will also provide important safety information about the use of preoperative FOLFIRINOX that will provide a foundation for future chemotherapy/targeted therapy combinations in this setting.

2. OBJECTIVES

2.1 Primary Objective

To evaluate the rate of pathologic complete response to neoadjuvant FOLFIRINOX in patients with resectable pancreatic cancer.

2.2 Secondary Objectives

1. To describe the adverse events associated with FOLFIRINOX when administered preoperatively in patients with resectable pancreatic cancer.
2. To estimate the fraction of patients who can successfully undergo surgery after neoadjuvant chemotherapy.
3. To estimate the overall resectability rate, rate of R0 resection, disease free survival (DFS), overall survival (OS), overall response rate (ORR; complete response (CR) + partial response (PR)), and disease control rate (DCR; CR + PR + stable disease (SD)) after administration of FOLFIRINOX in patients with resectable pancreatic cancer.

2.3 Tertiary Objectives

1. Assess changes in quality of life (global assessment and functional assessment of anorexia/cachexia therapy) from baseline to 4 weeks (+/- 2 weeks) post-neoadjuvant chemotherapy.

2.4 Correlative Objectives

1. Evaluate change in CA 19-9 and other tissue markers before and after treatment and correlate with outcomes.
2. Correlate pathologic tumor response with findings from next generation sequencing (NGS).
3. Outcome and survival data including DFS and OS will be correlated with NGS findings and other future research studies.
4. Any residual tissue and other biologic samples (blood, serum and plasma) will be stored for future research

3. OUTCOME MEASURES

3.1 Primary Outcome Measure

- Rate of complete pathologic response

3.2 Secondary Outcome Measures

- Percentage of patients to undergo surgical resection after receiving neoadjuvant FOLFIRINOX
- Disease free survival and overall survival for patients with resected pancreatic cancer

3.3 Tertiary Outcome Measures

- Patient-Generated Subjective Global Assessment (PG-SGA) score at baseline and 4 weeks post neo-adjuvant therapy
- Functional Assessment of Anorexia/Cachexia Therapy (FAACT) at baseline and 4 weeks post neo-adjuvant therapy

3.4 Correlative Outcome Measures

- Tissues pre (when feasible) and post therapy will be collected and stored for further analysis and future research.
- Blood pre (when feasible) and post therapy will be collected and stored for further analysis and future research.
- The planned analysis will include next generation sequencing on tissues collected before and after therapy. These tissues will be compared to germline evaluation from blood samples collected from peripheral blood.

4. ELIGIBILITY CRITERIA

All of the following criteria must be met in order to participate in this study:

4.1 Inclusion Criteria

1. ≥ 18 years old at the time of informed consent
2. Able to provide written informed consent and HIPAA authorization
3. ECOG performance status of 0 or 1
4. Patient must be eligible for abdominal surgery

5. Cytologically or histologically confirmed adenocarcinoma of the pancreas that has been documented to be resectable by standardized radiographic criteria by a pancreatic surgeon
6. Women of childbearing potential definition (WOCBP) must have a negative serum or urine pregnancy test performed within 14 days prior to initiation of FOLFIRINOX. Any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) is classified as WOCBP if she meets the following criteria:
    a. Has not undergone a hysterectomy or bilateral oophorectomy; or
    b. Has not been naturally postmenopausal for at least 24 consecutive months (i.e. has had menses at any time in the preceding 12 consecutive months).
7. WOCBP and men must agree to use adequate contraception prior, to study entry, for the duration of study participation, and 8 weeks after the end of treatment.
8. Patients must have adequate organ function as defined by the following laboratory values at study entry:
    a. Hemoglobin ≥ 9 g/dL (transfusions are acceptable)
    b. ANC ≥ 1.5 x 10^9/L
    c. Platelets ≥ 100 x 10^9/L
    d. Creatinine ≤ 1.5 x ULN, or creatinine clearance ≥ 50 mL/min (estimated by Cockcroft-Gault or measured)
    e. Total bilirubin ≤ 2 x ULN
    f. AST/ALT ≤ 3 x ULN

4.2 Exclusion Criteria

1. Prior therapy for pancreatic adenocarcinoma
2. Other malignancies within the past 3 years except for the following: adequately treated cervical or vulvar carcinoma in situ, treated basal cell or squamous carcinoma of the skin, superficial bladder tumors (Ta, Tis & T1), ductal carcinoma in situ (DCIS) of the breast and low grade prostate cancer. Any cancer curatively treated >3 years prior to entry with no clinical evidence of recurrence is permitted.
3. Hypersensitivity to 5FU, oxaliplatin (or other platinum agents), irinotecan (or to their excipients).
4. Participation in any investigational drug study within 4 weeks preceding the start of study treatment. Patients are not permitted to participate in another investigational drug study while being treated on this protocol.
5. Inability to receive a port or PICC line.
6. History of or suspected Gilbert's Disease (testing not required if presence is not suspected).
7. Baseline peripheral neuropathy/paresthesia grade > 1.
8. Active hepatitis B, unless patient has been on antiviral agents for at least 2 months (baseline testing not required).
9. Active clinically serious infections (> grade 2).
10. Major surgery or significant traumatic injury within 8 weeks of first study drug. A core pancreatic or liver biopsy does not preclude the patient from the study.
11. Unable or unwilling to discontinue use of ketoconazole or St John's wort. Use of phenytoin, carbamazepine, phenobarbital, rifampin and rifabutin is discouraged, but not contraindicated. If patients require phenytoin, carbamazepine or phenobarbital monitoring of drug levels is suggested during the study.

12. Pregnant or lactating women.
13. Psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial.

5. STUDY DESIGN

This is a single arm, non-randomized, open label, prospective, phase II study for patients with resectable pancreatic cancer.

6. PATIENT REGISTRATION

All patients will be registered with the Indiana University Simon Cancer Center (IUSCC) Clinical Trials Office (CTO). Regulatory files will be maintained by the CTO and applicable regulatory documents must be completed and on file prior to registration of any patients. Potential patients will be identified in the Oncology surgery clinic, endoscopy suite and pancreatic cancer referral program.

Patients who are interested in this study at the time of their work-up and appear to be eligible for this trial will undergo the Informed Consent Process and be screened for eligibility. The original signed IRB approved Informed Consent Document and completed eligibility checklist will be forwarded to the CTO designee for eligibility verification and registration in the OnCore® database.

The expected duration of subject participation is 8-10 months (including time for surgery and recovery). Accrual is expected to be approximately 2 patients per month at Indiana University for a yearly accrual of approximately 24 patients and a total accrual of 48 patients. The approximate time to complete study enrollment will be approximately 24 months.

7. TREATMENT PLAN

7.1 Treatment Dosage and Administration

Patients on this trial will be treated with neoadjuvant FOLFIRINOX for 2 cycles (1 cycle = 28 days). Patients will receive FOLFIRINOX on an outpatient basis on days 1 and 15 of each cycle. Following neoadjuvant treatment, patients will undergo repeat imaging (CT or MRI) to be reassessed for resectability of the tumor. Further adjuvant treatment will be determined at the treating physician's discretion (i.e. chemoradiotherapy or adjuvant chemotherapy). It is important to note that post-neoadjuvant therapy is determined by the treating physician per their institutional guidelines and standard of care. While this study will collect data regarding disease progression and survival from the post-neoadjuvant period, this protocol does not dictate post-neoadjuvant treatment which may be done at other institutions.

For patients with an R1 resection, any chemoradiotherapy will be included in the 24 weeks of perioperative therapy. Chemoradiotherapy and the timing in which it will be given will be determined at the treating physician's discretion based on margin status and the patient's recovery. Furthermore, patients who receive chemoradiotherapy may also receive adjuvant chemotherapy; however, this will be based on the treating physician's discretion. Recommended radiosensitization will be through 5FU 200 mg/m2/Day continuous infusions M-F of each week or capecitabine 825 mg/m2 PO BID M-F for the duration of radiation therapy. Patients who

receive adjuvant therapy will receive treatment based upon treating physician's discretion with a recommended duration of therapy lasting 6 months accounting for preoperative therapy.

The neoadjuvant FOLFIRINOX regimen starting doses are: oxaliplatin 85 mg/m^2, followed by leucovorin 400 mg/m^2 given simultaneously with irinotecan 180 mg/m^2, followed by 5FU 400 mg/m^2 bolus and then 2400 mg/m^2 (Table 1). Patients require a PORT, PICC or other IV access to allow administration of 5FU via a continuous infusion pump. All agents should be administered within SOC drug administration guidelines. Appropriate dose modifications for each agent are described in Section 9.0. See drug monographs/package inserts for full details on each agent.

Table 1: Chemotherapy Drugs and Modes of Administration**

Agent	Dose*	Route	Schedule
Oxaliplatin	85 mg/m^2 in 250 cc D5W	IV **before** irinotecan	Day 1,15 of each 28 day cycle
Leucovorin	400 mg/m^2 in 100 cc D5W with irinotecan.	IV **with** irinotecan infusion via Y-site connection	Day 1, 15 of each 28 day cycle
Irinotecan	180 mg/m^2 in 500 cc D5W with leucovorin.	IV **with** leucovorin infusion via Y-site connection	Day 1, 15 of each 28 day cycle
5FU	400 mg/m^2	IV bolus **after** irinotecan	Day 1, 15 of each 28 day cycle
5FU	2400 mg/m^2	IV **after** 5FU bolus	Day 1, 15 of each 28 day cycle

*Dose should be recalculated for patients with > 10% weight change

** Information contained in this table is intended to be used as a guideline for administering FOLFIRINOX chemotherapy, and modifications to this table can be made based upon institutional guidelines or physician discretion. These modifications will not be recorded as deviations for this protocol.

7.2 Recommended Pre-medications/Precautions and Hydration

Table 2: Recommended Pre-medications, Hydration and Prophylactic Medications*			
Agent	**Dose/Precautions**	**Route**	**Schedule**
Ondansetron (or formulary equivalent)	24 mg Instruct patient to avoid exposure to cold (food, liquids, air) for 5 days following oxaliplatin	PO 30 minutes prior to oxaliplatin	Days 1, 15
Dexamethasone	12 mg	PO 30 minutes prior to oxaliplatin	Days 1, 15
Atropine	0.4 mg	IV PRN for abdominal cramping or diarrhea during or after irinotecan	Days 1, 15
Promethazine	25 mg	IV q6h PRN for nausea or vomiting	Days 1-28
D5W	100 cc/h	IV during treatment for infusions in D5W + to flush lines between medications.	Days 1, 15
0.9% Normal Saline	2 L	IV prior to/during/after treatment	Days 1, 15
Loperamide (home instructions)	4 mg at onset of diarrhea, then 2mg q2h prn until diarrhea stops for at least 12 hours	PO	Days 1-28
Pegafilgrastim	6 mg	SQ	Days 1, 15

* Information contained in this table is intended to be used as a guideline, and modifications including any additions or omissions to this table can be made based upon institutional guidelines or physician discretion. These changes will not be recorded as deviations for this protocol.

7.3 Concomitant Medications

All pre-medications, medications for hydration, prophylactic medications and medications given as a result of an adverse event will be recorded in the OnCore® system. Growth factors may be utilized at the investigator's discretion.

8. TOXICITIES TO BE MONITORED/DOSAGE MODIFICATIONS

Adverse events will be recorded for all patients beginning at C1D1 (i.e. start of neoadjuvant treatment) through 30 days post completion of neoadjuvant therapy or progression.

Each patient will be assessed for the development of any toxicity according to the Study Calendar (Section 10). Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

The treating physician may use his/her best clinical judgment when determining dose adjustments and/or holds. Dose adjustments of each agent may be made independently of dose modifications of the other agents (Table 3), and are based on the specific types of toxicities observed (Table 4). Agents held more than 14 days for toxicity should be discontinued. If more

than 2 dose reductions of a single agent in a patient are required, that agent will be discontinued. Once a dose reduction has been performed, no intra-patient dose re-escalation is permitted. Patients that have treatment delays for more than 14 days during any of the 6 cycles of chemotherapy should be removed from the study.

Additional detailed information on the potential adverse events and risks associated with each agent is included in Section 13.

Table 3: Dose Levels for Toxicity

Dose Level	Irinotecan	5FU Bolus / Infusion	Oxaliplatin	Leucovorin*
Starting dose (level 1)	180 mg/m^2	400/2400 mg/m^2	85 mg/m^2	400 mg/m^2
-1	150 mg/m^2	320/2000 mg/m^2	65 mg/m^2	400 mg/m^2
-2	120 mg/m^2	240/1600 mg/m^2	50 mg/m^2	400 mg/m^2

**If 5FU is discontinued, leucovorin is simultaneously discontinued.*

Table 4: Dose Modifications for Toxicity

On Day 1 or Day 15	Toxicity at any point during cycle	Dose Level for Subsequent Administration		
Hematologic Toxicities				
If ANC <1.5 on the day of treatment, treatment will be delayed[2] for 1 week. Resume treatment when ANC ≥1.5.	**Neutropenia**	**Irinotecan**	**5FU**	**Oxaliplatin**
	Grade 2	Maintain dose	Maintain dose	Maintain dose
	Grade 3	↓1 dose level	↓1 dose level	↓1 dose level
	Grade 4	↓2 dose levels	↓2 dose levels	↓2 dose levels
	Febrile neutropenia	↓2 dose levels	↓2 dose levels	↓2 dose levels
If platelets <75K on the day of treatment, delay[1] treatment for 1 week Resume treatment when platelets ≥75K.	**Thrombocytopenia[2]**	**Irinotecan**	**5FU**	**Oxaliplatin**
	≤Grade 1	Maintain dose	Maintain dose	Maintain dose
	Grade 2-3	↓1 dose level	↓1 dose level	↓1 dose level
	Grade 4	↓2 dose levels	↓2 dose levels	↓2 dose levels
Non-Hematologic Toxicities				
If mucositis is >Grade 2 on the day of treatment, treatment will be delayed[1] for 1 week. Resume treatment when mucositis <Grade 2. Consider use of mouth wash/rinse.	**Mucositis**	**Irinotecan**	**5FU**	**Oxaliplatin**
	≤Grade 2	Maintain dose	Maintain dose	Maintain dose
	Grade 3	Maintain dose	↓1 dose level	Maintain dose
	Grade 4	Maintain dose	↓2 dose levels	Maintain dose

Table 4: Dose Modifications for Toxicity

If diarrhea is ≥Grade 2, on the day of treatment, treatment will be delayed[1] 1 week. Once diarrhea is <Grade 2, proceed with dose adjusted per table.	**Diarrhea**	**Irinotecan**	**5FU**	**Oxaliplatin**
	Grade 2	↓1 dose level	Maintain dose	Maintain dose
	Grade 3	↓1 dose level	↓1 dose level	Maintain dose
	Grade 4	↓2 dose levels	↓2 dose levels	↓1 dose level

Electrolyte abnormalities, regardless of grade, do not require dose reductions or dose delays but should be corrected with aggressive supplementation.	**Electrolyte Abnormalities**	**Irinotecan**	**5FU**	**Oxaliplatin**
	Any Grade	Maintain dose. Treating physician may reduce dose for grade 3-4, if deemed appropriate		

Non-Hematologic Toxicities

On Day 1 or Day 15	**Toxicity at any point during cycle**	**Dose Level for Subsequent Administration**		
If HFSR is >Grade 2, delay[1] treatment for 1 week. Once HFSR is ≤Grade 2, proceed with dose adjusted per table.	**HFSR**	**Irinotecan**	**5FU**	**Oxaliplatin**
	≤Grade 2	Maintain dose	Maintain dose	Maintain dose
	Grade 3	Maintain dose	↓1 dose level	Maintain dose
	Grade 4	Maintain dose	↓2 dose levels	Maintain dose
If neuropathy Grade 2 and persisting between treatments, or ≥Grade 3, delay[1] treatment for 1 week. Once neuropathy is ≤Grade 2 and not persisting, proceed with dose adjusted per table.	**Neuropathy- motor and/or sensory**	**Irinotecan**	**5FU**	**Oxaliplatin**
	Grade 2 and persisting between treatments, OR new onset Grade 3 resolving to ≤Grade 2 between treatments	Maintain dose	Maintain dose	↓1 dose level
	First recurrence of Grade 3 resolving to ≤Grade 2 between treatments	Maintain dose	Maintain dose	↓1 further dose level (i.e. to dose level -2)
	Second recurrence of Grade 3 resolving to ≤Grade 2 between treatments, OR Grade 3 persistent between treatments, OR any Grade 4	Maintain dose	Maintain dose	Discontinue
If bilirubin is >2mg/dL, delay[1] treatment for 1 week. Once ≤2mg/dL, proceed with dose adjusted per table.	**Increased Bilirubin[3]**	**Irinotecan**	**5FU**	**Oxaliplatin**
	>2 mg/dL	↓2 dose levels	Maintain dose	Maintain dose
	>3 mg/dL	Discontinue	Maintain dose	Maintain dose
	Hypersensitivity Reaction	**Irinotecan**	**5FU**	**Oxaliplatin**
	Grade 1-2	Maintain dose	Maintain dose	Hypersensitivity treatment PRN. May retreat at next treatment

Table 4: Dose Modifications for Toxicity				
				day (1 or 15)
	≥ Grade 3 Or if recurrent >Grade 1	Maintain dose	Maintain dose	Hypersensitivity treatment. Discontinue permanently
Non-Hematologic Toxicities				
Delay[1] dose of suspected offending agent(s) for 1 week, until toxicity resolves to ≤Grade 2, then resume treatment with dose adjusted per table.	**Other Not-Specified[4]**	**Irinotecan**	**5FU**	**Oxaliplatin**
	≥ Grade 3	↓1 dose level (if suspected offending agent)	↓1 dose level (if suspected offending agent)	↓1 dose level (if suspected offending agent)
	Grade 4	If suspected offending agent, ↓1-2 dose levels. If attribution not known, then decrease all agents. May discontinue at PI discretion.	If suspected offending agent, ↓1-2 dose levels. If attribution not known, then decrease all agents. May discontinue at PI discretion.	If suspected offending agent, ↓1-2 dose levels. If attribution not known, then decrease all agents. May discontinue at PI discretion.

[1] Delay offending agent(s) as identified in table. If have to delay treatment >14 days on any of the 6 cycles of chemotherapy, discontinue agent(s). May continue non-offending agents per investigator discretion.

[2] If suspect hemolytic uremic syndrome (HUS) and/or thrombitic thrombycytopenic purpura (TTP), which is generally based on the presence of severe hemolysis, hemoglobinemia, and renal failure, draw the following lab tests: creatinine, BUN, CBC, INR, PTT, fibrinogen, (fibrogen degradation products (FDP), antithrombin III (ATIII), vonWillebrand's factor (VWF), antinuclear antigen (ANA), rheumatoid factor (RF), C3, C4, CH50, antiplatelet antibodies, platelet-associated IgG, and circulating immune complexes; and urinalysis. In such cases, inpatient evaluation and referral to hematology are recommended. Oxaliplatin should be discontinued permanently.

[3] If any suspicion of veno-occlusive disease (VOD) of liver (including hyperbilirubinemia, ascites, unexplained weight gain, hepatomegaly, splenomegaly, esophageal varices, or other of signs portal hypertension), then hold chemotherapy. If diagnosed clinically, the discontinue chemotherapy completely.

[4] Do not adjust doses for alopecia or nausea (N) and vomiting (V) unless N&V persist for >48 hours despite maximum anti-emetic support. For all other ≥ Grade 3 non-hematologic toxicities not described above, hold suspected agent(s) and monitor toxicity at least weekly. For Grade 3 toxicities associated primarily with laboratory abnormalities only (e.g. elevation of ALT, AST, lipase, Grade 3 or Grade 4 hypophosphatemia without clinical or other evidence of pancreatitis or other hepatic dysfunction (e.g.

Table 4: Dose Modifications for Toxicity
concomitant elevated bilirubin), study treatment may continue without interruption if this is deemed medically acceptable by the investigator.

9. STUDY PROCEDURES

9.1 EUS or CT-Guided Biopsy Procedure

Pancreatic cancer is commonly staged by the means of endoscopic ultrasound (EUS). This is a standard of care procedure which includes minimal sedation and upper endoscopy. A linear echoendoscope will be utilized to identify the pancreatic mass. A fine needle aspirate (FNA) or core biopsy will be performed at the same time. As with standard practice, biopsy will be performed with on-site cytology review to confirm malignancy. All diagnostic biopsies must be reviewed by the Pathology Department per the institutional guidelines.

If patients do not proceed to surgery after neoadjuvant treatment (may occur if the patient refuses surgery, is not eligible for surgery or has progression of disease), then an optional biopsy may be completed at the end of treatment. In these cases, a CT-guided biopsy will likely be performed. EUS biopsies are typically performed for patients who have localized disease while CT-guided biopsy is typically performed when metastatic disease is suspected.

Biopsies may be performed prior to patient enrollment as they are standard of care for pancreatic cancer diagnosis. Therefore, tissue samples being stored with the Pathology Department (i.e. archival tissue) in lieu of fresh tissue collection may be requested after enrollment to satisfy the baseline tissue collection requirement of this study. Additionally, it may be difficult to coordinate fresh tissue collect at the time of surgical resection (see below) or biopsy; therefore, archival tissue may also be collected to satisfy the post-neoadjuvant treatment tissue collection requirement of this study.

Additional details regarding tissue collection can be found in Section 12.1.

9.2 Surgical Resection

Approximately 4 weeks (+/- 2 weeks) after the completion of the neoadjuvant treatment, patients will undergo standard of care operative exploration and complete extirpative surgery. Operative planning will be based on the original review of the patients' initial (i.e. pre-treatment) staging CT or MRI scan and the scan obtained after completion of the neoadjuvant protocol. All patients will undergo two modalities of operative exploration for occult metastatic disease undetectable with conventional cross-sectional imaging. Prior to laparotomy, patients will undergo a formal two-port staging laparoscopy to exclude the presence of occult metastatic disease involving the liver or peritoneal surfaces. Suspicious nodules possibly representing metastatic disease will be biopsied to confirm a pathologic diagnosis of metastatic pancreatic adenocarcinoma. Proof of metastatic cancer (i.e. stage IV cancer) will exclude patients from operative resection of the primary pancreatic cancer. In the absence of metastatic disease detectable with staging laparoscopy, patients will undergo a formal laparotomy with abdominal exploration to exclude occult metastatic disease involving the peritoneal surfaces or liver.

In the absence of occult metastatic disease, patients will undergo the planned operative procedure to resect the primary pancreatic adenocarcinoma completely. Based on preoperative imaging,

patients will undergo either a pancreatoduodenectomy (PD) or distal pancreatectomy and splenectomy (DPS). PD will be performed for patients with head and/or neck of pancreas cancers. DPS will be performed for patients with body and/or tail of pancreas cancers. PD and DPS will be performed according to standardized techniques which are employed routinely at Indiana University Hospital.

All margins of resection will be sampled intraoperatively to ensure complete clearance. For PD, the neck of pancreas and bile margins will be reviewed with frozen section histopathologic analysis. For DPS, the proximal pancreatic margin (i.e. body or neck of pancreas) will be reviewed intraoperatively. Final margin status (R0 versus R1) of the resected specimens will be recorded in addition to the intraoperative margin status assessments.

All complications within 30 days of operative resection will be recorded prospectively and comprehensively according to the data acquisition guidelines of the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP). All patients undergoing pancreatectomy at Indiana University Hospital are included in the ACS-NSQIP database which has been modified to contain complications variables specific to pancreatic procedures.

Patients will receive a routine, formal clinical evaluation by their respective surgeon as per institutional guidelines and standard of care. Postoperative complications will be recorded during this evaluation and will be treated according to standardized practices. Patients will be evaluated for post-operative adjuvant chemotherapy within 4-6 weeks from the date of the operation as is routinely done after surgery. Further adjuvant treatment will be determined at the treating physician’s discretion (i.e. chemoradiotherapy or adjuvant chemotherapy).

10. STUDY CALENDAR

1 cycle = 2 treatments over 28 days (treatments are given every 2 weeks) D1=Day 1 D15=Day 15	Baseline[1]	Cycles 1-2		Surgical Evaluation/EOT[2]	Long-term Follow-up[9] Post-neoadjuvant tx
	-28 days	Day of Cycle (± 7 days)		4 (+/- 2) weeks post neoadjuvant tx	
		D1	D15		
REQUIRED ASSESSMENTS					
Medical history	X				
Height	X				
Physical examination	X	X	X		
BP, weight	X	X	X		
ECOG performance status	X	X	X		
Complete metabolic panel	X	X	X		
Calculated creatinine clearance	X	X	X		
Platelets, ANC & Hgb	X	X	X		
CA 19-9	X				
Urine pregnancy[3]	X				
AE and concomitant medication assessment	X	X	X	X[10]	
Overall survival					X
Disease progression					X
DISEASE ASSESSMENT					
MRI or CT chest, abdomen, pelvis	X			X[5]	X[4]
Surgical resection (if applicable)				X	
TREATMENT					
Neoadjuvant FOLFIRINOX		X	X		
CORRELATIVE STUDIES					
Tissue collection	X[6]			X	
Blood collection	X[6]			X	
ASSESSMENTS					
PG-SGA questionnaire	X[7]			X[8]	
FAACT questionnaire	X[7]			X[8]	

Calendar Footnotes:

[1] Baseline assessments performed within 7 days of Cycle 1 Day 1 do not need to be repeated.

[2] All patients will have a surgical evaluation visit 4 (+/-2) weeks of completing or discontinuing neoadjuvant chemotherapy as part of their routine care. Information collected during this visit will be used for the EOT visit for this study.

[3] Required only for women of child-bearing potential.

[4] Disease progression will be assessed via radiology report from any MRI or CT scans done during the follow-up period per standard of care.

[5] Repeat imaging may be performed prior to surgical resection at the treating physician's discretion.

[6] Whenever possible

[7] PG-SGA and FAACT assessments not completed at baseline can be completed on C1D1 as long as they are done before treatment begins.

[8] PG-SGA and FAACT assessments should be completed within 4 (+/-2) weeks of completing or discontinuing neoadjuvant chemotherapy.

[9] Follow-up for survival and disease progression will be done every 3-6 months years 1-3, every 6 months years 4-5, and every 12 months thereafter.

[10] May be done by telephone in lieu of an in-person visit.

11. CRITERIA FOR EVALUATION/REMOVAL FROM STUDY

Definitions Associated with Response Evaluation Criteria in Solid Tumors (RECIST) version 1.

Measurable disease - At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

11.1 Measurable

Tumor lesions – Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 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 slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the *short* axis will be measured and followed.

11.2 New Lesions

There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

11.3 Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). 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.

Target Lesions	Non-Target Lesions	New Lesion?	Best 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

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

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

11.3.1 Missing assessments and in-evaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

11.3.2 Definitions of Pathological Response

Histopathologic response after neoadjuvant therapy will be evaluated according to the Evan's criteria as detailed below. The evaluation includes assessment of the amount of variable carcinoma remaining in conjunction with cytologic changes.

Evans' criteria for pathologic response following neoadjuvant therapy (22)	
Grade	**Tumor regression**
I	<10% to no tumor cells destroyed
II	**IIa**: 10-50% of tumor cells destroyed
	IIb: 50-90% of tumor cells destroyed
III	>90% of tumor cells destroyed
	IIIM: sizable pools of cellular mucin
IV	No viable tumor cells
	IVM: Acellular pools of mucin

11.4 Methods of Measurement

Imaging based evaluation is preferred to evaluation by clinical examination. The same imaging modality must be used throughout the study to measure disease. All measurements should be

recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

11.4.1 CT and MRI

CT is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

11.4.2 Cytology and Histology

All cytological and surgical pathology specimens will be prepared in the Indiana University Health Pathology Department. Cytologic and histologic techniques can be used to differentiate between complete and partial responses. Cytologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met response or stable disease criteria. All surgical pathologic specimens were re-reviewed and scored by an expert pathologist.

11.4.3 Tumor markers

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

11.5 Criteria for removal from treatment

A patient is considered discontinued from the study when the decision to permanently stop treatment is made. Patients will be removed from the study when any of the following criteria apply:

Unacceptable adverse events, or change in underlying condition such that the patient can no longer tolerate therapy, including:

a. Delay >14 days for administering scheduled chemotherapy due to toxicities
b. Withdrawal of informed consent
c. Investigator's discretion
d. Pregnancy

This decision should be made by the principal investigator and co-investigators. The reason for study removal and the date the patient was removed should be documented in the electronic case report form (eCRF). The patient should be followed per protocol.

12. CORRELATIVE SAMPLE COLLECTION & ASSESSMENT, ANALYSIS

12.1 Tissue Collection

The collection of the pancreatic tumor tissue pre- and post-neoadjuvant treatment is an important part of this trial. The goal of these collections is to generate findings from next generation sequencing (NGS) (see 12.2.1 for more details) to predict the pathological response versus progression. Additionally, future, yet undetermined, research studies will be done on any unused

tissue samples that were collected as part of this study. The outcome and survival data will be correlated with next generation sequencing and other future research.

The tissue will be obtained at the time of diagnosis as a standard of care to establish the diagnosis. If there is additional tissue available from the diagnostic biopsy samples, we plan on requesting them either at the time of biopsy (i.e. fresh tissue sample collection for patients who are already enrolled to this study) or from the Pathology Department (i.e. archival tissue). For patients who have biopsies at institutions outside of IUH, the PI and/or his designee will make requests for any additional tissue from those respective institutions' pathology departments.

After the second cycle of neoadjuvant chemotherapy, additional tumor tissue samples that would otherwise be discarded, will be obtained at the time of surgical resection or biopsy (if applicable). If patients do not proceed to surgery (may occur if the patient refuses surgery, is not eligible for surgery or has progression of disease), then an optional biopsy may be completed at the end of neoadjuvant treatment. All research tissue samples will be stored in the IUSCC Tissue Bank or IU CTSI Specimen Storage Facility.

Please refer to the study laboratory manual for complete instructions regarding tissue collection, processing, transfer and storage.

12.2 Blood Collection

Blood samples for future, yet undetermined, research studies (in addition to the blood samples taken as part of standard of care) will be collected prior to treatment (i.e. at baseline or C1D1 as long as completed before treatment begins) whenever possible and at the time of surgical evaluation (i.e. 4 weeks [+/-2 weeks] post neoadjuvant chemotherapy). These blood samples will be stored in the IUSCC Tissue Bank or IU CTSI Specimen Storage Facility.

Please refer to the study laboratory manual for complete instructions regarding tissue collection, processing, transfer and storage.

12.3 Next Generation Sequencing Methods (Blood and Tissue)

Genomic sequencing of samples derived from this trial will be performed at IU to ascertain markers of response as well as to inform future studies. From the tumor biopsies, Next-generation DNA and RNA sequencing will be performed per available technologies at the time of analysis. One such method that may be used is described below.

For each sample, DNA & RNA will be extracted from tumor biopsies along with DNA from matched whole blood. Briefly, 40ng of DNA will undergo a highly multiplexed PCR reaction to amplify all exons of 409 genes known to be mutated in cancer (Sanger Gene Census) using the Ion Ampliseq Comprehensive Cancer Panel. This panel is specifically designed for amplification of both formalin-fixed paraffin embedded samples as well fresh/frozen tissue. Subsequent to amplification, libraries will be sequenced on an Ion Proton Sequencer using 200bp fragment chemistry and an Ion Proton I chip. It is estimated that each sample will have 1500-2000X average coverage of each cancer gene, enabling low allele frequency somatic mutation detection. Each sequencing run will be evaluated for technical quality control metrics. For bioinformatics analysis, reads will be mapped to the human genome using the TMAP algorithm. After mapping, somatic variants will be called (point mutations, indels, and copy number variation), using the

Ion Reporter pipeline (Life Technologies). Annotation of identified variants will be performed by cross-referencing the following databases: NIH dbSNP, 1000 genomes project, COSMIC (Catalog of Somatic Mutations in Cancer), and TCGA (The Cancer Genome Atlas). Identification of cancer driver variants, association with therapeutic interventions, and mutational network analyses will be performed using Ingenuity Variant Analysis (Ingenuity Systems). All data and analyses will be stored on the HIPPA-compliant Indiana University Scholarly Data Archive.

For expression analysis 10ng of RNA (extracted as described above) will undergo library preparation using the Ion Ampliseq Transcriptome Human Gene Expression Kit. This will allow for accurate quantitative expression of ~20,000 genes in the human genome. Standard workflow for gene-level expression will be conducted using Torrent Suite Version 5.0. The AmpliSeq Transcriptome Plugin tool will be used to generate standard expression files.

12.3 Assessments

Patients will be given the following questionnaires to complete via paper or in electronic format (online, email, or on a tablet) prior to treatment (i.e. at baseline or C1D1 as long as completed before treatment begins) and at the time of surgical evaluation (i.e. 4 weeks [+/-2 weeks] post neoadjuvant chemotherapy).

12.3.1 Scored Patient-Generated Subjective Global Assessment (PG-SGA)

The Scored Patient-Generated Subjective Global Assessment (PG-SGA) includes the four patient-generated historical components (Weight History, Food Intake, Symptoms and Activities and Function), the professional part (Diagnosis, Age, Metabolic stress, and Physical Exam), the Global Assessment (A = well nourished, B = moderately malnourished or suspected malnutrition, C = severely malnourished), the total numerical score, and nutritional triage recommendations. Subsequently, the Scored PG-SGA allows for triaging of specific nutrition interventions, as well as facilitating quantitative outcomes data collection.[23]

12.3.2 Functional Assessment of Anorexia/Cachexia Therapy (FAACT)

The Functional Assessment of Anorexia/Cachexia Therapy (FAACT) is a comprehensive questionnaire used for patient self-report of anorexia and appetite assessment that contains general core questions of the Functional Assessment of Chronic Illness Treatment (FACIT) plus questions about nutritional issues including appetite.[24]

12.4 Study Identifiers

The PI will have ownership of any tissue or blood samples that are stored for future research. Distribution of samples will be at PI discretion; however, samples will not be sold. Any samples that are distributed to researchers outside of the study team, will anonymized and only identified by a coded number.

13. DRUG INFORMATION

13.1 Oxaliplatin (Eloxatin®)

Oxaliplatin is a platinum-based drug that forms crosslinks of guanine that inhibit DNA replication and transcription. Cytotoxicity is cell-cycle nonspecific. It is indicated for the treatment of metastatic CRC in combination with 5FU and leucovorin.

Supply and Supplier

Oxaliplatin as Eloxatin® is available from Sanofi-Aventis in powder form in two strengths (50 mg or 100 mg), and as a sterile, preservative-free, aqueous solution at a concentration of 5 mg/ml in 3 sizes: 50 mg, 100 mg or 200 mg. It must be diluted prior to intravenous infusion. See Full Prescribing Information at: http://products.sanofi-aventis.us/eloxatin/eloxatin.html for complete information. Commercially available supplies of either Eloxatin® or generic oxaliplatin will be used for this study.

Preparation, Storage and Stability

The appropriate dose of oxaliplatin (see Section 7.1) should be reconstituted, diluted and stored according to the package insert provided by the manufacturer and according to local pharmaceutical regulations. **Reconstitution or final dilution must never be performed with a sodium chloride solution or other chloride containing solutions.**

Premedication

Patients should be prescribed medications to prevent and treat nausea and vomiting as per institutional guidelines**.**

Dosage and Administration

See Section 7.1.

Handling and Disposal

As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of infusion solutions prepared from oxaliplatin. The use of gloves is recommended. If a solution of oxaliplatin contacts the skin, wash the skin immediately and thoroughly with soap and water. If oxaliplatin contacts the mucous membranes, flush thoroughly with water. Procedures for the handling and disposal of anticancer drugs should be considered.

Adverse Events

Incidence rates of adverse events associated with oxaliplatin are provided in the products' Full Prescribing Information (http://products.sanofi-aventis.us/eloxatin/eloxatin.html). Some of the adverse events expected with oxaliplatin treatment are listed below.

More than 1100 patients with stage II or III colon cancer and >4000 patients with advanced CRC have been treated in clinical studies with Eloxatin®. The most common adverse reactions in these trials (incidence ≥ 40% of patients) were peripheral sensory neuropathy, neutropenia, thrombocytopenia, anemia, nausea, increase in transaminases and alkaline phosphatase, diarrhea, emesis, fatigue and stomatitis.

Hematologic: When oxaliplatin was used in combination with 5FU and leucovorin in previously untreated advanced CRC, the percent of patients who experienced hematological toxicities (all grades/grade ≥3) were: anemia (27%/3%) leukopenia (85%/20%), neutropenia (81%/53%), infection with grade ≥3 neutropenia (8%), febrile neutropenia (4%) and thrombocytopenia (71%/5%). Epistaxis occurred in 10% of patients, versus 1% in those receiving irinotecan plus 5FU and leucovorin.

Gastrointestinal: When oxaliplatin was used in combination with 5FU and leucovorin in previously untreated advanced CRC, the percent of patients who experienced gastrointestinal toxicities (all grades/grade ≥3) were: nausea (71%/6%), diarrhea (56%/12%), vomiting (41%/4%), and stomatitis (38%/0%). Premedication with antiemetics, including 5-HT3 blockers, is recommended. Diarrhea and mucositis may be exacerbated by the addition of oxaliplatin to 5FU/leucovorin, and should be managed with appropriate supportive care. Since cold temperature can exacerbate acute neurological symptoms, ice (mucositis prophylaxis) should be avoided during the infusion of oxaliplatin.

Dermatologic: When oxaliplatin was used in combination with 5FU and leucovorin in previously untreated advanced CRC, the percent of patients who experienced hand-foot syndrome was 7%.

Intravenous Site Reactions: Extravasation, in some cases including necrosis, has been reported. Injection site reaction, including redness, swelling, and pain, has been reported.

Anticoagulation and Hemorrhage: There have been reports while on study and from post-marketing surveillance of prolonged prothrombin time and INR occasionally associated with hemorrhage in patients who received oxaliplatin plus 5FU/leucovorin while on anticoagulants. Patients receiving oxaliplatin plus 5FU/leucovorin and requiring oral anticoagulants may require closer monitoring.

Renal: About 5-10% of patients in all clinical trial groups in the oxaliplatin trials in CRC had some degree of elevation of serum creatinine.

Thromboembolism: When oxaliplatin was used in combination with 5FU and leucovorin in previously untreated advanced CRC, the percent of patients who experienced thromboembolic events was 6%.

The following toxicities are noted with particular Warnings and Precautions in the prescribing information for Eloxatin®:

1. Neuropathy: Oxaliplatin is associated with two types of neuropathy:
    a. **An acute, reversible, primarily peripheral, sensory neuropathy that is of early onset, occurring within hours or one to two days of dosing, that resolves within 14 days, and that frequently recurs with further dosing.** The symptoms may be precipitated or exacerbated by exposure to cold temperature or cold objects and they usually present as transient paresthesia, dysesthesia and hypoesthesia in the hands, feet, perioral area, or throat. Jaw spasm, abnormal tongue sensation, dysarthria, eye pain, and a feeling of chest pressure have also been observed. The acute, reversible pattern of sensory neuropathy was observed in about 56% of study patients who received oxaliplatin with 5FU/leucovorin. In any individual cycle acute neurotoxicity was observed in approximately 30% of patients. In adjuvant patients the median cycle of onset for grade 3 peripheral sensory neuropathy was 9 in the previously treated patients the median number of cycles administered on the oxaliplatin with 5FU/leucovorin combination arm was 6.

An acute syndrome of pharyngolaryngeal dysesthesia seen in 1–2% (grade 3/4) of patients previously untreated for advanced colorectal cancer, and the previously treated patients, is characterized by subjective sensations of dysphagia or dyspnea, without any laryngospasm or bronchospasm (no stridor or wheezing). Ice (mucositis prophylaxis) should be avoided during the infusion of oxaliplatin because cold temperature can exacerbate acute neurological symptoms.

b. **A persistent (>14 days), primarily peripheral, sensory neuropathy that is usually characterized by paresthesias, dysesthesias, hypoesthesias, but may also include deficits in proprioception that can interfere with daily activities (e.g. writing, buttoning, swallowing, and difficulty walking from impaired proprioception).** These forms of neuropathy occurred in 48% of the study patients receiving oxaliplatin with 5FU/leucovorin. Persistent neuropathy can occur without any prior acute neuropathy event. The majority of the patients (80%) who developed grade 3 persistent neuropathy progressed from prior Grade 1 or 2 events. These symptoms may improve in some patients upon discontinuation of oxaliplatin.

   Overall, neuropathy was reported in patients previously untreated for advanced colorectal cancer in 82% (all grades) and 19% (grade 3/4), and in the previously treated patients in 74% (all grades) and 7% (grade 3/4) events. Information regarding reversibility of neuropathy was not available from the trial for patients who had not been previously treated for colorectal cancer.

The following warnings and precautions are less common but serious adverse events associated with oxaliplatin:

2. Anaphylactic Reactions: These have been reported, and may occur within minutes of oxaliplatin administration. Epinephrine, corticosteroids, and antihistamines have been employed to alleviate symptoms. Grade 3/4 hypersensitivity, including anaphylactic/anaphylactoid reactions, to oxaliplatin has been observed in 2–3% of colon cancer patients. These allergic reactions which can be fatal, can occur within minutes of administration and at any cycle, and were similar in nature and severity to those reported with other platinum-containing compounds, such as rash, urticaria, erythema, pruritus, and, rarely, bronchospasm and hypotension. The symptoms associated with hypersensitivity reactions reported in the previously untreated patients were urticaria, pruritus, flushing of the face, diarrhea associated with oxaliplatin infusion, shortness of breath, bronchospasm, diaphoresis, chest pains, hypotension, disorientation and syncope. These reactions are usually managed with standard epinephrine, corticosteroid, antihistamine therapy, and may require discontinuation of therapy. Drug-related deaths associated with platinum compounds from anaphylaxis have been reported.
3. Pulmonary Toxicity: Oxaliplatin has been associated with pulmonary fibrosis (<1% of study patients), which may be fatal. The combined incidence of cough and dyspnea was 7.4% (any grade) and <1% (grade 3) with no grade 4 events in the oxaliplatin plus infusional 5FU/leucovorin arm compared to 4.5% (any grade) and no grade 3 and 0.1% grade 4 events in the infusional 5FU/leucovorin alone arm in adjuvant colon cancer patients. In this study, one patient died from eosinophilic pneumonia in the oxaliplatin combination arm. The combined incidence of cough, dyspnea and hypoxia was 43% (any grade) and 7% (grade 3 and 4) in the oxaliplatin plus 5FU/leucovorin arm compared to 32% (any grade) and 5% (grade 3 and 4) in

the irinotecan plus 5FU/leucovorin arm of unknown duration for patients with previously untreated colorectal cancer. In case of unexplained respiratory symptoms such as non-productive cough, dyspnea, crackles, or radiological pulmonary infiltrates, oxaliplatin should be discontinued until further pulmonary investigation excludes interstitial lung disease or pulmonary fibrosis.

4. Hepatotoxicity: Hepatotoxicity appears to be related to oxaliplatin combination therapy. When oxaliplatin was used in combination with 5FU and leucovorin in previously untreated advanced CRC, the percent of patients who experienced hepatotoxicity (all grades/grade ≥3) were ALT elevation (6%/1%), AST elevation (17%/1%), alkaline phosphatase elevation (16%/0%), and total bilirubin elevation (6%/1%). In the study of oxaliplatin and 5FU/leucovorin versus 5FU/leucovorin alone in patients with colon cancer receiving chemotherapy as adjuvant treatment, hepatotoxicity was observed more frequently in the oxaliplatin arm, as evidenced by increases in transaminases (57% vs. 34%) and alkaline phosphatase (42% vs. 20%). The incidence of increased bilirubin was similar on both arms. Changes noted on liver biopsies include: peliosis, nodular regenerative hyperplasia or sinusoidal alterations, perisinusoidal fibrosis, and veno-occlusive lesions. Hepatic vascular disorders should be considered, and if appropriate, should be investigated in case of abnormal liver function test results or portal hypertension, which cannot be explained by liver metastases.

Drug Interactions

No specific cytochrome P-450-based drug interaction studies have been conducted. No pharmcokinetic interaction between 85 mg/m^2 oxaliplatin and 5FU/leucovorin has been observed in patients treated every 2 weeks. Increases of 5FU plasma concentrations by approximately 20% have been observed with doses of 130 mg/m^2 oxaliplatin dosed every 3 weeks. Because platinum-containing species are eliminated primarily through the kidney, clearance of these products may be decreased by co-administration of potentially nephrotoxic compounds; although, this has not been specifically studied

13.2 Irinotecan (Camptosar®)

Irinotecan hydrochloride is a semisynthetic derivative of camptothecin and is an antineoplastic agent of the topoisomerase I inhibitor class. It is a prodrug of the active metabolite, SN38, that produces DNA breakage and cell death.(21). It is indicated for the treatment of metastatic CRC in combination with 5FU and leucovorin.

Supply and Supplier

Irinotecan as Camptosar® is available from Pfizer in single-dose amber glass vials containing 40 mg/2 mL or 100mg/5mL, and must be diluted prior to intravenous infusion. See Full Prescribing Information at: https://www.pfizeroncology.com/sites/pop/PDFs/uspi_camptosar.pdf for complete information. Commercially available supplies of either Camptosar® or generic irinotecan will be used for this study.

Preparation, Storage and Stability

The appropriate dose of irinotecan (see Section 7.1) should be reconstituted, diluted and stored according to the package insert provided by the manufacturer and according to local pharmaceutical regulations.

Premedication

Patients should be prescribed medications to prevent and treat nausea and vomiting as per institutional guidelines**.**

Dosage and Administration

See Section 7.1.

Handling and Disposal

To minimize the risk of dermal exposure, always wear impervious gloves when handling vials containing irinotecan. This includes all handling activities in clinical settings, pharmacies, storerooms, and home healthcare settings, including during unpacking and inspection, transport within a facility, and dose preparation and administration. If a solution of irinotecan contacts the skin, wash the skin immediately and thoroughly with soap and water. If irinotecan contacts the mucous membranes, flush thoroughly with water. Procedures for proper handling and disposal of anti-cancer drugs should be considered.

Adverse Events

Incidence rates of adverse events associated with irinotecan are provided in the products' Full Prescribing Information (https://www.pfizeroncology.com/sites/pop/PDFs/uspi_camptosar.pdf). Some of the adverse events expected with irinotecan treatment are listed below.

Nausea, vomiting and diarrhea are common adverse events following treatment with irinotecan, and can be severe. When observed, nausea and vomiting usually occur during or shortly after infusion of irinotecan.

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 is severe. It may be accompanied by cholinergic symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal cramping. Early diarrhea and other cholinergic symptoms may be prevented or ameliorated by administration of atropine. 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. Patients with diarrhea should be carefully monitored, should be given fluid and electrolyte replacement if they become dehydrated, and should be given antibiotic support if they develop ileus, fever, or severe neutropenia.

Hepatic: In the clinical studies evaluating the weekly dosage schedule, NCI grade 3 or 4 liver enzyme abnormalities were observed in fewer than 10% of patients. These events typically occur in patients with known hepatic metastases.

Hematologic: Irinotecan commonly causes neutropenia, leucopenia (including lymphocytopenia) and anemia. Deaths due to sepsis following severe neutropenia have been reported in patients receiving irinotecan. Individuals who are homozygous for the UGT1A1*28 allele (approximately 10% of North American population) are at increased risk for neutropenia following initiation of irinotecan treatment. Serious thrombocytopenia is uncommon. SN-38, the active metabolite of irinotecan, is predominantly converted to its glucuronide metabolite, which

is essentially inactive, and subsequently eliminated in bile and feces. Based on this, patients with known defective UGT1A1 (Gilbert's syndrome) will be excluded from this trial.

Body as a Whole: Asthenia, fever, and abdominal pain are generally the most common events of this type.

Hypersensitivity: Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have been observed.

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

Renal Impairment/Renal Failure: Rare cases of renal impairment and acute renal failure have been identified, usually in patients who became volume depleted from severe vomiting and/or diarrhea.

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

Respiratory: In clinical studies, ≥Grade 3 dyspnea was reported in 4% of patients. Of note, over half of these patients had lung metastases. Interstitial pulmonary disease, which can be fatal, is uncommon. Risk factors include pre-existing lung disease, use of pneumotoxic drugs, radiation therapy, and colony stimulating factors.

Drug Interactions

Exposure to irinotecan and its active metabolite SN-38 is substantially reduced when patients are concomitantly receiving CYP3A4 enzyme-inducing drugs such as the anti-convulsants phenytoin, phenobarbital or carbamazepine, as well as other agents such as St. John's Wort. Strong inhibitors of CYP3A4 enzymes such as the anti-fungal ketoconazole and the HIV anti-retrovirals (e.g. atazanavir), have increased exposure to irinotecan and SN-38 and should be avoided in patients receiving irinotecan. See https://www.pfizeroncology.com/sites/pop/PDFs/uspi_camptosar.pdf for further information. See Section 7.3 for further information on prohibited concomitant drugs, and drugs to be used with caution.

13.3 5FU

5FU is an antineoplastic anti-metabolite that interfers with the synthesis of DNA and to a lesser extent RNA by blocking the methylation reaction of deoxyuridylic acid to thymidylic acid. It is indicated for the treatment of metastatic CRC.

Supply and Supplier

The following information was taken from the prescribing information for Teva USA's Adrucil® (5FU). Additional details may be found at:
http://www.tevausa.com/assets/base/products/pi/Adrucil_PI.pdf.

Each 10 mL contains 500 mg of FU (50 mg/mL) and sodium hydroxide to adjust pH to approximately 9.2. Commercially available supplies of either Adrucil® or another generic 5FU will be used for this study based on cost and availability.

Preparation, Storage and Stability

The appropriate dose of 5FU (see Section 7.1) should be reconstituted, diluted and stored according to the package insert provided by the manufacturer and according to local pharmaceutical regulations.

Premedication/Hydration

Patients should receive premedication and hydration as described earlier.

Dosage and Administration

See Section 7.1.

Handling and Disposal

To minimize the risk of dermal exposure, always wear impervious gloves when handling vials containing 5FU. This includes all handling activities in clinical settings, pharmacies, storerooms, and home healthcare settings, including during unpacking and inspection, transport within a facility, and dose preparation and administration. If a solution of 5FU contacts the skin, wash the skin immediately and thoroughly with soap and water. Procedures for proper handling and disposal of anti-cancer drugs should be considered.

Adverse Events

The most common toxicities seen with 5FU therapy include stomatitis, esophagopharyngitis (which may result in sloughing and ulceration), diarrhea, anorexia, nausea and vomiting. Neutropenia commonly follows treatment with white count nadir observed between days 9 and 14 following therapy. Mild alopecia has been reported, though is usually not complete. Dermatitis, in the form of a pruritic maculopapular rash that usual appears on the extremities and (less frequently) trunk, is generally reversible and responsive to symptomatic treatment. This dermatitis may be increased with sun exposure.

Other less common adverse reactions are:
Hematologic: pancytopenia, thrombocytopenia, agranulocytosis, anemia.

Cardiovascular: myocardial ischemia, angina.

Gastrointestinal: gastrointestinal ulceration and bleeding.

Allergic Reactions: anaphylaxis and generalized allergic reactions.

Neurologic: acute cerebellar syndrome (which may persist following discontinuance of treatment), nystagmus, headache.

Dermatologic: dry skin; fissuring; photosensitivity, as manifested by erythema or increased pigmentation of the skin; vein pigmentation; palmar-plantar erythrodysesthesia syndrome, as manifested by tingling of the hands and feet followed by pain, erythema and swelling.

Ophthalmic: lacrimal duct stenosis, visual changes, lacrimation, photophobia.

Psychiatric: disorientation, confusion, euphoria.

Miscellaneous: thrombophlebitis, epistaxis, nail changes (including loss of nails)

13.4 Leucovorin

Leucovorin, also known as folinic acid or citrovorum factor is a chemically reduced derivative of folic acid. Leucovorin is readily converted to another rduced folate, 5,10-methylenetetrahydrofolate, which acts to stabilize the binding of fluorodeoxyuridylic acid to thymidylate synthase, thereby enhancing the inhibition of this enzyme. It is used to enchance the effects of fluoropyrimdines such as 5FU.

Supply and Supplier

The following information was taken from the prescribing information for Sagent Pharmaceutical's leucovorin calcium.

Leucovorin calcium is commercially available as a sterile, single-use vial containing either 100mg or 350mg each. Commercially available supplies of generic leucovorin calcium will be obtained from Sagent or another manufacturer and used for this study.

Preparation, Storage and Stability

The appropriate dose of leucovorin (see Section 7.1) should be reconstituted and diluted and stored according to the package insert provided by the manufacturer and according to local pharmaceutical regulations.

Dosage and Administration

See Section 7.1.

Adverse Events Associated with Leucovorin

Leucovorin should not be used for pernicious anemia and other megalobastic anemias secondary to the lack of vitamin B12. A hematologic remission may occur while neurologic manifestations continue to progress.

Leucovorin enhances the toxicity of 5FU. When these drugs are administered concurrently in the treatment of advanced colorectal cancer, as they are in this study, gastrointestinal toxicities (particularly stomatitis and diarrhea) are observed more commonly and may be more severe and of prolonged duration. Seizures and/or syncope have been reported rarely in cancer patients receiving leucovorin, usually in combination with fluoropyrimidine administratiaon, and most commonly in those with CNS metastases or other predisposing factors, however, a causal relationship has not been established.

Allergic sensitization, including anaphylactoid reactions and urticaria, has been reported following administration of leucovorin.

Drug Interactions

Folic acid in large amounts may counteract the antiepileptic effect of phenobarbital, phenytoin and primidone, and increase the frequency of seizures in susceptible pediatric patients.

14. STATISTICAL METHODS

14.1 Sample size analysis and accrual

The pathological complete response with traditional chemotherapy in pancreatic cancer is very low (no reported complete response in neoadjuvant studies). We aim to evaluate the complete response rate and the correlation with outcome. So we assume the pathological complete response in traditional chemotherapy to be 1%. We expect that the pathological complete response after 2 cycles of FOLFIRINOX therapy is about 10%. We plan to enroll 48 patients over a 24 months period. Assuming 90% of patients are evaluable for response, we will have 43 patients evaluable for pathological complete response. Patients will be considered non-evaluable and be replaced with new subjects per analysis datasets section below. With evaluable patients, we have 82% power detect a significant difference from the traditional chemotherapy with a 5% Type I error rate using a two sided one-sample test for proportion.

14.2 Analysis datasets

Population	Definition
Enrolled	This will comprise all patients who meet the eligibility criteria and are registered onto the study.
Efficacy Evaluable	This will comprise all patients who complete at least 2 treatments and either undergo at least one post-baseline assessment or die before any evaluation.
Not Evaluable for Efficacy	This will comprise of patients who do not complete 2 out of 4 treatments unless it is related to profound toxicity leading to treatment discontinuation.
Safety	This will comprise all patients that contribute data to the safety analysis. This population should be specifically defined in the protocol.

14.3 Statistical analysis plan

Primary Outcome:

- Pathologic complete response: the proportion of the 48 patients having a pathologic complete response with a 95% confidence interval (using normal approximation) will be calculated.

Secondary Outcomes:

- *Safety:* Adverse events of grades 3, 4, 5 by the CTCAE v4.3 criteria for each category listed in section 2.1.6 will be summarized. The proportion of patients with each category of AE will be calculated with a 95% confidence interval. After the enrollment of the first 20 patients, we will evaluate the rate of surgical resection. If >6 patients are not able to proceed with surgery due to excessive toxicity or progression (not including occult metastatic peritoneal disease that was found during surgery and not on imaging) the study will discontinue due to unacceptable toxicity.

- *Ability of patients to undergo surgical resection after receiving neoadjuvant FOLFIRINOX*: the proportion of patients who are able to go through surgery among those who have resectable tumor will be calculated accompanied with a 95% confidence interval.

- *Rate of resectability* will be evaluated by determining the proportion of patients who are able to undergo surgery with resection of their primary tumor (R0 vs R1) resection. A 95% confidence interval will be constructed for the rate.

- *Disease free survival (DFS):* DFS is defined as time from registration to evidence of tumor recurrence (including clinical deterioration related to the underlying pancreatic cancer, as assessed by the investigator) or death from any cause. Kaplan-Meier curve for DFS will be plotted. Median DFS time will be calculated accompanied with a 95% confidence interval.

- *Overall survival*: time from registration to death for 48 patients with right censoring will be analyzed using Kaplan-Meier estimate. Median survival time will be obtained accompanied with a 95% confidence interval.

- *Objective response rate:* proportion of patients with complete responses (CR) or partial responses (PR) after 4 cycles of FOLFIRINOX treatment will be constructed with a 95% confidence interval.

- *Disease control rate:* Proportion of patients with complete responses (CR), partial responses (PR), or stable disease (SD) after 4 cycles of FOLFIRINOX treatment will be obtained with a 95% confidence interval.

Tertiary Outcomes:

- Quality of life measures (from PG-SGA and FAACT) will be summarized with descriptive statistics and compared between baseline and 4 weeks post neo-adjuvant therapy with paired t-tests.

Correlative Outcomes:

- Change of biomarkers (including Ca19-9 and other tissue markers) from baseline to after 2 cycles of therapy will be calculated. Paired t-test will be used to test the change. We will correlate the change of Ca19-9 with patients' pathologic complete response using logistic regression model or overall survival using Cox proportional hazards model as appropriate. Biomarkers will also be correlated with PFS and other response outcomes similarly.

- Differential expression will be performed in R using DESeq2. These files will be downloaded and uploaded to Partek Genomics Suite v6.6 for visualization. Pathway analysis will be performed using Ingenuity Pathway Analysis. CIBERSORT analysis to identify the immune cell make up based on gene expression will also be performed. Selected differentially expressed markers will be correlated with outcomes as describe above.

14.4 Criteria for stopping study

The study will be discontinued if 25-30% of patients are unable to complete surgery due to toxicity. Analysis will be conducted after the first 20 patients are enrolled onto the study. If >6 patients are not able to proceed with surgery due to excessive toxicity the study will discontinue due to unacceptable toxicity.

15. DATA FORMS AND SUBMISSION SCHEDULE

This study will utilize electronic Case Report Form completion in the OnCore® database. A calendar of events and required forms are available in OnCore®. The OnCore® database is a comprehensive database used by the IUSCC Clinical Trials Office (CTO) and supported by the Indiana Clinical and Translational Sciences Institute (CTSI).

Access to data through OnCore® is restricted by user accounts and assigned roles. Once logged into the OnCore® system with a user ID and password, OnCore® defines roles for each user which limits access to appropriate data. New username and passwords can be obtained by going to the following link: https://redcap.uits.iu.edu/surveys/?s=sYN36a9U5c. For further questions regarding your oncore account you can contact the CTO Cancer Center Oncore Support via email at: oncorecc@iupui.edu.

All source documents are to remain in the patient's clinic file. All documents should be kept according to applicable federal guidelines. Clinical trial data in OnCore® are periodically monitored by the IU Simon Cancer Center Data Safety Monitoring Committee.

Generally, clinical and correlative data will be electronically captured in OnCore®. If procedures on the study calendar are performed for standard of care, at minimum, that data will be captured in the medical record. Select standard of care data will also be captured in OnCore®, according to study-specific objectives. Please see the OnCore® data collection guidelines for further details. Tissues will be stored in the IUSCC and data will be kept in OnCore® in a BSM.

16. PATIENT CONSENT AND PEER JUDGMENT

The protocol and informed consent form for this study must be approved in writing by the appropriate Institutional Review Board (IRB) prior to any patient being registered on this study.

Changes to the protocol, as well as a change of principal investigator, must also be approved by the Board. Records of the Institutional Review Board review and approval of all documents pertaining to this study must be kept on file by the investigator (housed in the Clinical Trials Office) and are subject to inspection at any time during the study. Periodic status reports must be submitted to the Institutional Review Board at least yearly, as well as notification of completion of the study and a final report within 3 months of study completion or termination.

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

17. DATA AND SAFETY MONITORING

17.1 Data Safety Monitoring Committee

The Data Safety Monitoring Committee (DSMC) of the Indiana University Simon Cancer Center (IUSCC) is responsible for patient safety and privacy protection, compliance with required reporting, and study integrity for all trials conducted at IUSCC. Members are subject matter experts from multiple disciplines including medical oncology, pediatrics, biostatistics, behavioral oncology, radiation oncology, urology, surgery, gynecologic oncology, data and project management and research administration who are appointed by the DSMC Chair. The DSMC will provide independent oversight of the clinical trial so that study integrity is assured. However, the DSMC is not serving as a Data and Safety Monitoring Board (DSMB) for this study. The DSMC will meet per the currently approved DSMP, led by the DSMC Chair and Coordinator, and will review all adverse events, monitoring and auditing reports, unanticipated problems and study non-compliance events that require expedited reporting. Meeting minutes will be maintained in the IUSCC Clinical Trials Office (CTO). Specifically the DSMC has the following responsibilities:

- Assessment of the adequacy of trial-specific Data Monitoring and Safety Plan (DSMP) of studies that are not subject to external monitoring, including investigator initiated studies, and establish risk based monitoring determination of trial specific DSMB.

- Review safety data for investigator initiated trials including all adverse events, unanticipated problems and study non-compliance events requiring expedited reporting.

- Conduct routine study monitoring and auditing in compliance with the IUSCC data quality control review process.

17.2 Data and Safety Monitoring Plan

This trial will comply with the current requirements of the Data and Safety Monitoring Plan (DSMP) of the IUSCC. The CTO of the IUSCC will be the Coordinating Center for this phase 2 trial. Investigators will conduct continuous review of data and patient safety. **Monthly review meetings** are required and will include the Principal Investigator, clinical research specialist and/or study nurse (or other members will be present at the Principal Investigator's discretion). **Monthly** meeting summaries should include review of data, the number of patients, significant toxicities as described in the protocol, and responses observed. Summaries will be submitted to DSMC@iupui.edu and reviewed monthly by DSMC. **Monthly** meeting summaries will include and document review of data and patient safety by including: the number of patients, significant toxicities as described in the protocol, responses observed, eligibility of patients enrolled at each site, serious adverse events (SAEs) or unanticipated problems (UPs) (both IUSCC and those reported from other institutions), dose adjustments, and protocol deviations. Meeting minutes will be submitted and reviewed by the DSMC.

Study Monitoring for Moderate Risk Trials
All trials conducted at the IUSCC are subject to auditing and/or monitoring. Reports will be reviewed by the full DSMC at the time of study review (Reference Risk Table in full DSMC Charter).

Early Study Closure
At any time during the conduct of the trial, if it is the opinion of the investigators that the risks (or benefits) to the patient warrant early closure of the study, this recommendation should be made in writing to the Data Safety Monitoring Committee. Alternatively, the DSMC may initiate suspension or early closure of the study based on its review.

Reporting Guidelines
The DSMC has streamlined the reporting process by utilizing reports from OnCore®. This has allowed direct view of reports within the Clinical Trials Management System (CTMS); thus, discontinuing all paper reports. SAE reports are entered into OnCore® monthly and reviewed by the DSMC chair and/or coordinator monthly. Findings will be reported to the full DSMC at the time of the studies DSMC review.

Reporting Death
Death will be captured in the Case Report Form and reported per local IRB reporting guidelines.

Study Accrual Oversight
Accrual data will be entered into the IU Simon Cancer Center OnCore® system. The Protocol Progress Committee (PPC) will review study accrual twice per year while the PPC coordinator will review accrual quarterly.

Continuing Review
All Continuing Reviews (CR) will be reviewed annually or as dictated by the Institutional Review Board. Participating sites will submit a copy of the CR with attachments to the IUSCC Multicenter Network Associate Administrator, or designee.

Protocol Deviations
Protocol deviations will be entered into OnCore® and reviewed by the DSMC chair and/or coordinator. Findings will be reported to the full DSMC at the time of DSMC review.

Unanticipated Problems
Investigators are required to submit unanticipated problems to the DSMC (through OnCore®) concurrent with their submission of them to the IRB. **Prompt** reporting of unanticipated problems to the IRB is defined as within 5 days for on-site studies.

Unanticipated problems that will be reported **promptly** to the IRB include:
- Major protocol deviation/violation
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject (e.g. purposeful and for subject safety)
- Complaint of a subject that indicates unexpected risks, or complaint that cannot be resolved by the research team

- Publication in the literature, safety monitoring report, interim result or other finding that indicates an unexpected change to the risks or potential benefits of the research, in terms of severity or frequency
- Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research study
- Investigator- or sponsor-initiated suspension or hold
- Serious or continuing non-compliance
- Adverse events

18. REPORTING ADVERSE EVENTS

18.1 Definitions of Adverse Events

18.1.1 Adverse Event (AE)

An **adverse event** is defined as an unplanned, unwanted medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event can be **ANY** unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of 'unrelated', 'unlikely', 'possible', 'probable', or 'definite'). An AE may also include a newly occurring event or a previous condition that has increased in severity or frequency since the administration of the investigational product. Adverse events will be graded according to the NCI Common Toxicity Criteria, Version 4.0. A copy of the current CTCAE version 4 is available at http://ctep.cancer.gov/reporting/.

18.1.2 Unexpected Adverse Event

An adverse event not mentioned in the Investigator's Brochure or package insert or the specificity or severity of which is not consistent with the Investigator's brochure or package insert.

18.1.3 Unanticipated Problem (UP)

An unanticipated problem is any incident, experience, or outcome that meets all of the following criteria:

1) unexpected (in terms of nature, severity, or frequency) given (a) the research procedures are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being study;
2) related or possibly related to participation in the research; and
3) suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

Only a small subset of adverse events occurring in human subjects participating in research will meet these three criteria for an unanticipated problem. Furthermore, there are other types of incidents, experiences, and outcomes that occur during the conduct of human subjects research that represent unanticipated problems but are not considered adverse events. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In

other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs.

18.1.4 Determining Attribution to the Investigational Agent(s)

Attribution: An assessment of the relationship between the AE and the medical intervention. CTCAE does not define an AE as necessarily *"caused by a therapeutic intervention"*. AEs will be monitored until they are resolved or are clearly determined to be due to a subject's stable or chronic condition or intercurrent illness.

After naming and grading the event, the clinical investigator must assign an attribution; or the determination of whether an adverse event is related to a medical treatment or procedure. The categories of attribution are described below:

Relationship	**Attribution**	**Description**
Unrelated to investigational agent/intervention	Unrelated	The AE is clearly **NO**T related
	Unlikely	The AE is **doubtfully related**
Related to investigational agent/intervention	Possible	The AE **may be related**
	Probable	The AE **is likely related**
	Definite	The AE **is clearly related**

18.1.5 Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence resulting in one or more of the following:

- Results in death or ANY death occurring within 28 days of last dose of study drug (even if it is not felt to be drug related)
- Is life-threatening (defined as an event in which the patient 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 prolongation of existing hospitalization
  NOTE: Hospitalizations that are not considered SAEs are:
  - Hospitalization planned prior to first administration of study drug
  - Hospitalization for elective treatment of a pre-existing condition unrelated to the study medication
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention (e.g. medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.
- Pregnancy
  Pregnancy of a patient or of the female partner of a male patient during the study or within 30 days after the last dose of study drug should be reported via an SAE report. Should pregnancy occur in a female participant during the treatment

period, study drug should be discontinued immediately. Should a pregnancy occur in a female companion of a male participant during the treatment period, the male participant can continue treatment immediately. Any such pregnancy is to be followed until final outcome.

18.2 Adverse Event (AE) Reporting

Adverse events (AEs) will be recorded from the time of first study drug administration and for at least 30 days after treatment discontinuation, regardless of whether or not the event(s) are considered related to trial medications. All AEs considered related to trial medication will be followed until resolution, return to baseline, or deemed clinically insignificant, even if this occurs post-trial.

18.2.1 Reporting to the Data Safety Monitoring Committee (DSMC):

Regardless of study sponsorship, the DSMC chair and/or coordinator will review all expedited SAE reports through OnCore®. Expedited reports are completed per IRB guidelines and may include the IRB Prompt Reporting form, and/or non-compliance form. Submission of this information to the DSMC is **additional to** any other protocol-specified regulatory bodies (e.g. FDA, pharmaceutical company) to be notified. When follow-up information is received, a follow-up report should also be created in OnCore®. The DSMC chair and/or coordinator will review expedited SAE reports monthly.

18.2.2 Reporting to the IRB

Each participating site will report adverse events and unanticipated problems to their IRB per local guidelines. Any event that requires expedited reporting to the local IRB will also be submitted to the IU Simon Cancer Center.

Unanticipated problems involving risks to subjects or others will be reported **promptly** to the IRB if they:

- caused harm;
- were unexpected; AND
- were related or possibly related to the research intervention.

If the serious adverse event does not meet all three (3) criteria listed above, the event does not have to be promptly reported to the Indiana University IRB. However, it should be reported at the time of continuing review.

Prompt reporting of unanticipated problems to the IRB is defined as within 5 business days from becoming aware of the event.

18.3 Record Retention

All documentation of adverse events and records of all IRB correspondence will be stored in accordance with all applicable federal guidelines.

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21. APPENDICES

Appendix I

NCI Common Toxicity Criteria

Version 4.0

Due to the size of the latest version of the Common Toxicity Criteria, copies of this appendix are not included with this protocol document.

An electronic copy is available on the CTEP web site, http://ctep.cancer.gov/reporting/ctc.html

Appendix II

Performance Status Scales/Scores

ECOG or Zubrod		Karnofsky		Lansky	
Score	Activity	Score	Activity	Score	Activity
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	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.	80	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all selfcare 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.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

Appendix III

DSMC Check Sheet

Meeting Minutes Form for DSMC
send to dsmc@iupui.edu or file in binder

Meeting Date:			
Team/Program: **(include meeting sign in sheet)**			
Protocol & Status (open/closed to accrual) **(one protocol per sheet)**			
PI:			
	Y	N	
Weekly and Monthly meetings should include discussion on data, dose levels, accrual numbers, deviation summaries and SAE reports (per IUSCC DSMP).			
Has accrual been reviewed and entered into Oncore?			
Have all SAE's been entered into Oncore?			
Is there documentation for study discontinuation?			
Have all deviations been entered into OnCore?			
Have study deviation summaries been reviewed by the team ***(CTO continue to keep deviation logs signed by PI) ?***			
Record any dose limiting toxicities (DLT's) on this form for any phase I investigator initiated trial, HOG or on a multi-site trial in which IUSCC is the lead site.			

If any of your answers are "NO" please explain in the space below.

***Notes**	

This form is to be used for Investigator Initiated and HOG trials (High risk weekly, Moderate risk Monthly, Low risk quarterly)

Appendix IV

Scored Patient-Generated Subjective Global Assessment (PG-SGA)

Patient ID_____ Patient Initials_____ Date_____

Scored Patient-Generated Subjective Global Assessment (PG-SGA)

History: Boxes 1 - 4 are designed to be completed by the patient.
[Boxes 1-4 are referred to as the PG-SGA Short Form (SF)]

Patient Identification Information

1. Weight *(See Worksheet 1)*

In summary of my current and recent weight:

I currently weigh about _____ pounds
I am about _____ feet _____ inches tall

One month ago I weighed about _____ pounds
Six months ago I weighed about _____ pounds

During the past two weeks my weight has:

☐ decreased (1) ☐ not changed (0) ☐ increased (0)

Box 1 ☐

2. Food intake: As compared to my normal intake, I would rate my food intake during the past month as

- ☐ unchanged (0)
- ☐ more than usual (0)
- ☐ less than usual (1)

I am now taking

- ☐ *normal food* but less than normal amount (1)
- ☐ little solid food (2)
- ☐ only liquids (3)
- ☐ only nutritional supplements (3)
- ☐ very little of anything (4)
- ☐ only tube feedings or only nutrition by vein (0)

Box 2 ☐

3. Symptoms: I have had the following problems that have kept me from eating enough during the past two weeks (check all that apply)

- ☐ no problems eating (0)
- ☐ no appetite, just did not feel like eating (3)
- ☐ nausea (1)
- ☐ constipation (1)
- ☐ mouth sores (2)
- ☐ things taste funny or have no taste (1)
- ☐ problems swallowing (2)
- ☐ pain; where? (3) _____
- ☐ other (1)** _____
- ☐ vomiting (3)
- ☐ diarrhea (3)
- ☐ dry mouth (1)
- ☐ smells bother me (1)
- ☐ feel full quickly (1)
- ☐ fatigue (1)

**Examples: depression, money, or dental problems

Box 3 ☐

4. Activities and Function:
Over the past month, I would generally rate my activity as:

- ☐ normal with no limitations (0)
- ☐ not my normal self, but able to be up and about with fairly normal activities (1)
- ☐ not feeling up to most things, but in bed or chair less than half the day (2)
- ☐ able to do little activity and spend most of the day in bed or chair (3)
- ☐ pretty much bed ridden, rarely out of bed (3)

Box 4 ☐

The remainder of this form is to be completed by your doctor, nurse, dietitian, or therapist. Thank you.

Additive Score of Boxes 1-4 ☐ **A**

email: faithotterymdphd@aol.com or info@pt-global.org

Scored Patient-Generated Subjective Global Assessment (PG-SGA)

Worksheet 1 – Scoring Weight Loss

To determine score, use 1-month weight data if available. Use 6-month data only if there is no 1-month weight data. Use points below to score weight change and add one extra point if patient has lost weight during the past 2 weeks. Enter total point score in Box 1 of PG-SGA.

Weight loss in 1 month	Points	Weight loss in 6 months
10% or greater	4	20% or greater
5-9.9%	3	10- 19.9%
3-4.9%	2	6- 9.9%
2-2.9%	1	2- 5.9%
0-1.9%	0	0- 1.9%

Numerical score from Worksheet 1 ☐

Additive Score of Boxes 1-4 (See Side 1) ☐ **A**

5. Worksheet 2 – Disease and its relation to nutritional requirements:

Score is derived by adding 1 point for each of the following conditions:

- ☐ Cancer
- ☐ AIDS
- ☐ Pulmonary or cardiac cachexia
- ☐ Chronic renal insufficiency
- ☐ Presence of decubitus, open wound or fistula
- ☐ Presence of trauma
- ☐ Age greater than 65

Other relevant diagnoses (specify) _____

Primary disease staging (circle if known or appropriate) I II III IV Other ____

Numerical score from Worksheet 2 ☐ **B**

6. Worksheet 3 – Metabolic Demand

Score for metabolic stress is determined by a number of variables known to increase protein & caloric needs. **Note:** Score fever intensity or duration, whichever is greater. The score is additive so that a patient who has a fever of 38.8 ºC (3 points) for < 72 hrs (1 point) and who is on 10 mg of prednisone chronically (2 points) would have an additive score for this section of 5 points.

Stress	none (0)	low (1)	moderate (2)	high (3)
Fever	no fever	> 99 and < 101	≥ 101 and < 102	≥ 102 ºF
Fever duration	no fever	< 72 hours	72 hours	> 72 hours
Corticosteroids	no corticosteroids	low dose (< 10 mg prednisone equivalents/day)	moderate dose (≥ 10 and < 30 mg prednisone equivalents/day)	high dose (≥ 30 mg prednisone equivalents/day)

Numerical score from Worksheet 3 ☐ **C**

7. Worksheet 4 – Physical Exam

Exam includes a subjective evaluation of 3 aspects of body composition: fat, muscle, & fluid. Since this is subjective, each aspect of the exam is rated for degree. Muscle deficit/loss impacts point score more than fat deficit/loss. Definition of categories: 0 = no abnormality, 1+ = mild, 2+ = moderate, 3+ = severe. Rating in these categories is *not* additive but are used to clinically assess the degree of deficit (or presence of excess fluid).

Muscle Status		Fat Stores	
temples (temporalis muscle)	0 1+ 2+ 3+	orbital fat pads	0 1+ 2+ 3+
clavicles (pectoralis & deltoids)	0 1+ 2+ 3+	triceps skin fold	0 1+ 2+ 3+
shoulders (deltoids)	0 1+ 2+ 3+	fat overlying lower ribs	0 1+ 2+ 3+
interosseous muscles	0 1+ 2+ 3+	**Global fat deficit rating**	**0 1+ 2+ 3+**
scapula (latissimus dorsi, trapezius, deltoids)	0 1+ 2+ 3+	**Fluid status**	
thigh (quadriceps)	0 1+ 2+ 3+	ankle edema	0 1+ 2+ 3+
calf (gastrocnemius)	0 1+ 2+ 3+	sacral edema	0 1+ 2+ 3+
Global muscle status rating	**0 1+ 2+ 3+**	ascites	0 1+ 2+ 3+
		Global fluid status rating	**0 1+ 2+ 3+**

Point score for the physical exam is determined by the overall subjective rating of the total body deficit.

No deficit	score = 0 points
Mild deficit	score = 1 point
Moderate deficit	score = 2 points
Severe deficit	score = 3 points

Again, muscle deficit/loss takes precedence over fat loss or fluid excess.

Numerical Score for Worksheet 4 ☐ **D**

Total PG-SGA Score (Total numerical score of A+B+C+D) ☐

Clinician Signature _____ RD RN PA MD DO Other _____ Date _____

Global PG-SGA Category Rating (Stage A, Stage B or Stage C) ☐

Worksheet 5 – PG-SGA Global Assessment Categories

	Stage A	Stage B	Stage C
Category	**Well-nourished**	**Moderate/suspected malnutrition**	**Severely malnourished**
Weight	No weight loss **OR** recent non-fluid wt gain	≤ 5% loss in 1 month (≤10% in 6 months) **OR** Progressive weight loss	> 5% loss in 1 month (>10% in 6 months) **OR** Progressive weight loss
Nutrient intake	No deficit **OR** Significant recent improvement	Definite decrease in intake	Severe deficit in intake
Nutrition Impact Symptoms (NIS)	None **OR** significant recent improvement allowing adequate intake	Presence of NIS (Box 3 of PG-SGA)	Presence of NIS (Box 3 of PG-SGA)
Functioning	No deficit **OR** Significant recent improvement	Moderate functional deficit **OR** Recent deterioration	Severe functional deficit **OR** Recent significant deterioration
Physical Exam	No deficit **OR** chronic deficit but with recent clinical improvement	Evidence of mild to moderate loss of muscle mass &/or muscle tone on palpation &/or loss of SQ fat	Obvious signs of malnutrition (e.g., severe loss muscle, fat, possible edema)

Nutritional Triage Recommendations: Additive score is used to define specific nutritional interventions including patient & family education, symptom management including pharmacologic intervention, and appropriate nutrient intervention (food, nutritional supplements, enteral, or parenteral triage).

First line nutrition intervention includes optimal symptom management.

Triage based on PG-SGA point score

- **0-1** No intervention required at this time. Re-assessment on routine and regular basis during treatment.
- **2-3** Patient & family education by dietitian, nurse, or other clinician with pharmacologic intervention as indicated by symptom survey (Box 3) and lab values as appropriate.
- **4-8** Requires intervention by dietitian, in conjunction with nurse or physician as indicated by symptoms (Box 3).
- **≥ 9** Indicates a critical need for improved symptom management and/or nutrient intervention options.

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Appendix V

Functional Assessment of Anorexia/Cachexia Therapy (FAACT)

Patient ID_____ Patient Initials_____ Date_____

FAACT (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 <u>past 7 days</u>.**

	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

FAACT (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

FAACT (Version 4)

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

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C6	I have a good appetite	0	1	2	3	4
ACT1	The amount I eat is sufficient to meet my needs	0	1	2	3	4
ACT2	I am worried about my weight	0	1	2	3	4
ACT3	Most food tastes unpleasant to me	0	1	2	3	4
ACT4	I am concerned about how thin I look	0	1	2	3	4
ACT6	My interest in food drops as soon as I try to eat	0	1	2	3	4
ACT7	I have difficulty eating rich or "heavy" foods	0	1	2	3	4
ACT9	My family or friends are pressuring me to eat	0	1	2	3	4
O2	I have been vomiting	0	1	2	3	4
ACT10	When I eat, I seem to get full quickly	0	1	2	3	4
ACT11	I have pain in my stomach area	0	1	2	3	4
ACT13	My general health is improving	0	1	2	3	4