**Alliance for Clinical Trials in Oncology- Chicago Office**
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allianceforclinicalrialsinoncology.org

July 25, 2022

Sanjay Mohan, MD, MSCI
Chair, NCI Adult CIRB - Late Phase Emphasis

Re: CIRB Approval Pending Modification of Initial Review of A021806 (PVD 07/01/22)

Dear Dr. Mohan:

On July 20, 2022, the NCI Adult CIRB - Late Phase Emphasis reviewed A021806 Protocol Version Date 07/01/22 and granted approval pending modification. The CIRB determined that the regulatory and CIRB SOP requirements for approval are met, but the CIRB requests minor, directed modifications. Our responses to the CIRB's review letter received on July 21, 2022, are provided below in bold.

Thank you for your review. Please let us know what further information we may provide.

Sincerely,

Cristina Ferrone, MD
Alliance A021806 Study Chair

Ardaman Shergill MD MSPH
GI Committee Executive Officer, Alliance

Cc: E. Paskett, Ph. D.; M. Kelly, MA; A. Shergill, MD, MSPH; J. Taylor, MA

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A response to the following is required:

**Consent Form(s):**

1. Page 14, under "Optional quality of life study – physical and emotional well-being surveys", correct the 4th paragraph prompt which precedes the second set of 5 bullets to state "If you are in Group 2, you will be asked to fill out this form at 5 times:" This correction is in keeping with protocol section 14.1.3.

**RESPONSE: The 4th paragraph prompt, which precedes the second set of 5 bullets has been corrected to state Group 2.**

**ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY**

# PROTOCOL UPDATE TO ALLIANCE A021806

## A PHASE III TRIAL OF PERIOPERATIVE VERSUS ADJUVANT CHEMOTHERAPY FOR RESECTABLE PANCREATIC CANCER

| | | | |
|---|---|---|---|
| [X] | **Update:** | [ ] | **Status Change:** |
| [X] | Eligibility changes | [ ] | Activation |
| [ ] | Therapy / Dose Modifications / Study Calendar changes | [ ] | Closure |
| [X] | Informed Consent changes | [ ] | Suspension / temporary closure |
| [ ] | Scientific / Statistical Considerations changes | [ ] | Reactivation |
| [X] | Data Submission / Forms changes | | |
| [X] | Editorial / Administrative changes | | |
| [ ] | Other: | | |

***No recommended IRB level of review is provided by the Alliance since the CIRB is the IRB of record for this trial.***

***The site has 30 days after the posting of this amendment to implement it at their site. Please refer to the amendment application and CIRB guidelines for further instructions.***

**UPDATES TO THE PROTOCOL:**

**Cover Page (p. 1)**

- The IND status has been updated to Exempt.
- The ClinicalTrials.gov Identifier, "NCT04340141," has been added.
- Jamie Crawley has replaced Alexandra Levasseur as Protocol Coordinator.

**Study Resources (p. 2)**

- In the Study Resources table, under 'Expedited Adverse Event Reporting', the CTEP-AERS URL has been replaced with: https://ctepcore.nci.nih.gov/ctepaers.
- The contact information for IROC Ohio has been updated.
- Maria Andrea Monckeberg has replaced Zoe Mgo as the Pharmacy Liasison.

**CTSU Contact Information (p. 3)**

- CTSU Address and Contact information table has been updated with the current CTSU template language.

**Section 3.0 Patient Selection**

- "Psychiatric illness which would prevent the patient from giving informed consent and/or in the absence of a healthcare proxy to ensure the patient would be able to participate" has been removed from the On-Study Guidelines to comply with the current Alliance model protocol template

**Section 4.0 Patient Registration**

- Sections 4.2, 4.2.3 and 4.5 have been updated to align with the current CTSU boilerplate language.

**Section 6.0 Data and Specimen Submission**

- Sections 6.1 and 6.1.1 have been updated per the current CTSU template.
- Section 6.3.1.1 has been updated per the current CTSU template.
- Section 6.6 has been created to incorporate the following ICAREdata language:

  **Selected sites will be participating in the ICAREdata® project. - The Integrating Clinical Trials and Real-world Endpoints data (ICAREdata) initiative is a program led by the Alliance Data Innovation Lab which is a component of the Alliance for Clinical Trials in Oncology.**

  **The ICAREdata® project aims to expand the ability to achieve clinical research goals by providing new ways to collect data required for clinical trials. Today, virtually all clinical trials data are collected using special forms and computer applications, such as a software known as Medidata Rave. Instead of using these "add on" data collection systems, the ICAREdata project will gather study data directly from the Electronic Health Record (EHR). As with all research data collections, data collected by the ICAREdata project are stored in a secured repository.**

  **Select institutions will be invited to participate and will receive training on the specific ICAREdata® requirements. As with all clinical trials data management, the nature of data collected using the ICAREdata methods will be specific to a particular research protocol, and might include demographic information, diagnosis, laboratory values, physician assessments, and other results, such as adverse event reports. The Data Innovation Lab will manage data collection, working with the IT department at these sites to configure the EHR to deliver mCODE (minimal common oncology data elements) data and other required outcome data in the form of structured ICAREdata questions. Clinicians will provide the study required data by answering standardized questions or data fields as part of their encounter visit with the subjects. The IT departments will also work to implement the data transfer capability from the site EHR to the Alliance Data Innovation Lab via a secure/tested extraction method.**

  **Investigators and research staff at limited select sites that utilize the EHR research adverse events data collection tool will be asked to complete a brief voluntary survey. The research staff and investigator's email addresses at these predetermined sites will be submitted at the time of Adverse Events data collection tool training. The survey will take approximately 5 minutes to complete. It will solicit feedback on the investigators and study staff experiences including overall staff acceptance, usability, preferences for using the tool to document any adverse events. The plan survey administration timeline is at baseline and then a select period thereafter. Ultimately, the survey will be used to gather general feedback of the usability of the tool across multiple site level stakeholders.**

**Data will be encrypted at-rest and in-transit using a secure interface with an established authorization protocol handled by the ICAREdata infrastructure. Alliance Data Lab staff will issue a client ID and credentials to participating ICAREdata sites that will be used to authenticate those sites for access to the ICAREdata infrastructure service/extraction method to submit data. The clinical site will be responsible for securely storing these credentials (e.g., installed on a server that an IT administrator manages) such that those staff responsible for submitting data will have the proper access. Data will be stored and maintained in HIPAA compliant data repositories (such as AWS) and access controlled by an identity server with strict management to ensure confidentiality, integrity, and availability of PHI. Strict access controls will be maintained. Only authorized Alliance Data Lab personnel will have access to the data and scope of access will be further controlled based on role and level of need to know.**

**Participating institutions may email the Alliance Data Innovation Lab at ICAREdata@alliancefoundationtrials.org with any questions.**

**Section 13.7 Inclusion of Women and Minorities**

- The ethnic and racial categories lists have been removed to align with the current Alliance model protocol template.

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**UPDATES TO THE MODEL CONSENT:**

**Title Page (p. 1)**
The ClinicalTrials.gov Identifier, "NCT04340141," has been added.

**Who will see my medical information? (p. 11-12)**
The following ICAREdata language has been added:

**Alliance for Clinical Trials in Oncology and Alliance Data Innovation Lab**

**The Alliance for Clinical Trials in Oncology and Alliance Data Innovation Lab, (a component of Alliance), are working on a special project called ICAREdata®. The goal of the ICAREdata® project is to develop ways to make it easier to provide health information that is necessary to answer research questions in future studies.**

**As a part of the main study your doctor will be collecting information about your health and your study treatments. This information is usually collected using a system that is separate from your hospital health record. The ICAREdata® study is being done to see if there is an easier, simpler way to collect your health information for research studies. The health information being collected by ICARE data® is limited to the same information that would usually be collected from your hospital health record when you participate in a research study. To do this, the study will also collect your health information pertaining to this clinical trial directly from your hospital or medical center's health records. The study may also compare these two ways of collecting your health information. The researchers will see if these two ways of reporting health information give the same result. This research may help to create a way to collect health information that is much faster and easier than how it is currently collected. If these two ways of collecting health information give the same result, then the easier ICAREdata methods can be used in future studies.**

**As part of this research study your health information pertaining to this clinical trial will be collected directly from your hospital health records. The information will be sent electronically in a secure record file to the Alliance Data Innovation Lab. This information will be compared to the information collected in the usual way for research as described above. Your health information will become a part of research data that is being used to improve data collection in people with cancer.**

**Your privacy is very important to the study researchers. They will make every effort to protect it. Here are just a few of the steps they will take:**

- **All identifiers, such as your name, initials, and contact information will be removed from your health information. Your name will be replaced with a code number. There will be a master list linking the code numbers to names, but they will keep it separate from the rest of the information.**
- **Researchers outside of the Alliance Data Innovation Lab who study your information will not know who you are. They also must agree that they will not try to find out who you are.**
- **Your personal information will not be given to anyone unless it is required by law.**
- **If research results are published, your name and other personal information will not be used.**

**After identifiers have been removed, your information may be shared with other researchers (researchers who are not part of the Alliance Data Innovation Lab). Your health information will only be used for research in preventing, diagnosing, and treating cancer, or improving the health of people with cancer.**

**<u>Optional quality of life study – physical and emotional well-being surveys (p.14)</u>**

The 4th paragraph prompt, which precedes the second set of 5 bullets has been changed from Group "1" to Group "2".

**A replacement protocol and consent document have been issued.**

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**ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL**

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ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A021806

# A PHASE III TRIAL OF PERIOPERATIVE VERSUS ADJUVANT CHEMOTHERAPY FOR RESECTABLE PANCREATIC CANCER

*Commercial agents: 5-Fluorouracil (NSC#19893); Leucovorin Calcium (NSC#3590); Oxaliplatin (NSC#266046); Irinotecan (NSC#616348)*
*IND Exempt*

**ClinicalTrials.gov Identifier: NCT04340141**


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Participating NCTN Groups: Alliance / Alliance for Clinical Trials in Oncology (lead), CCTG/ Canadian Cancer Trials Group, ECOG-ACRIN / ECOG-ACRIN Cancer Research Group, NRG / NRG Oncology, SWOG / SWOG

## Study Resources

| | |
|---|---|
| **Expedited Adverse Event Reporting**<br>https://ctepcore.nci.nih.gov/ctepaers | **Medidata Rave® iMedidata Portal**<br>https://login.imedidata.com |
| **OPEN (Oncology Patient Enrollment Network)**<br>https://open.ctsu.org | **Biospecimen Management System**<br>http://bioms.allianceforclinicaltrialsinoncology.org |

## Protocol Contacts

**A021806 Nursing Contact**
Barbara Kleiber, RN
The Ohio State University
Tel: 614-293-1815
*barbara.kleiber@osumc.edu*

**A021806 Pharmacy Liaison**
Maria Andrea Monckeberg, MS, RPh, BCOP Rhode Island Hospital Tel: 401.444.2824
*mamonckeberg@lifespan.org*

**Alliance Biorepository at Washington University**
Washington University at St. Louis
BJC Institute of Health
425 S. Euclid Ave., Room 1H-05-135
St. Louis, MO 63110-1005
Tel: 314-454-7615 Fax: 314-454-5525
*tbank@wudosis.wustl.edu*

**IROC Ohio (Alliance Imaging Core Lab)**
The Ohio State University
Wright Center of Innovation
395 W. 12th Ave., RM #428
Columbus, OH 432140
Tel: 614-293-2929 Fax: 614-293-9275
*Alliance021806@irocohio.org*

| **Protocol-related questions may be directed as follows:** | |
|---|---|
| **Questions** | **Contact (via email)** |
| Questions regarding patient eligibility, treatment, and dose modification: | Study Chair, Nursing Contact, Protocol Coordinator, and (where applicable) Data Manager |
| Questions related to data submission, RAVE or patient follow-up: | Data Manager |
| Questions regarding the protocol document and model informed consent: | Protocol Coordinator |
| Questions related to IRB review: | Alliance Regulatory Inbox<br>regulatory@allianceNCTN.org |
| Questions regarding CTEP-AERS reporting: | Alliance Pharmacovigilance Inbox<br>pharmacovigilance@alliancenctn.org |
| Questions regarding specimens/specimen submissions: | Alliance Biorepository at Washington University |
| Questions regarding drug administration: | Pharmacy Liaison |

## CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

| **For regulatory requirements:** | **For patient enrollments:** | **For data submission:** |
|---|---|---|
| Regulatory documentation must submitted to the Cancer Trials Support Unit (CTSU) v via the Regulatory Submission Portal:<br><br>(Sign in at https://www.ctsu.org, and select the Regulatory > Regulatory Submission.)<br><br>Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support.<br><br>Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878) for regulatory assistance. | Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org.<br><br>Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com. | Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions. |
| The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS). | | |
| Supplies can be ordered by downloading and completing the CTSU Supply Request Form (available on the protocol-specific page on the CTSU website) and submitting it as specified on the form. | | |
| **For clinical questions (i.e. patient eligibility or treatment-related)** see Protocol Contacts, Page 2. | | |
| **For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission)** contact the CTSU Help Desk by phone or e-mail:<br>CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative. | | |
| **The CTSU website is located at** https://www.ctsu.org. | | |

**A Phase III Trial of Perioperative versus Adjuvant Chemotherapy for Resectable Pancreatic Cancer**

**Pre-registration Eligibility Criteria (see Section 3.2)**

- Histologic or cytologic proof of pancreatic adenocarcinoma or adenosquamous carcinoma
- TNM Stage: Tx-4, N0-1, M0
- Local radiographic reading consistent with resectable disease
- Measurable disease and/or non-measurable disease

**Registration Eligibility Criteria (see Section 3.3)**

- Confirmation of resectable disease by real-time central imaging review by the Alliance Imaging Core Lab at IROC Ohio
- Determined to be appropriate candidate for curative-intent pancreatectomy
- No prior radiation therapy, chemotherapy, targeted therapy, investigational therapy or surgery for pancreatic cancer
- Not pregnant and not nursing
- Age ≥ 18 years
- ECOG Performance Status 0-1
- Total Neuropathy Score < 2
- No known Gilbert's Syndrome or known homozygosity for UGATA1A1*28 polymorphism
- No comorbid conditions that would prohibit curative-intent pancreatectomy
- Chronic concomitant treatment with strong inhibitors and/or inducers of CYP3A4 is not allowed.

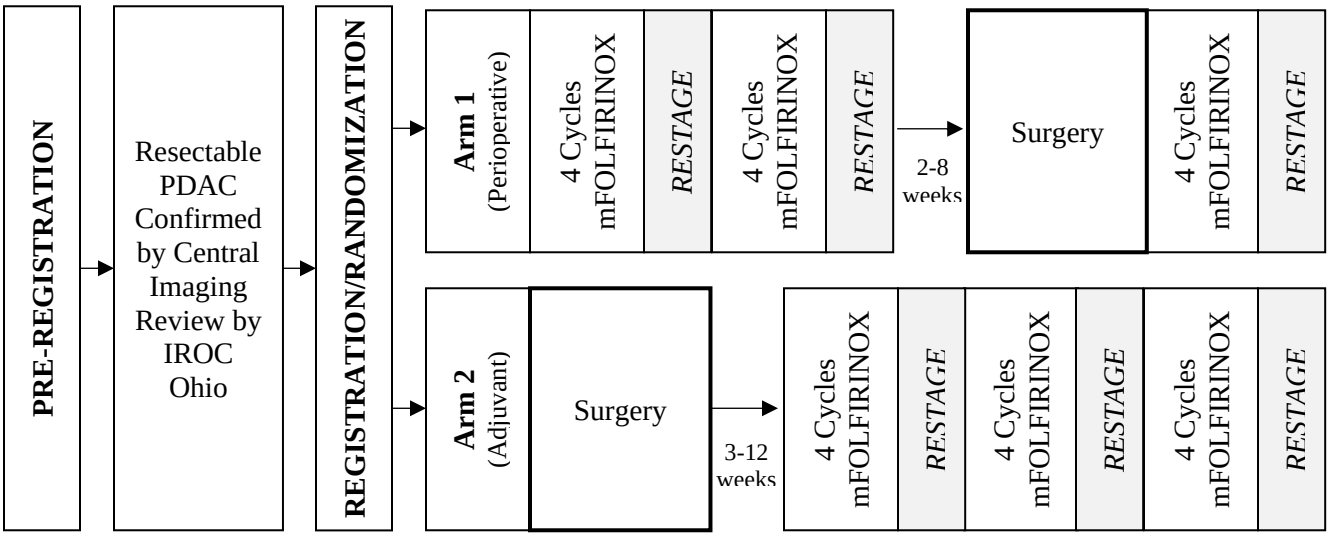
**Required Initial Laboratory Values:**

| | |
|---|---|
| Absolute Neutrophil Count: | ≥ 1500/µL |
| Platelet Count: | ≥ 100,000/µL |
| Total Bilirubin: | ≤ 1.5 x upper limit of normal (ULN)* |
| Creatinine: | ≤ 1.5 x ULN |
| **OR** | |
| Calc. CrCl: | ≥ 30 mL/min** |

*If obstructive jaundice present, biliary drainage must be initiated and Total Bilirubin ≤ 3.0
**Calculated using the Cockcroft-Gault equation

**Schema**

One Cycle = 14 Days




Treatment/intervention is to continue as outlined above or until disease recurrence, unacceptable toxicity, or withdrawal of consent. Patients will be followed for 6 years or until death, whichever comes first.

**Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.**

Imaging and surgery must be performed at the registering institution. Chemotherapy may be administered at a non-registering institution. If the Group credited for enrollment is a non-Alliance Group, then other requirements from the credited Group may apply.

## Table of Contents

# 1.0 BACKGROUND

## 1.1 Background and Rationale for Trial Design

Pancreatic adenocarcinoma (PDAC) is the 4th most common cause of cancer death in the United States with a quarter of patients alive after a year and only 7% achieving survival greater than 5 years [1]. Standard of care for patients with resectable PDAC is an operation followed by adjuvant chemotherapy which has been shown to improve survival [2]. Unfortunately, nearly half of patients fail to complete chemotherapy after pancreatectomy [3]. This has led to an increased interest in the use of neoadjuvant therapy. Pre-operative chemotherapy is currently recommended in consensus guidelines for borderline resectable disease to address occult micrometastatic disease, improve compliance with chemotherapy, potentially downstage tumors, increase R0 resection rates, and better select patients who will benefit from a resection [4, 5]. Preliminary results from the recently reported PREOPANC-1 randomized phase III trial demonstrated that patients with resectable and borderline resectable PDAC perform better in terms of survival if gemcitabine-based therapy is given in the neoadjuvant versus adjuvant setting [6].

In addition to the appropriate setting in which to deliver chemotherapy, the optimal chemotherapeutic regimen remains to be elucidated for patients with PDAC. FOLFIRINOX is superior to gemcitabine in advanced pancreatic cancer [7]. Additionally, the recently reported PRODIGE24/CCTG PA.6 trial demonstrated that modified FOLFIRINOX (mFOLFIRINOX) was superior to gemcitabine in the adjuvant setting [2]. These data support the use of FOLFIRINOX as the standard chemotherapy regimen for patients who can tolerate the increased associated toxicity of this regimen.

The use of FOLFIRINOX in the neoadjuvant setting has shown promise. Neoadjuvant FOLFIRINOX decreases nodal positivity, increases margin-negative resection rates, and improves overall survival in a retrospective analysis of borderline resectable patients [8]. A recent phase II trial from Massachusetts General Hospital demonstrated that neoadjuvant FOLFIRINOX x 8 cycles in patients with borderline resectable disease was well tolerated and led to margin-negative resection rates in greater than 90% of patients who underwent resection [9].

Although upfront resectable PDAC by radiologic criteria demonstrates no clinical evidence of distant disease, up to 17% have occult metastatic disease identified at the time of the operation and over 70% of patients are found to have nodal metastases on pathology after resection [10, 11]. In addition, only 19% are alive at 5 years after curative-intent pancreatectomy [12, 13]. These data favor the principal that the majority of patients with upfront resectable PDAC have occult micrometastatic disease at presentation. The current standard of care for patients with upfront resectable PDAC involves an operation followed by adjuvant chemotherapy [14]. A propensity-matched analysis of over 15,000 patients with upfront resectable disease from the National Cancer Database demonstrated that neoadjuvant therapy has a significant survival benefit in early-stage, resected pancreatic head adenocarcinoma [15].

While the use of neoadjuvant chemotherapy may have benefits, there is concern that patients who undergo systemic therapy first with no clinical evidence of systemic disease may lose an opportunity, or "window," for their primary tumor to be resected if there is disease progression during the period of neoadjuvant therapy. Data from a prospective single-arm trial evaluating neoadjuvant gemcitabine and oxaliplatin in resectable pancreatic cancer in which diagnostic laparoscopy to exclude metastatic disease was performed prior to the start of neoadjuvant therapy demonstrated a rate of resectability of 77% [16]. Resectability rates of 89% were seen from another prospective trial with a similar design using laparoscopy followed by neoadjuvant

gemcitabine and cisplatin [17]. These data may suggest that a significant percentage of patients may progress during therapy. However, an alternative hypothesis supports the notion that such patients that progress during systemic therapy likely have occult micrometastatic disease with an aggressive disease biology that likely existed at the time of laparoscopy. Nevertheless, there is considerable equipoise within the surgical and medical oncology community with regards to the use of neoadjuvant chemotherapy in the resectable population.

We propose a randomized phase III trial comparing perioperative mFOLFIRINOX versus adjuvant mFOLFIRINOX therapy for patients with resectable PDAC. Specifically, this trial design compares treatment with neoadjuvant mFOLFIRINOX followed by an operation and completion of adjuvant therapy versus an up-front operation followed by adjuvant mFOLFIRINOX. We hypothesize that patients who receive perioperative mFOLFIRINOX will have a higher 2-year OS rate in comparison to those treated with adjuvant mFOLFIRINOX for the following reasons: 1) increased rates of tolerability of FOLFIRINOX in the neoadjuvant setting; 2) increased R0 resection rates after neoadjuvant FOLFIRINOX; 3) enhanced delivery of multi-modality therapy to more patients; and 4) low rate of receiving or completing chemotherapy in the adjuvant setting.

### 1.2 Pertinent Existing Data

A trial investigating a neoadjuvant strategy utilizing FOLFIRINOX in resectable PDAC is timely and would standardize how to best treat this subgroup of patients. Current existing data supports the use of combination chemotherapy for resectable pancreatic cancer.

FOLFIRINOX has previously been shown to be superior to gemcitabine in the metastatic setting, and recently in the adjuvant setting for patients with resected PDAC [2, 7]. The PRODIGE24/CCTG PA.6 trial, which randomized patients after an operation, demonstrated that FOLFIRINOX in the adjuvant setting was superior to gemcitabine in patients with good performance status. In this trial, the mFOLFIRINOX regimen (no bolus fluorouracil, dose-reduced irinotecan) demonstrated a median OS of 54.4 months compared to 35.0 months in patients who received gemcitabine [2].

A strategy involving neoadjuvant chemotherapy has been shown to be superior to adjuvant chemotherapy in resectable and borderline resectable PDAC. Preliminary results from the recently reported randomized phase III PREOPANC-1 trial demonstrated that in patients with resectable and borderline resectable PDAC, neoadjuvant therapy is superior to adjuvant therapy using gemcitabine chemotherapy [4]. This landmark study demonstrated a median OS of 29.9 months for patients who underwent neoadjuvant gemcitabine (plus gemcitabine-based chemoradiation) followed by curative-intent surgery compared to 16.8 months in patients who received adjuvant gemcitabine after resection. The results from the trial proposed herein would be anticipated to show superior outcomes given the proposed use of mFOLFIRINOX over gemcitabine which was utilized in the PREOPANC-1 trial.

The JSAP-05 trial demonstrated superiority of gemcitabine + S-1 in the neoadjuvant setting for resectable and borderline resectable pts with vein involvement [18]. The trial randomized 364 pts, to either neoadjuvant chemotherapy with gemcitabine plus S-1 followed by resection followed by adjuvant S-1 or to surgical resection followed by adjuvant S-1 therapy. The neoadjuvant therapy arm demonstrated a median overall survival of 36.72 months compared with 26.65 months in the adjuvant therapy only arm.

A phase II trial using total neoadjuvant therapy with 8 cycles FOLFIRINOX plus individualized chemoradiotherapy in patients with borderline resectable PDAC led to an R0 resection in 31 of 32 patients who underwent resection [8]. Patients who were resected demonstrated favorable

outcomes in terms of survival with a 2-year disease free survival rate of 55% and overall survival rate of 72%.

Collectively, a trial investigating a neoadjuvant strategy utilizing FOLFIRINOX in resectable PDAC is timely and would standardize how to best treat this subgroup of patients.

### 1.3 Trial Importance

Identifying the optimal sequencing of therapy in resectable PDAC is an area that urgently needs further investigation in a cooperative group trial setting. Even with modern surgical techniques and contemporary systemic therapy, margin-negative pancreatectomy followed by standard adjuvant chemotherapy leads to unacceptably high rates of recurrence with a small minority of patients achieving long-term survival. Given the high rate of nodal metastases as well as distant recurrence in upfront resectable PDAC, the optimal strategy in delivering systemic therapy needs further study.

The importance of investigating a strategy involving neoadjuvant FOLFIRINOX in the upfront resectable disease population is underscored by the recent level one evidence demonstrating the superiority of a neoadjuvant strategy over an adjuvant strategy in PDAC utilizing gemcitabine chemotherapy. Yet, gemcitabine is not the optimal chemotherapeutic regimen when compared to FOLFIRINOX in the adjuvant setting for patients randomized post operatively. Although FOLFIRINOX therapy has been associated with increased toxicity, receiving this therapy prior to an operation has been prospectively shown to lead to high rates of tolerability (>80%) in addition to an R0 resection in 90% of those who are able to undergo pancreatectomy in a single institution phase II trial [8]. This data, in combination with evidence demonstrating that only half of patients are able to complete therapy in the adjuvant setting after pancreatectomy, further highlights the importance of investigating this strategy in a prospectively randomized fashion [3].

This trial does not directly compete with other ongoing trials, as this study uniquely investigates the sequencing of mFOLFIRINOX in patients with resectable PDAC. There is currently no level one evidence in support for or against the use of mFOLFIRINOX perioperatively as compared to adjuvantly in patients with resectable PDAC. An outcome demonstrating superiority of neoadjuvant FOLFIRINOX from this trial would be practice changing and would most certainly change the standard of care for patients with resectable PDAC.

In addition to OS, the trial will also address key issues including the effect of perioperative and adjuvant therapy on DFS and R0 resection rates when patients are randomized at the time of diagnosis. The ability to tolerate chemotherapy in the neoadjuvant versus the adjuvant setting will also be clarified.

## 2.0 OBJECTIVES

### 2.1 Primary Objective

To evaluate and compare overall survival (OS) in patients with resectable pancreatic adenocarcinoma treated with perioperative mFOLFIRINOX and surgery versus up-front surgery followed by adjuvant mFOLFIRINOX

### 2.2 Secondary Objectives

**2.2.1** To evaluate and compare disease-free survival (DFS) in patients with resectable pancreatic adenocarcinoma treated with perioperative mFOLFIRINOX and surgery versus up-front surgery followed by adjuvant mFOLFIRINOX

**2.2.2** To evaluate and compare time to locoregional recurrence (TLR) in patients with resectable pancreatic adenocarcinoma treated with perioperative mFOLFIRINOX and surgery versus up-front surgery followed by adjuvant mFOLFIRINOX

**2.2.3** To evaluate and compare time to distant metastases (TDM) in patients with resectable pancreatic adenocarcinoma treated with perioperative mFOLFIRINOX and surgery versus up-front surgery followed by adjuvant mFOLFIRINOX

**2.2.4** To evaluate and compare the R0 resection rate in patients with resectable pancreatic adenocarcinoma treated with perioperative mFOLFIRINOX and surgery versus up-front surgery followed by adjuvant mFOLFIRINOX

**2.2.5** To evaluate and compare rate of unresectability in patients with resectable pancreatic adenocarcinoma treated with perioperative mFOLFIRINOX and surgery versus up-front surgery followed by adjuvant mFOLFIRINOX

**2.2.6** To evaluate rate of pathologic complete response in patients randomized to the perioperative therapy arm

**2.2.7** To evaluate and compare mFOLFIRINOX dose intensity delivered and number of cycles received in patients with resectable pancreatic adenocarcinoma treated with perioperative mFOLFIRINOX and surgery versus up-front surgery followed by adjuvant mFOLFIRINOX

**2.2.8** To evaluate and compare adverse event profile in patients with resectable pancreatic adenocarcinoma treated with perioperative mFOLFIRINOX and surgery versus up-front surgery followed by adjuvant mFOLFIRINOX

**2.2.9** To compare physical functioning, nausea/vomiting, and diarrhea, as measured with the EORTC QLQ-C30 between patients with resectable pancreatic adenocarcinoma treated with perioperative mFOLFIRINOX and surgery versus up-front surgery followed by adjuvant mFOLFIRINOX

**2.2.10** To prospectively assess the influence of diet, body mass index, weight loss, physical activity, and other lifestyle habits on the disease-free survival and overall survival among patients with localized pancreatic cancers

**2.2.11** To assess the influence of diet, obesity, physical activity, and other lifestyle habits on the risk of toxicity associated with chemotherapy

**2.2.12** To evaluate the ability of CT-based radiomics in distinguishing post-neoadjuvant chemotherapy (NAC) fibrosis from viable tumor in patients randomized to the perioperative therapy arm

**2.2.13** To determine whether CT-based radiomics retrieved from baseline examination may act as non-invasive predictors of survival outcome in patients randomized to the adjuvant therapy arm

### 2.3 Other Objective

Results of the primary analysis will be examined for consistency, while taking into account the stratification factors and/or covariates of baseline QOL and fatigue.

### 2.4 Exploratory Objective

**2.4.1** Exploratory analyses will investigate the interaction of diet and molecular markers within tumors on the prognosis of patients with localized pancreatic cancer.

## 3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

### 3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Medical condition such as uncontrolled infection, uncontrolled diabetes mellitus, or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers, breast ductal carcinoma in situ, or cervical carcinoma in situ. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for $\geq$ 2 years.

In addition:

- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).

### 3.2 Pre-Registration Eligibility Criteria (Step 0)

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

___ **3.2.1 Documentation of Disease**

**Pathology:** Histologic or cytologic proof of pancreatic adenocarcinoma or adenosquamous carcinoma.

**TNM Stage:** Tx-4, N0-1, M0*

*M0 disease does not include spread to distant lymph nodes and organs

**Resectable Primary Tumor:** Local radiographic reading must be consistent with resectable disease defined as the following on 1) arterial and venous phase contrast-enhanced abdominal/pelvic CT scan or abdominal/pelvic MRI scan **and** 2) chest CT:

- No involvement or abutment of the celiac artery, common hepatic artery, superior mesenteric artery, or replaced right hepatic artery (if applicable)
- Less than 180° interface between tumor and vessel wall of the portal vein or superior mesenteric vein, and patent portal vein/splenic vein confluence
- No evidence of metastatic disease

___ **3.2.2 Measurable disease or non-measurable disease as defined in Section 11.0.**

Non-measurable disease is defined as cytologic or histologic confirmation of adenocarcinoma of adenosquamous carcinoma by fine needle aspiration or core-biopsy of the pancreas without measurable disease by radiographic imaging.

## 3.3 Registration Eligibility Criteria (Step 1)

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e. has had menses at any time in the preceding 12 consecutive months).

___ **3.3.1 Disease Status**

Confirmation of resectable disease by real-time central imaging review by the Alliance Imaging Core Lab at IROC Ohio.

Determined to be appropriate candidate for curative-intent pancreatectomy by surgeon intending to perform the resection.

___ **3.3.2 Prior Treatment**

No prior radiation therapy, chemotherapy, targeted therapy, investigational therapy, or surgery for pancreatic cancer.

___ **3.3.3 Not pregnant and not nursing,** because this study involves an agent that has known genotoxic, mutagenic, and teratogenic effects.

Therefore, for women of childbearing potential only, a negative pregnancy test done ≤ 14 days prior to registration is required.

___ **3.3.4 Age ≥ 18 years**

___ **3.3.5 ECOG Performance Status 0-1**

___ **3.3.6 Total Neuropathy Score < 2**

___ **3.3.7 Required Initial Laboratory Values**

- Absolute Neutrophil Count (ANC) ≥ 1,500/µL
- Platelet Count ≥ 100,000/µL
- Total Bilirubin ≤ 1.5 x upper limit of normal (ULN)*
- Creatinine ≤ 1.5 x ULN

**OR**

Calc. Creatinine Clearance ≥ 30 mL/min**

*If obstructive jaundice is present, then biliary drainage must be initiated and Total Bilirubin ≤ 3.0.

**Calculated using the Cockcroft-Gault equation

___ **3.3.8 Comorbid Conditions**

No known Gilbert's Syndrome or known homozygosity for UGAT1A1*28 polymorphism.

No comorbid conditions that would prohibit curative-intent pancreatectomy.

___ **3.3.9 Concomitant Medications**

Chronic concomitant treatment with strong inhibitors of CYP3A4 is not allowed on this study. Patients on strong CYP3A4 inhibitors must discontinue the drug prior to registration. See Section 8.1.11 for more information.

Chronic concomitant treatment with strong inducers of CYP3A4 is not allowed on this study. Patients on strong CYP3A4 inducers must discontinue the drug prior to registration. See Section 8.1.12 for more information.

## 4.0 PATIENT REGISTRATION

### 4.1 Cancer Therapy Evaluation Program Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, Rave, or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR – MD, DO, or international equivalent;
- NPIVR – advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);

- AP – clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications (e.g., Roster Update Management System (RUMS), OPEN, Rave,);
- Associate (A) – other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) – individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

| Documentation Required | IVR | NPIVR | AP | A | AB |
|---|---|---|---|---|---|
| FDA Form 1572 | ✓ | ✓ | | | |
| Financial Disclosure Form | ✓ | ✓ | ✓ | | |
| NCI Biosketch (education, training, employment, license, and certification) | ✓ | ✓ | ✓ | | |
| GCP training | ✓ | ✓ | ✓ | | |
| Agent Shipment Form (if applicable) | ✓ | | | | |
| CV (optional) | ✓ | ✓ | ✓ | | |

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators act as the Site-Protocol PI, consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a participating organization (i.e., Alliance).

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

### 4.2 Cancer Trials Support Unit Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

**IRB Approval**

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at

the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria to complete processing of the IRB/REB approval record:

- Holds an Active CTEP status;
- Active status at the site(s) on the IRB/REB approval (*applies to US and Canadian sites only*) on at least one participating organization's roster;
- If using NCI CIRB, active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- Lists all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

**Additional Requirements**

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB signatory Institution (US sites only); and
- Compliance with all protocol-specific requirements (PSRs).

**Protocol Specific Requirements for A021806 Site Registration**

This is a study with a radiation and/or imaging (RTI) component and the enrolling site must be aligned to an RTI provider. To manage provider associations or to add or remove associated providers, access the Provider Association page from the Regulatory section on the CTSU members' website at https://www.ctsu.org/RSS/RTFProviderAssociation. Sites must be linked to at least one Imaging and Radiation Oncology Core (IROC) credentialed provider to participate on trials with an RTI component. Enrolling sites are responsible for ensuring that the appropriate agreements and IRB approvals are in place with their RTI provider. A primary role on any roster is required to update provider associations, though all individuals at a site may view provider associations. To find who holds primary roles at your site, please view the Person Roster Browser under the RUMS link on the CTSU website.

To complete protocol-specific credentialing the RT/I provider or enrolling site should follow instructions in the protocol to submit documentation or other materials to the designated IROC Quality Control (QC) center. Upon the IROC QC center approving the RT/I provider for the study modality, IROC will automatically send the approval to the Regulatory Support System (RSS) to comply the protocol specific requirement. IROC will continue to copy the provider and/or enrolling site on modality approvals.

Upon site registration approval in RSS, the enrolling site may access OPEN to complete enrollments. The enrolling site will select their credentialed provider treating the subject in the OPEN credentialing screen, and may need to answer additional questions related to treatment in the eligibility checklist.

### 4.2.1 Downloading Site Registration Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and its associated investigators and staff on a participating roster. To view/download site registration forms:

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of your screen
    - Enter the protocol number in the search field at the top of the protocol tree, or
    - Click on the By Lead Organization folder to expand, then select *Alliance*, and protocol number *A021806*;
- Click on *Documents*, *Protocol Related Documents, and* use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.)

### 4.2.2 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the *Regulatory* section and select *Regulatory Submission* Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org in order to receive further instruction and support.

### 4.2.3 Checking Site Registration Status

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration*; and
- Enter the site's 5-character CTEP Institution Code and click on Go:
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined above. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

#### 4.2.4 Credentialing

IROC Imaging Credentialing is required for all participating institutions.

See Section 15.0 for credentialing requirements.

### 4.3 Patient Pre-registration (Step 0) Requirements

**Informed Consent:** The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.

Patients with impaired decision making capacity may be enrolled on this study, where institutional policy and IRB of record allow.

After the patient has been pre-registered, the staging scans should be sent to IROC Ohio per Section 6.3 for real-time central imaging review and eligibility confirmation. Registration should occur within 21 days of pre-registration.

**Pre-registration Form:** Upon completion of the screening process, the Site is responsible for entering applicable data collected during Step 0, and using the "Pre-registration Form" in Medidata Rave®, irrespective of completing Step 1 of the enrollment process.

### 4.4 Patient Registration/Randomization (Step 1) Requirements

**Local Review of Case:** Patient case must be evaluated by a medical oncologist and surgeon prior to registration.

**Central Review Confirmation:** The Alliance Imaging Core Lab at IROC Ohio will notify the pre-registering site within 5 business days of receipt whether the patient is eligible based on the central imaging review. IROC Ohio will send an email confirmation to the pre-registering site whether the patient is eligible, and they will also carbon copy the Alliance Registration office. The Registration Office will open the gate for the patient registration to proceed. The radiology review will enter the central review results into Rave.

**Patient-completed Booklets:** Patient questionnaire booklets are to be ordered prior to the registration of any patients. Patient-completed booklets can be ordered by downloading and completing the CTSU supply request form (located under the site registration documents section of the A021806 CTSU website) and submitting it through the CTSU Regulatory Portal. Samples of the booklets are found in Appendix I which are to be used for reference and IRB submission only. They are not to be used for patient completion. There is one booklet for PRO-CTCAE which is required per the Study Calendar for all patients. There is a second QOL booklet for patients who consent for the Quality of Life study (A021806-HO1). There is no booklet for the Registration Fatigue/Uniscale Assessment (first page of Appendix I, required for all patients per the Study Calendar). If needed, the first page of Appendix I can be adapted to use as a source document.

**Diet and Lifestyle Questionnaires:** The Diet and Lifestyle Questionnaire booklets will be sent to the enrolling institution at the time of each patient registration to the A021806-HO2 substudy.

A sample of the booklets can be found on the Alliance and CTSU websites as separate documents, and they are to be used for reference and IRB submission only. They are not to be used for patient completion. The Diet and Lifestyle Questionnaires are available in English and French.

**Protected Health Information:** For local site HIPAA documentation, please note that the following personal health information (PHI) may be released outside of the Alliance.

- Tumor tissue for retrospective central pathology review
- Diet and Lifestyle Questionnaires for A021806-HO2 substudy

These tissue specimens will be sent to the A021806 Pathology Co-Chair, Dr. Wendy Frankel, at her laboratory at The Ohio State University. These tissue samples will be labeled with patient initials, patient ID, and collection date.

The Diet and Lifestyle Questionnaires collected for the A021806-HO2 substudy will be sent to the A021806 Diet and Lifestyle Co-Chair, Dr. Jeffrey Meyerhardt, at the Dana-Farber Cancer Institute. These booklets will be labeled with patient initials, patient ID, and collection date.

### 4.5 Patient Pre-registration and Registration/Randomization Procedures

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be on a LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrar(s) must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at

https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

To receive site reimbursement for specific tests and/or bio-specimen submissions, completion dates must be entered in the OPEN Funding screen post registration. Please refer to the protocol-specific funding page on the CTSU members' website for additional information. Timely entry of completion dates is recommended as this will trigger site reimbursement.

## 4.6 Registration to Correlative and Companion Studies

### 4.6.1 Registration to Substudies described in Section 14.0

There are three substudies within Alliance A021806. These correlative science studies must be offered to all patients enrolled on Alliance A021806 (although patients may opt to not participate). These substudies do not require separate IRB approval. The substudies included within Alliance A021806 are:

- Quality of Life Study, Alliance A021806-HO1 (Section 14.1)
- Diet and Lifestyle Study, Alliance A021806-HO2 (Section 14.2)
- Imaging Study, Alliance A021806-IM1 (Section 14.3)

If a patient answers "yes" to "I choose to take part in the quality of life study (physical and emotional well-being surveys) and will fill out these forms," Question #2 in the model consent, they have consented to participate in the substudy described in Section 14.1. The patient should be registered to Alliance A021806-HO1 at the same time they are registered to the treatment trial (A021806). Questionnaires should be submitted per Section 6.4.

If a patient answers "yes" to "I choose to take part in the quality of life study (diet and lifestyle surveys) and will fill out these forms," Question #3 in the model consent, they have consented to participate in the substudy described in Section 14.2. The patient should be registered to Alliance A021806-HO2 at the same time they are registered to the treatment trial (A021806). Questionnaires should be submitted per Section 6.5.

If a patient answers "yes" to "I choose to take part in the imaging study and will have my scans analyzed," Question #1 in the model consent, they have consented to participate in the substudy described in Section 14.3. The patient should be registered to Alliance A021806-IM1 at the same time they are registered to the treatment trial (A021806). Images should be submitted per Section 6.3.

## 4.7 Stratification Factors and Treatment Assignments

The stratification factors for this trial include the following:

- **Location of Tumor:** Pancreatic Head vs. Non-Head Tumors
- **ECOG Performance Status:** 0 vs. 1

The randomization routine is found in Section 13.0 (Statistical Considerations).

## 5.0 STUDY CALENDAR

Pre-Study Testing Intervals: The pre-study testing intervals are guidelines only. Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients on this trial.

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

To be completed ≤ 28 DAYS before pre-registration: Any scan which is utilized for tumor measurement.

To be completed ≤ 21 DAYS before registration: All laboratory studies, history and physical.

| | Prior to Pre-registration * | Prior to Registration * | Day 1 of Each Cycle of mFOLFIRINOX * | Surgery | Post-treatment Follow up ** |
|---|---|---|---|---|---|
| **Tests & Observations** | | | | | |
| H&P, weight, PS | | X | X(1) | | X |
| Height | | X | | | |
| Pulse, Blood Pressure | | X | X | X | |
| Adverse Event Assessment – CTCAE | | X | X | X | |
| Adverse Event Assessment – PRO-CTCAE | | X(2) | X(2) | A(2) | |
| Registration Fatigue/ Uniscale Assessment | | X(3) | | | |
| **Laboratory Studies** | | | | | |
| CBC w/ Differential, Platelets | | X | X | X | B |
| Chemistry (Creatinine, Electrolytes, AST, ALT, Alk. Phos., Albumin, Total Bilirubin) | | X | X | X | B |
| Serum or Urine HCG | | X(4) | | | |
| CA 19-9 | | C | C | C | X |
| **Staging** | | | | | |
| CT/MRI Chest/Abd/Pelvis | X(5) | D(5) | D(5) | D(5) | D(5) |
| **Correlative Studies: For patients who consent to participate** | | | | | |
| QOL Study (A021806-HO1) | *At baseline, during treatment, and end of chemotherapy; see Sections 6.4 and 14.1.* | | | | |
| Diet & Lifestyle Study (A021806-HO2) | *At baseline and then 1 year after registration; see Sections 6.5 and 14.2.* | | | | |
| Imaging Study (A021806-IM1) | *Images will be collected for retrospective analyses; see Section 14.3.* | | | | |
| A021806 Biobanking | *Blood and tissue samples will be collected; see Sections 6.2 and 14.4.* | | | | |

* Labs, tests, and observations completed prior to registration may be used for Day 1 of Cycle 1 tests for Arm 1 patients if obtained ≤ 7 days prior to treatment. For subsequent cycles, labs, tests, and observations may be obtained ≤ 72 hours prior to day of treatment. Scans may be obtained +/- 7 days from scheduled day of assessment.

** Physical examination, labs, and staging scans are required every 16 weeks (+/- 1 month) until 2 years after registration or until disease recurrence; thereafter, survival information is required every 6 months until 6 years after registration. For patients who discontinue treatment for progressive/recurrent disease or are removed from protocol therapy, survival information is required every 6 months for 6 years after registration; see Section 12.0.

1 Drug dosages do not need to be changed unless the calculated dose changes by ≥ 10%.

2 Patients complete PRO-CTCAE by paper booklet ordered through the CTSU website. See Section 4.4 for ordering instructions; see Section 9.1 for administration instructions; see Appendix I for PRO-CTCAE assessments for IRB submission and review only. PRO-CTCAE booklets should be administered at the following time points: ≤ 21 days prior to treatment/intervention, Day 1 of each cycle of mFOLFIRINOX (+/- 3 days), and prior to surgery (+/- 7 days).

3 To be completed after pre-registration but ≤ 21 days prior to treatment; see Appendix I.

4 For women of childbearing potential; see Section 3.3. Must be done ≤ 14 days prior to registration.

5 Baseline and restaging abdominal scans can include either a CT or an MRI, although CT is preferred. Baseline and restaging chest scans must include a CT. The same method of scanning used at baseline should be used for all subsequent evaluations. The CT scans must be acquired with 3 mm or less slice thickness; CT scans should be of diagnostic quality and performed with IV contrast unless there is a medical contraindication; MRI is the preferred imaging modality for patients with a medical contraindication to contrast. See Section 6.3 for image submission and Section 7.3 for imaging guidelines. Baseline scans are to be centrally reviewed in real-time by IROC Ohio per Section 7.3. Supporting documentation is to be submitted, per Section 6.1.3.

A. Surgery-related AEs should be assessed and reported within 30 days of surgery see Section 9.2.

B. CBC with differential, platelets, and chemistry labs during the post-treatment follow-up period should be performed as clinically indicated (e.g. presence of fatigue, nausea, etc.).

C. CA 19-9 to be performed ≤ 28 days prior to registration. For patients who have normal CA 19-9 at baseline, continued testing of CA 19-9 is not required. For patients who have abnormal CA 19-9 at baseline, CA 19-9 should be performed every 28 days (+/- 14 days) during treatment. Any measurements of biochemical response should occur in conjunction with the radiographic assessments for disease status.

D. Restaging scans should be performed for both Arm 1 and Arm 2 patients at the following time points: after Cycle 4 of mFOLFIRINOX, after Cycle 8 of mFOLFIRINOX (for Arm 1 patients, this should occur after Cycle 8, but before surgery), and after Cycle 12 of mFOLFIRINOX.

# 6.0 DATA AND SPECIMEN SUBMISSION

## 6.1 Data Collection and Submission

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must either click on the link in the email or login to iMedidata via the CTSU members' website under *Data Management* > *Rave Home*, and click to *accept* the invitation in the Tasks pane located in the upper right-corner of the iMedidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Rave section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.

A Data Submission Schedule is available on the Alliance study webpage within the Case Report Forms section. A Data Submission Schedule is also available on the CTSU website within the study-specific folders.

### 6.1.1 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status, and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status and DQP Reports modules.

### 6.1.2 Patient-completed Booklets

Patient-completed questionnaire booklets for this study are to be ordered prior to the registration of any patients (see Section 4.4). Samples of questionnaire booklets are available in Appendix I for reference and IRB submission only. They are not to be used for patient completion. Booklets must be given to patients to complete and patients should be instructed to return the booklets to site staff either in person, and site staff will enter patient responses into Rave.

Note: If the patient consented for the Diet and Lifestyle substudy (A021806-HO2), then these booklets will automatically be sent to the enrolling site within 2 weeks of patient registration. Samples of the questionnaire booklets are available as separate documents on the Alliance and CTSU websites for reference and IRB submission only. They are not to be used for patient completion.

### 6.1.3 Supporting Documentation to be Submitted to the Alliance

This study requires supporting documentation for diagnosis, response, and progression/recurrence. Supporting documentation will include imaging reports (to be submitted to both IROC Ohio and via Rave), pathology/cytology reports, operative reports, and other documents/notes/reports, and these must be submitted at the following time points:

- Baseline: imaging report, pathology/cytology report, clinic note
- Restaging: imaging reports
- Surgery: operative report, pathology report
- Progression/Recurrence: imaging report, pathology report (if applicable)

Supporting documentation is to be submitted via Rave.

## 6.2 Specimen Collection and Submission

Correlative Science Manual: The Alliance A021806 Correlative Science Manual (CSM) contains instructions for specimen collection, processing, and shipping. The manual can be

found on the study-specific webpage on the Alliance, BioMS, and CTSU websites. Questions regarding the CSM should be directed to the contact(s) specified in the manual.

For all patients registered to Alliance A021806: Retrospective histopathology review will be conducted using the paraffin-embedded pancreatic tissue from the surgical specimens. The submission of these samples for histopathology review is required for all patients registered to this study, including those who are found to be ineligible and those who do not receive protocol therapy.

For patients registered to substudy A021806 Biobanking: All participating institutions must ask patients for their consent to participate in the biobanking for future correlative studies, although patient participation is optional. Rationale for these studies are described in Section 14.4. For patients who consent to participate, blood, tissue, and/or stool will be collected at the following time points for these future studies:

| | **Prior to initiation of therapy** | **Prior to surgery** | **At surgery** | **After 4 cycles of adjuvant therapy** | **End of treatment** | **At recurrence** |
|---|---|---|---|---|---|---|
| **Mandatory for all patients registered to A021806:** | | | | | | |
| **Tumor Tissue Block** | | | X | | | |
| **For patients registered to A021806 Biobanking, submit the following:** | | | | | | |
| **Archival Tumor Tissue from Diagnostic Biopsy/ FNA (*or fresh tissue from baseline biopsy if obtained as SOC*)** | X | | | | | |
| **Plasma and Buffy Coats from Whole Blood** | 3 x 10 mL | 3 x 10 mL (Arm 1 only) | | 3 x 10 mL | 3 x 10 mL (Arm 2 only) | 3 x 10 mL |
| **Tumor Tissue from Biopsy/FNA (*only if obtained as SOC*)** | | | | | | X |
| **Stool** | X | X (Arm 1 only) | | X (Arm 2 only) | X | |

### 6.3 Imaging Submission

Collection of CT and/or MRI images is required for all patients consented on A021806. Images and local interpretation reports will be collected digitally for archival and retrospective purposes at the following time points:

- Baseline
- Restaging (after every 4 cycles of mFOLFIRINOX)
- Post-operative Restaging
- Post-treatment Follow-up (every 16 weeks [+/- 4 weeks] after completion of protocol therapy until 2 years after registration or disease progression/recurrence)

The complete CT or MRI (and non-contrast CT) scan data in digital DICOM format should be submitted electronically to the Imaging and Radiation Oncology Core at Ohio (IROC Ohio)

within no more than 3 business days upon patient registration (baseline) or upon image acquisition completeness (restaging). BMP files, JPG files, or hard copies (films) are not acceptable.

Imaging data should be submitted electronically to IROC Ohio via TRIAD (Section 6.3.1). The standard TRIAD-based data transfer approach will be provided separately through IROC efforts via the specific trial e-mail, Alliance021806@irocohio.org, per the request of participating sites before their first imaging data submission.

If the TRIAD approach is not achievable at a site, alternatively the site needs to de-identify the patient data using institutional procedures to remove patient name and medical record number while preserving the Alliance patient ID number (e.g. 112136) and protocol number (e.g. A021806), and use the following electronic approaches for data submission:

1) Web Transfer (http://upload.imagingcorelab.com)

   Any PCs with internet access and web browser (e.g. Internet Explorer, Mozilla Firefox) can be used to web transfer DICOM images and other required files to IROC Ohio. The standard Web Transfer information will be provided separately through the specific trial e-mail, Alliance021806@irocohio.org, per the request of participating sites before the first imaging data submission.

2) FTP Transfer

   Any FTP software can be used to initiate access to the secure FTP Server of IROC Ohio. The standard FTP access information will be provided separately through the specific trial e-mail, Alliance021806@irocohio.org, per the request of participating sites before the first imaging data submission.

3) Mail/CD Shipment

   If neither of the electronic data transfer approaches can be achieved, then the de-identified images in digital DICOM format may be burned to a CD and mailed to IROC Ohio (however, electronic submission is preferred). Submit only one of the patient's images per CD, with the Alliance patient ID number, study type, date of scans, and name of submitting institution.

   **Submit these data to:**

   IROC Ohio
   Attn: A021806
   The Ohio State University
   Wright Center of Innovation
   395 W. 12th Avenue, Suite 428
   Columbus, Ohio, 43210

   Tel: 614-293-2929
   Fax: 614-293-9275
   E-mail: Alliance021806@irocohio.org

If the imaging data submission is done via web transfer, FTP transfer, or mail/CD shipment, send an e-mail to IROC Ohio at the specific trial email, Alliance021806@irocohio.org, to inform them that the study has been submitted from the institution. Please include the following basic information of submitted data sets:

1) Alliance Patient ID Number
2) Scan Time Point (i.e. Baseline)
3) Date of Scans
4) Institution Name

IROC Ohio will notify the site within 2 business days of the data receipt and within 3 business days following the data receipt of the quality check report via the trial specific email Alliance021806@irocohio.org.

For any questions about or problems with data submission to IROC Ohio, please call the IT Group at 614-293-2929 for help.

For patients who consent to the imaging study, A021806-IM1 (model consent question, "I choose to take part in the imaging study and will have my scans analyzed"), the imaging scans and local interpretation reports submitted to the Alliance Imaging Core Lab (ICL) at IROC Ohio as part of the main study (A021806) will be used for the retrospective imaging analyses outlined in Section 14.3.

### 6.3.1 Digital Imaging Data Submission Using Transfer of Images and Data

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

#### 6.3.1.1 TRIAD Access Requirements

- A valid Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) (CTEP-IAM) account.
- Registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR). Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.

TRIAD Site User role on an NCTN or ETCTN roster. All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

#### 6.3.1.2 TRIAD Installation

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at https://triadinstall.acr.org/triadclient/.

This process can be done in parallel to obtaining your CTEP-IAM account username and password and RCR registration.

For questions, contact TRIAD Technical Support staff via email TRIAD-Support@acr.org or 1-703-390-9858.

#### 6.3.1.3 Procedures for Data Submission via TRIAD

The standard TRIAD-based data transfer approach will be provided separately through IROC efforts via the specific trial e-mail, Alliance021806@irocohio.org, per the request of participating sites before their first imaging data submission.

### 6.4 Submission of Patient-completed Measures

Patient-completed questionnaire booklets for this study are to be ordered prior to the registration of any patients (see Section 4.4). Samples of questionnaire booklets are available in Appendix I for reference and IRB submission only. They are not to be used for patient completion. Booklets must be given to patients to complete and patients should be instructed to return the booklets to site staff in person and site staff will enter patient responses into Rave. At visits in which booklets are to be completed, the booklet should be given to the patient before any discussion of the patient's health status or test results. Booklet administration schedule is provided below.

Verbal administration of the measures for visually impaired patients is permitted if the measure and verbal administration of the measure is conducted in a language understandable to the patients.

The EORTC QLQ-C30 is available in English and French. The translated measures are available on the A021806 CTSU and Alliance study pages. Ad-hoc translation of patient-completed measures is not permitted.

Please note that PRO-CTCAE is contained in a separate booklet and is required for all patients per the study calendar. The schedule below only pertains to patients who consent to participate in the optional Quality of Life study (A021806-HO1).

| | **≤ 14 Days Prior to Initiation of Treatment/ Intervention** | **Prior to Cycle 1 (but after surgery)*** | **Prior to Cycle 5** | **After End of Cycle 8 (but prior to surgery)**** | **Prior to Cycle 9** | **At End of Chemotherapy** |
|---|---|---|---|---|---|---|
| For patients registered to A021806-HO1, submit patient-completed questionnaires† at the following time points: | | | | | | |
| **EORTC QLQ-C30** | X | X | X | X | X | X |

* For Arm 2 only.

** For Arm 1 only.

† See Appendix I for EORTC QLQ-C30 questionnaire for IRB submission and review only. Patients must complete the questionnaires in booklet format. See Section 4.4 for ordering instructions.

Submission of Completed Booklets: The data from the booklets are to be entered into Medidata Rave® by site staff.

### 6.5 Diet and Lifestyle Questionnaire Completion and Submission (A021806-HO2)

The patient-completed questionnaire booklets for this substudy will be sent to the registering institution within two (2) weeks of patient registration/randomization (see Section 4.4 for further information). Samples of the questionnaire booklets are available as separate documents on the Alliance and CTSU websites for reference and IRB submission only. **They are not to be used for patient completion.** The booklets must be given to patients to complete and patients should be instructed to return the booklet to site staff in person; it is recommended that the measure be completed during a physician visit and/or chemotherapy session. Patients must complete the questionnaire in booklet format.

Verbal administration of the measure for visually impaired patients is permitted if the measure and verbal administration of the measure is conducted in a language understandable to the patients.

The first booklet is to be administered after registration but within 4 weeks of initiating chemotherapy (Arm 1) or prior to surgery (Arm 2). The second (i.e. follow-up) booklet is to be administered 1 year after registration (+/- 14 days).

The Diet and Lifestyle Questionnaires are available in English and French. Ad-hoc translation of patient-completed measures is not permitted.

Submission of Completed Booklets: The completed booklets are to be returned to the Diet and Lifestyle Coordination Office by site staff via the pre-paid envelope provided to the following address:

Diet and Lifestyle Survey Coordination Office

Attn: Alliance A021806

Dana-Farber Cancer Institute

450 Brookline Avenue

Boston, MA 02215

### 6.6 ICAREdata™

Selected sites will be participating in the ICAREdata® project. - The Integrating Clinical Trials and Real-world Endpoints data (ICAREdata) initiative is a program led by the Alliance Data Innovation Lab which is a component of the Alliance for Clinical Trials in Oncology.

The ICAREdata® project aims to expand the ability to achieve clinical research goals by providing new ways to collect data required for clinical trials. Today, virtually all clinical trials data are collected using special forms and computer applications, such as a software known as Medidata Rave. Instead of using these "add on" data collection systems, the ICAREdata project will gather study data directly from the Electronic Health Record (EHR). As with all research data collections, data collected by the ICAREdata project are stored in a secured repository.

Select institutions will be invited to participate and will receive training on the specific ICAREdata® requirements. As with all clinical trials data management, the nature of data collected using the ICAREdata methods will be specific to a particular research protocol, and might include demographic information, diagnosis, laboratory values, physician assessments, and other results, such as adverse event reports. The Data Innovation Lab will manage data collection, working with the IT department at these sites to configure the EHR to deliver mCODE (minimal common oncology data elements) data and other required outcome data in the form of structured ICAREdata questions. Clinicians will provide the study required data by answering standardized questions or data fields as part of their encounter visit with the subjects. The IT departments will also work to implement the data transfer capability from the site EHR to the Alliance Data Innovation Lab via a secure/tested extraction method.

Investigators and research staff at limited select sites that utilize the EHR research adverse events data collection tool will be asked to complete a brief voluntary survey. The research staff and investigator's email addresses at these predetermined sites will be submitted at the time of Adverse Events data collection tool training. The survey will take approximately 5 minutes to complete. It will solicit feedback on the investigators and study staff experiences including overall staff acceptance, usability, preferences for using the tool to document any adverse events. The plan survey administration timeline is at baseline and then a select period thereafter. Ultimately, the survey will be used to gather general feedback of the usability of the tool across multiple site level stakeholders.

Data will be encrypted at-rest and in-transit using a secure interface with an established authorization protocol handled by the ICAREdata infrastructure. Alliance Data Lab staff will issue a client ID and credentials to participating ICAREdata sites that will be used to authenticate those sites for access to the ICAREdata infrastructure service/extraction method to submit data. The clinical site will be responsible for securely storing these credentials (e.g., installed on a server that an IT administrator manages) such that those staff responsible for submitting data will have the proper access. Data will be stored and maintained in HIPAA compliant data repositories (such as AWS) and access controlled by an identity server with strict management to ensure confidentiality, integrity, and availability of PHI. Strict access controls will be maintained. Only authorized Alliance Data Lab personnel will have access to the data and scope of access will be further controlled based on role and level of need to know.

Participating institutions may email the Alliance Data Innovation Lab at ICAREdata@alliancefoundationtrials.org with any questions.

## 7.0 TREATMENT PLAN/INTERVENTION

Protocol treatment/intervention is to begin ≤ 21 days of registration.

For questions regarding treatment, please see the study contacts page.

It is acceptable for individual chemotherapy doses to be delivered ≤ a 24-hour (business day) window before and after the protocol-defined date for Day 1 of a new cycle. For example, if the treatment due date is a Friday, the window for treatment includes the preceding Thursday through the following Monday. In addition, patients are permitted to have a new cycle of chemotherapy delayed up to 7 days for major life events (e.g., serious illness in a family member, major holiday, vacation that cannot be rescheduled) without this being considered a protocol violation. Documentation to justify this delay should be provided.

Imaging and surgery must be performed at the registering institution. Chemotherapy may be given at a non-registering institution. All protocol conduct must be followed, and the registering institution is responsible for ensuring all data is reported per protocol. Please refer to the Alliance Policy and Procedures document posted on the Alliance website for the policy on engagement in research by non-registering institutions. If the NCTN Group credited for enrollment is a non-Alliance Group, then other requirements from the credited Group may apply.

Patients will be randomized to either Arm 1 or Arm 2.

- Patients on Arm 1 will receive 8 cycles of mFOLFIRINOX* prior to surgery, and restaging scans will be performed after Cycles 4 and 8; see Section 7.3. After completion of pre-operative therapy, patients who are considered appropriate candidates for surgical resection will proceed to surgery per Section 7.2. Surgery must occur 2 to 8 weeks after the last day of the last cycle of pre-operative chemotherapy (e.g. C8D14). Patients considered inappropriate for surgical resection will be removed from protocol therapy/intervention and will be followed per Section 5.0.

  After surgery, Arm 1 patients will receive 4 additional cycles of mFOLFIRINOX, and restaging scans will be performed after Cycle 12; see Section 7.3. Post-operative therapy should begin 3 to 12 weeks after the date of surgery.

  *For patients who have obstructive jaundice at the time of diagnosis/registration and undergo biliary drainage, chemotherapy can be initiated while waiting for total bilirubin levels to decline to normal range (total bilirubin ≤ 3.0 mg/dL). Treatment should be administered without irinotecan (i.e. mFOLFOX) until the total bilirubin is within normal limits (or ≤ 1.5

x ULN) for a maximum of two (2) cycles. Once total bilirubin has normalized, patients should receive mFOLFIRINOX as detailed in Section 7.1.

- Patients on Arm 2 will proceed directly to up-front surgical resection per Section 7.2. Surgery must occur within 3 weeks after registration. After surgery, Arm 2 patients will receive 12 cycles of mFOLFIRINOX, and restaging scans will be performed after Cycles 4, 8, and 12; see Section 7.3. Post-operative therapy should begin 3 to 12 weeks after the date of surgery.

Treatment/intervention will continue as outlined above or until disease recurrence/progression, unacceptable toxicity, or withdrawal of consent; see Section 12.0 for information regarding discontinuation of treatment/intervention.

See Section 8.1 for ancillary therapy and concomitant medication guidance.

## 7.1 Chemotherapy

Arm 1: 8 cycles of neoadjuvant mFOLFIRINOX, then 4 cycles of adjuvant mFOLFIRINOX

Arm 2: 12 cycles of adjuvant mFOLFIRINOX

One cycle of mFOLFIRINOX = 14 days.

Cycles of mFOLFIRINOX are delivered as follows*:

- Oxaliplatin: 85 mg/m$^2$ IV over 2 hours on Day 1, followed by,
- Irinotecan: 150 mg/m$^2$ IV over 90 minutes on Day 1, followed by,
- Leucovorin**: 400 mg/m$^2$ IV over 2 hours on Day 1, followed by,
- 5FU***: 2400 mg/m$^2$ IV over 46-48 hours on Days 1-3

* Minor variations in the timing of mFOLFIRINOX delivery due to local institutional policy are allowed so long as dose and dose modifications do not vary.

** Alternatively, leucovorin may be administered concurrently with the last 30 min of oxaliplatin, and the entire 90 minutes of irinotecan.

*** 5FU is administered via IV infusion only; there is no bolus injection of 5FU. White blood cell growth factor is strongly recommended after completion of 5FU, and should be administered according to institutional procedures if permitted. See Section 8.1.7 for further details.

Patients on Arm 1 who are unable to complete all 8 cycles of neoadjuvant mFOLFIRINOX due to toxicity will be permitted to continue on protocol treatment/intervention and receive protocol-specified surgical resection and post-operative chemotherapy. Documentation should be included in Rave.

## 7.2 Surgery

Surgical resection of the primary tumor and regional lymph nodes in the absence of disease progression must occur 2-8 weeks following completion of pre-operative chemotherapy for Arm 1 patients or within 3 weeks after registration for Arm 2 patients. Those who undergo surgery outside of these range will remain on study. Sites should inform the Study Chair, Study Co-Chair, and Data Manager of the scheduled date of surgery per Section 7.2.3.

It is presumed that multidisciplinary teams enrolling patients on this study will have surgeons with significant experience in the management of these tumors. At a minimum, surgeons operating in the context of this study should be skilled and credentialed at their institution to perform pancreatic surgery; a specific number of cases is not required. Surgical management of resectable pancreatic tumors requires resection of the major mesenteric vasculature in the

minority of cases following receipt of systemic chemotherapy. Should this be necessary, the surgeon should be skilled and credentialed or should team with a transplant or vascular surgery colleague who themselves are skilled and credentialed to perform vascular portions of the operations, if needed.

### 7.2.1 Surgical Quality Assurance

General Considerations

Pancreaticoduodenectomy should occur within 2-8 weeks after the last day of the last cycle of pre-operative chemotherapy for patients in Arm 1 (perioperative arm) or within 3 weeks after registration for patients in Arm 2. Staging laparoscopy may be performed at the time of planned laparotomy but is not required. Either standard or pylorus-preserving pancreaticoduodenectomy may be performed. Surgical drains and enteral tubes (e.g. gastrostomy and/or jejunostomy tubes) may be placed at the discretion of the operating surgeon.

The operation should be performed in accordance with techniques espoused in the first edition of Operative Standards for Cancer Surgery, published by the American College of Surgeons and the Alliance for Clinical Trials in Oncology [19].

Specific Considerations

Exploration of the peritoneal cavity should include evaluation for radiographically occult macroscopic peritoneal or hepatic metastases. Lymph node sampling or frozen section lymph node biopsy is not required or recommended as part of the intraoperative assessment for extra-pancreatic disease, but it is at the discretion of the operating surgeon.

For pancreaticoduodenectomy, a standard lymphadenectomy should be performed routinely, to include lymph node stations 8a, 12a2, 12p2, 12b2, 12c, 13a, 13b, 14a, 14b, 17a, and 17b. Other lymph node stations should be detailed, if performed, in the operative report.

For pancreaticoduodenectomy, the retroperitoneal dissection along the medial edge of the uncinate process and the right lateral border of the superior mesenteric artery (SMA) is believed to be an important oncologic part of the operation. All soft tissue to the right of the SMA should be removed. This requires exposure and dissection along the right lateral border of the SMA.

For subtotal or distal pancreatectomy, lymph nodes stations 10, 11, and 18 should be included in the resection. Resection of lymph nodes in stations 8a and 9 should be included in the resection specimen in cases of cancer located in the body of the pancreas.

Vascular resection and/or reconstruction of the superior mesenteric vein (SMV), portal vein, SMV/portal vein confluence, or hepatic artery will be performed at the discretion of the operating surgeon. In general, vascular resection should be performed when necessary to achieve an R0 resection. The operating surgeon or a vascular/transplant surgeon consult can perform this reconstruction. The technical details of the operation should be delineated in the operative report.

Intraoperative Frozen Section Assessment of Surgical Margins

Frozen section evaluation of the pancreatic parenchymal and hepatic (or bile) duct margins should be performed. In the event of a positive frozen section margin at either of these loci, further resection in an effort to achieve microscopically negative margins should be

performed if possible. However, the extent of additional parenchymal resection should be left to the discretion of the operating surgeon.

The SMA margin should be evaluated on permanent section only.

Specimen Orientation for Surgical Pathology

The operating surgeon should ensure that the specimen is oriented for the surgical pathologist. Relevant margins evaluated by intraoperative frozen section (i.e. the hepatic [bile] duct, and pancreatic parenchymal) should be identified. Any segment of resected vascular structure (e.g. SMV or portal vein) should be identified and marked. The SMA margin (the soft tissue immediately adjacent to the SMA) should be separately inked using the principles outlined in the 8th edition AJCC staging system for exocrine pancreatic cancer. Note: The SMA margin cannot be identified accurately after the specimen has been fixed in formalin or after the specimen has been dissected for histopathologic analysis.

Aborting Surgery

The planned resection should be aborted if the operating surgeon identifies:

- Metastatic disease in distant organs (e.g. liver). Presumed disease should be biopsied and confirmed as metastatic cancer on frozen section.
- Localized cancer that is nonetheless, in the opinion of the operating surgeon, unsafe to resect. In such cases, the specific reasons for aborting the operation should be enumerated in the operative report.

Operative Note Dictation and Editing: Resection Classification

The attending surgeon should dictate the operative note. The operative report should contain:

- A section detailing the operative findings with respect to the extent of disease and the primary tumor anatomy.
- A statement as to whether the surgeon believes there is residual macroscopic tumor following completion of the resection.

The surgeon should integrate the operative findings with the microscopic surgical margins reported on the final pathology report in order to assign a resection classification prefix of R0, R1, or R2 (defined below). Whenever possible, this prefix should be added to the final operative note before finalizing the document. An example of the final procedure description for a patient who underwent macroscopically complete tumor removal with a positive margin on permanent section final pathology is: "R1 pylorus-preserving pancreaticoduodenectomy." The definitions for the resection classification that should be utilized in operative notes include:

- R0 – macroscopically complete tumor removal with negative microscopic surgical margins (bile duct, pancreatic parenchyma, and SMA margins)
- R1 – macroscopically complete tumor removal with any positive microscopic surgical margin (bile duct, pancreatic parenchyma, or SMA margins)
- R2 – macroscopically incomplete tumor removal with known or suspected residual gross disease

Surgical Pathology

A local pathologist experienced in the diagnosis of pancreatic adenocarcinoma should carry out pathological examination of the resected pancreatic tumor specimen. Following local review, a tumor tissue block is required to be submitted for retrospective central histopathology review; see Section 6.2.

Three primary margins (bile duct and pancreatic neck, and SMA) should be identified and inked by the surgeon and/or pathologist. Any segment of resected vascular structure (e.g. SMV or portal vein) should be identified and marked. The SMA margin (the soft tissue immediately adjacent to the SMA) should be separately inked according to the procedures and recommendations of the American Joint Commission on Cancer 8th edition staging system and the College of American Pathologists guidelines for reporting of resected exocrine pancreatic cancer (2012). The tumor should be thoroughly sampled (at least one section per 1 mm of greatest tumor dimension, taken perpendicular to the inked SMA margin). The distance between the closest tumor cell and the inked SMA margin (the "SMA margin distance") should be reported.

Frozen Section Assessment of Margins

Section assessment of bile duct and pancreatic neck margins should be performed by the local pathologist in all cases as requested by the surgeon.

Permanent Section Assessments and Final Pathology Report

The pathology report should contain all of the elements outlined in the College of American Pathologists guidelines for reporting of resected exocrine pancreatic cancer (2012). In particular, there should be specific comment on:

- Histologic diagnosis with comment on the cell of origin (pancreatic vs. bile duct vs. ampulla)
- Degree of differentiation (well, moderate, poor)
- Total number of lymph nodes examined
- Number of positive nodes
- Final margins status for the bile duct, pancreatic parenchymal, and SMA margin
- Distance (in mm) from the tumor to the inked SMA margin
- Extent of tumor infiltration (if present) of the blood vessel wall for any resected major blood vessels including the maximum histologic depth of invasion (e.g. adventitia, media)

Retrospective Central Histopathology Review of Resected Tumor Specimen

A tumor tissue block (or representative slides) must be sent for retrospective central re-review to standardize determination of both treatment effect score and tumor grade.

Treatment effect score will be determined using the following system:

- Treatment Effect Score I: 0% residual tumor cells in the specimen (pCR)
- Treatment Effect Score II: 1 to < 5% residual tumor cells in the specimen
- Treatment Effect Score III: ≥ 5% residual tumor cells in the specimen

### 7.2.2 Definitions of Deviations in Surgical Protocol Performance

Minor Deviations

The following will be considered minor surgical deviations:

- Failure to perform a frozen section of bile duct or pancreatic neck margins at the time of surgery
- Documentation of a lymphadenectomy less extensive than that described above.

### 7.2.3 Surgical Quality Control

Sites scheduling patients for surgery should notify the Study Team of their intent to operate at the time the operation is scheduled. This notification should consist of an email to the Study Chair, Study Co-Chair, and Data Manager with the Alliance Patient ID number, scheduled date of surgery, and contact information for the operating surgeon and credited investigator on the OPEN Form.

For all patients who undergo surgery during protocol treatment (including resection or not), the Study Chair and Study Co-Chair will review the pre-operative imaging report, the operative note, the surgical pathology report, and the adverse events associated with surgery (30 days post-operative) within 90 days of surgery. This requires that sites upload the required source documentation in a timely manner (see Section 6.1) and complete the AE CRF without delinquency.

Specific attention will be paid to deviations as listed above or variations, as well as adverse events that occur in association with surgery. Operative reports and outcomes which, in the opinion of the Study Chair and Study Co-Chair, raise potential patient safety concerns will be discussed and reviewed with the credited investigator immediately. Two operations which lead to such a discussion may lead to the site being restricted from enrolling future patients.

## 7.3 Imaging

Collection of CT and/or MRI images is required for all patients consented on A021806. Quality images will be collected digitally for archival and retrospective purposes (see Section 7.3.1 for definitions of quality images). The same imaging modality used at baseline for each patient should be used for all subsequent evaluations to ensure accurate comparison. Images and local interpretation reports will be collected digitally for archival and retrospective purposes at the following time points:

- Baseline
- Restaging (after every 4 cycles of mFOLFIRINOX)
- Post-operative Restaging
- Post-treatment Follow-up (every 16 weeks [+/- 4 weeks] after completion of protocol therapy until 2 years after registration or disease progression/recurrence)

Images submitted at baseline for the eligibility review will be reviewed by the IROC Ohio Central Radiologists in real time; see Section 7.3.2.

See Section 6.3 for digital image submission instructions.

### 7.3.1 Definition of Quality Imaging

The following are recommended guidelines for CT scan quality:

- Neutral enteric contrast (water or volumen; no positive oral contrast)
- Exams to be obtained on a 16 or 64 multi-detector CT (MDCT)
- **Intravenous Contrast:** 150 mL (or weight based) administered by power injection device followed by 60 mL saline bolus tracking technique.
    - **Rate of Contrast:** at least 3-4 mL/second
- Minimum two post-contrast phases are needed (pre-contrast is optional to add):
    - Arterial Phase: ideally bolus track (delayed arterial phase)
    - Portal Venous Phase: 70-80 seconds
- Diagnostic Image Reconstruction:
    - 3 mm slice thickness, 3 mm reconstruction interval
    - 0.6 mm collimation (thinnest collimation)
    - **2 Reconstruction:** 1 mm x 0.8 mm recon (smallest slice with overlap)
    - **Reconstructions:** 3 mm x 3 mm coronal MPRs for all phases

The following are recommended guidelines for MRI scan quality:

- **Magnet:** 1.5 OR 3 T Magnet
- **Surface Coil:** Phased array torso coil
- **Sequences:**
    - Breath-hold T2-weighted imaging with a single/multishot fast spin-echo sequence or a half-Fourier acquisition single-shot
    - Turbo spin-echo sequence with or without fat saturation
    - **MRCP Sequence:** 2D and/or 3D. Breath-hold two-dimensional
    - Three-dimensional turbo spin-echo MR
    - DW imaging performed by using respiratory-triggered single-shot echo-planar imaging with b values of 0, 100, and 800 seconds/$mm^2$
    - Axial T1-weighted imaging with in-phase and opposed phase
    - Spoiled 3D gradient-echo sequences T1-weighted 3D GRE sequences:
        - Unenhanced
        - Arterial phase (AP)
        - Portal venous phase (PVP)
        - 3-minute late-phase
        - Subtraction images

### 7.3.2 Real-time Imaging Central Review

The following images and local interpretation reports will be collected and submitted for centralized, real-time review by the IROC Ohio Central Radiologists:

- Baseline

IROC Ohio will contact the Central Radiologists within 24 hours (except weekends and holidays) of images being received for scheduling a real-time remote review. IROC Ohio notifies both the participating site and Alliance of the central review results within 24 hours after receiving the results from the Central Radiologists. The overall turn-around time between imaging data receipt and central review results notification is within 24-72 hours after the imaging data receipt (except weekends and holidays). The radiology reviewer will enter the central review results into Rave.

Central review results will be reported back to the site PI for further evaluation and determination of patient status.

For any questions related to central review, participating sites may directly contact IROC Ohio instead of the central reviewer(s), either by the trial email at Alliance021806@irocohio.org or by phone at (614) 293-2929.

## 8.0 DOSE AND TREATMENT MODIFICATIONS

### 8.1 Ancillary Therapy, Concomitant Medications, and Supportive Care

#### 8.1.1 Patients should not receive any other treatment which would be considered treatment for the primary neoplasm or impact the primary endpoint.

This includes any surgical intervention, radiotherapy, cryotherapy, ablation, etc., performed on the primary neoplasm.

#### 8.1.2 Patients should receive full supportive care while on this study.

This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

#### 8.1.3 Treatment with hormones or other chemotherapeutic agents may not be administered except for:

- Steroids given for adrenal failure
- Hormones administered for non-disease-related conditions (e.g. insulin for diabetes)
- Intermittent use of dexamethasone as an antiemetic

#### 8.1.4 Antiemetics may be used at the discretion of the treating physician, with the exception of steroids above.

As this regimen has high emetogenic potential, it is suggested that all subjects on study should receive an aggressive prophylactic antiemetic regimen, consisting of a 5HT-3 antagonist, steroid, and NK1 antagonist.

#### 8.1.5 Diarrhea management is per the discretion of the treating physician.

This regimen has a high incidence of severe diarrhea. For symptoms of diarrhea (and/or abdominal cramping) that occur at any time during a treatment cycle, it is suggested that patients should be instructed to take an anti-diarrheal, such as loperamide. It is recommended that the anti-diarrheal should be started at the earliest sign of: (1) a poorly formed or loose stool; (2) an increase in bowel movements by 1 to 2 episodes per day

compared to baseline; or (3) an increase in stool volume or liquidity. Additional anti-diarrheal measures may be implemented at the discretion of the treating physician. Patients may also be instructed to increase fluid intake to help maintain fluid and electrolyte balance during episodes of diarrhea, and IV fluids and correction of electrolyte imbalances should be considered for severe diarrhea, at the discretion of the treating physician.

**8.1.6 Palliative radiation therapy may not be administered while a patient is on study.**

**8.1.7 Alliance Policy Concerning the Use of Growth Factors**

The use of prophylactic white blood cell (WBC) growth factor support is strongly recommended for all trial participants during chemotherapy starting with the first treatment cycle; however, local institutional policies should be followed where use of WBC growth factor support is restricted and/or prohibited; see Section 7.1. If used, these are to be obtained from commercial sources. In circumstances where a patient's neutrophil count is markedly elevated per institutional standard at the start of a new treatment cycle, growth factor may be omitted for that cycle per treating physician discretion and clinically recommended guidelines.

Blood products should be utilized as clinically warranted and following institutional policies and recommendations.

Use of epoetin (EPO), filgrastim (G-CSF), tbo-filgrastim, pegfilgrastim, sargramostim (GM-CSF), and/or WBC biosimilar products are permitted at the discretion of the treating physician per clinically recommended guidelines. Filgrastim/pegfilgrastim are preferred.

1. White blood cell growth factor may not be used:
    a. To avoid dose reductions, delays or to allow for dose escalations specified in the protocol.
    b. For the treatment of febrile neutropenia the use of CSFs should not be routinely instituted as an adjunct to appropriate antibiotic therapy. However, the use of CSFs may be indicated in patients who have prognostic factors that are predictive of clinical deterioration such as pneumonia, hypotension, multi-organ dysfunction (sepsis syndrome) or fungal infection, as per the ASCO guidelines. Investigators should therefore use their own discretion in using the CSFs in this setting. The use of CSF (filgrastim/pegfilgrastim) must be documented and reported. (e.g. on CRFs per protocol requirements)
    c. If white blood cell growth factors are used, they must be obtained from commercial sources. Selection of white blood cell growth factor products should be per institutional guidelines.

**8.1.8 Hypersensitivity/Infusion Reactions**

Treat hypersensitivity and infusion reactions to drugs as per institutional standards.

**8.1.9 Antibiotics**

Prophylactic oral antibiotic therapy is not recommended to be given at the start of study treatment. However, antibiotics should be considered for patients who have: (a) endobiliary stent(s) with an ANC that falls below 500 $mm^3$ or have fever; (b) diarrhea persisting for more than 48 hours despite treatment or fever with diarrhea.

### 8.1.10 Anticoagulants

Due to potential drug interactions, treatment dose warfarin for goal INR > 1.5 is not recommended. Other anticoagulants are recommended to be used for prophylaxis and treatment.

### 8.1.11 CYP3A4 Inhibitors

Chronic concomitant treatment with strong inhibitors of CYP3A4 is not allowed on this trial. The following drugs are EXAMPLES of strong inhibitors of CYP3A4 and are not allowed during treatment with irinotecan.

- Indinavir
- Clarithromycin
- Ketoconazole

Because lists of these agents are constantly changing, please consult and review any drugs for their potential to inhibit CYP3A4. Examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA website, or your local institution's pharmacist.

### 8.1.12 CYP3A4 Inducers

Chronic concomitant treatment with strong inducers of CYP3A4 is not allowed during on this trial. The following drugs are EXAMPLES of strong inducers of CYP3A4 and are not allowed during treatment with irinotecan.

- Rifampin
- Carbamazepine

Because lists of these agents are constantly changing, please consult and review any drugs for their potential to induce CYP3A4. Examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA website, or your local institution's pharmacist.

### 8.1.13 Biliary Obstruction

Biliary decompression should be performed if clinically warranted. Biliary decompression should ideally be performed prior to registration and should be accomplished endoscopically, preferably with a short metallic stent.

### 8.1.14 Cholinergic Reaction

Lacrimation, rhinorrhea, miosis, diaphoresis, hot flashes, flushing, abdominal cramping, diarrhea, or other symptoms of early cholinergic syndrome may occur during or shortly after receiving irinotecan. Atropine given as IV or SC may be used to treat these symptoms. In patients with troublesome or recurrent symptoms, prophylactic administration of atropine shortly before irinotecan therapy may be considered. Additional antidiarrheal measures may be used at the discretion of the treating physician. Combination anticholinergic medications containing barbiturates or other agents (e.g. DonnatalR) should not be used because these may affect irinotecan metabolism. Anticholinergics should be used with caution in patients with potential contraindications (e.g. obstructive uropathy, glaucoma, tachycardia, etc.).

### 8.1.15 Extravasation

Extravasation of oxaliplatin has been associated with necrosis. Extravasation should be treated according to institutional guidelines.

## 8.2 Dose Modifications

If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

Dose modifications of 5FU, irinotecan, and oxaliplatin may occur independently of each other based on the pattern of toxicity. Patients unable to tolerate either/both oxaliplatin or irinotecan due to toxicity will remain on treatment with the other drugs.

If 5FU is omitted, then leucovorin should also be omitted.

Once the dose of any drug has been reduced, the dose cannot be re-escalated.

If any drug is held for > 4 weeks from original date of start of new cycle, then that drug should be permanently discontinued.

If more than one of these apply, use the most stringent (i.e. the greatest dose reduction).

There are no further dose reductions beyond those listed in the tables below for each drug. If further dose reduction is required, then that drug should be discontinued.

AERS reporting may be required for some adverse events; see Section 9.0.

### 8.2.1 Dose Levels for mFOLFIRINOX

| Dose Level | 5FU infusion ($mg/m^2$) | Leucovorin ($mg/m^2$) | Irinotecan ($mg/m^2$) | Oxaliplatin ($mg/m^2$) |
|---|---|---|---|---|
| 0* | 2400 | 400 | 150 | 85 |
| -1 | 1920 | 400 | 120 | 65 |
| -2 | 1600 | 400 | 100 | 50 |
| -3 | 1360 | 400 | 75 | 40 |

*Dose level 0 refers to the starting dose.

### 8.2.2 Hematologic Toxicities

**NOTE:** Each new treatment cycle with mFOLFIRINOX should not begin until ANC ≥ 1,500 and platelet count ≥ 75,000. WBC growth factor prophylaxis within 48 hours after discontinuation of infusional 5FU is strongly recommended.

**For grade 2 neutropenia or thrombocytopenia**, delay mFOLFIRINOX until toxicity resolves to grade ≤ 1. If toxicity resolves within 7 days, then resume at the same dose level. If toxicity resolves in > 7 days, then resume 5FU at the same dose level and resume oxaliplatin and irinotecan with one dose level reduction.

**For recurring grade 2 neutropenia or thrombocytopenia**, delay mFOLFIRINOX until toxicity resolves to grade ≤ 1, then resume all agents with one dose level reduction.

**For grade 3 neutropenia**, delay mFOLFIRINOX until toxicity resolves to grade ≤ 1, then resume 5FU at the same dose level and resume oxaliplatin and irinotecan with one dose level reduction.

**For recurring grade 3 neutropenia**, delay mFOLFIRINOX until toxicity resolves to grade ≤ 1, then resume all agents with one dose level reduction.

**For grade 3 or 4 thrombocytopenia**, delay mFOLFIRINOX until toxicity resolves to grade ≤ 1, then resume all agents with one dose level reduction.

**For grade 4 neutropenia**, delay mFOLFIRINOX until toxicity resolves to grade ≤ 1, then resume all agents with one dose level reduction.

**For grade 3 or 4 febrile neutropenia (occurring at any point during the treatment cycle)**, reduce all agents by one dose level with the subsequent treatment cycle.

### 8.2.3 Gastrointestinal Toxicities

Diarrhea

**For grade 2 diarrhea (despite optimal medical management)**, delay mFOLFIRINOX until toxicity resolves to grade ≤ 1, then resume all agents at the same dose level.

**For second occurrence of grade 2 diarrhea (despite optimal medical management)**, delay mFOLFIRINOX until toxicity resolves to grade ≤ 1, then resume 5FU and oxaliplatin at the same dose level and resume irinotecan with one dose level reduction.

**For third occurrence of grade 2 diarrhea (despite optimal medical management)**, delay mFOLFIRINOX until toxicity resolves to grade ≤ 1, then resume irinotecan at the same dose level and resume 5FU and oxaliplatin with one dose level reduction.

**For fourth and all subsequent occurrences of grade 2 diarrhea (despite optimal medical management)**, delay mFOLFIRINOX until toxicity resolves to grade ≤ 1, then resume all agents with one dose level reduction.

**For grade 3 diarrhea (despite optimal medical management)**, delay mFOLFIRINOX until toxicity resolves to grade ≤ 1, then resume 5FU and oxaliplatin at the same dose level and resume irinotecan with one dose level reduction.

**For second occurrence of grade 3 diarrhea (despite optimal medical management)**, delay mFOLFIRINOX until toxicity resolves to grade ≤ 1, then resume irinotecan at the same dose level and resume 5FU and oxaliplatin with one dose level reduction.

**For third and all subsequent occurrences of grade 3 diarrhea (despite optimal medical management)**, delay mFOLFIRINOX until toxicity resolves to grade ≤ 1, then resume all agents with one dose level reduction.

**For grade 4 diarrhea (despite optimal medical management)**, discontinue mFOLFIRINOX.

Nausea or Vomiting

**For grade 3 nausea or vomiting (despite optimal medical management)**, delay mFOLFIRINOX until toxicity resolves to grade ≤ 1, then resume all agents with one dose level reduction.

**For grade 4 nausea or vomiting (despite optimal medical management)**, discontinue mFOLFIRINOX.

Mucositis

**For grade 3 oral mucositis (despite optimal medical management)**, delay mFOLFIRINOX until toxicity resolves to grade ≤ 1, then resume all agents with one dose level reduction.

**For grade 4 oral mucositis (despite optimal medical management)**, discontinue mFOLFIRINOX.

### 8.2.4 Hepatic Toxicities

**For grade 2-3 total bilirubin increased**, delay mFOLFIRINOX until toxicity resolves to grade ≤ 1, then resume all agents at the same dose level.

**For recurring grade 2-3 total bilirubin increased**, delay mFOLFIRINOX until toxicity resolves to grade ≤ 1, then resume all agents with one dose level reduction.

**For grade 3 AST/ALT increased**, delay mFOLFIRINOX until toxicity resolves to grade ≤ 1, then resume all agents at the same dose level.

**For recurring grade 3 AST/ALT increased**, delay mFOLFIRINOX until toxicity resolves to grade ≤ 1, then resume all agents with one dose level reduction.

**For grade 4 total bilirubin or AST/ALT increased**, discontinue mFOLFIRINOX.

### 8.2.5 Neurological Toxicities

**For grade 2 peripheral sensory or motor neuropathy persisting between treatments**, continue 5FU and irinotecan at the same dose level and reduce oxaliplatin by one dose level with the subsequent treatment cycle.

**For grade 3 peripheral sensory or motor neuropathy resolving to grade ≤ 2 between treatments**, continue 5FU and irinotecan at the same dose level and reduce oxaliplatin by one dose level with the subsequent treatment cycle.

**For grade 3 peripheral sensory or motor neuropathy persisting between treatments or grade 4 peripheral sensory or motor neuropathy**, continue 5FU and irinotecan at the same dose level and discontinue oxaliplatin with the subsequent treatment cycle.

### 8.2.6 Other Toxicities

**For pharyngeal dysesthesia**, it is recommended to increase the duration of oxaliplatin infusion to 6 hours with subsequent treatment cycles. Refer to Section 10.4 for guidance to distinguish pharyngeal dysesthesia from allergic reactions.

**For grade 3 toxicity considered at least possibly related to treatment**, delay mFOLFIRINOX until toxicity resolves to grade ≤ 1, then resume responsible agent(s) with one dose level reduction and resume non-responsible agent(s) at the same dose level.

**For grade 4 toxicity considered at least possibly related to treatment**, discontinue mFOLFIRINOX.

### 8.2.7 Dose Modifications for Obese Patients

There is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight. Therefore, all dosing is to be determined solely by actual weight without any modification unless explicitly described in the protocol. This will eliminate the risk of calculation error and the possible introduction of variability in dose administration. Failure to use actual body weight in the calculation of drug dosages will be considered a major protocol deviation. Physicians who are uncomfortable with calculating doses based on actual body weight should recognize that

doing otherwise would be a protocol violation. Physicians may consult the published guidelines of the American Society of Clinical Oncology Appropriate Chemotherapy Dosing for Obese Adult Patients with Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 30(13): 1553-1561, 2012.

#### 8.2.8 Cumulative Toxicities

During Cycles 6-12 of chemotherapy on either arm, if a patient develops cumulative toxicity (e.g. fatigue, asthenia, anorexia) that does not meet the formal AE criteria detailed in the previous sections, the treating physician may contact the Study Chair to discuss the possibility of reducing the patient's doses or simplifying the patient's regimen to either FOLFOX or FOLFIRI for the remaining treatment cycles.

## 9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. The CTCAE is available at ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms. Please refer the NCI Guidelines: Adverse Event Reporting Requirements for further details on AE reporting procedures.

Clinician graded CTCAE is the AE safety standard. PRO-CTCAE items are to complement CTCAE reporting. Patients will respond to PRO-CTCAE items, but no protocol-directed action will be taken. The specific PRO-CTCAE items for this protocol can be found in Appendix I. PRO-CTCAE is not intended for expedited reporting, real-time review, or safety reporting.

### 9.1 Routine Adverse Event Reporting

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times according to the study calendar in Section 5.0. For this trial, the Form, "Adverse Events" is used for routine AE reporting in Rave.

#### 9.1.1 Solicited Adverse Events

The following adverse events are considered "expected" and their presence/absence should be solicited, and severity graded, at baseline and for each cycle of treatment by CTCAE, PRO-CTCAE, or both.

| CTCAE v5.0 Term | CTCAE v5.0 System Organ Class (SOC) | PRO-CTCAE v1.0 Term |
|---|---|---|
| Blood bilirubin increased | Investigations | |
| Hypoalbuminemia | Investigations | |
| Weight loss | Investigations | |
| Wound infection | Infections and infestations | |
| Bile duct stenosis | Hepatobiliary disorders | |

| | | |
|---|---|---|
| Fatigue | General disorders | Fatigue, tiredness or lack of energy |
| | General disorders | Pain |
| Diarrhea | Gastrointestinal disorders | Loose or watery stools (diarrhea) |
| Nausea | Gastrointestinal disorders | Nausea |
| | Gastrointestinal disorders | Dry mouth |
| | Gastrointestinal disorders | Vomiting |
| | Gastrointestinal disorders | Heartburn |
| | Gastrointestinal disorders | Bloating of the abdomen (belly) |
| | Gastrointestinal disorders | Pain in the abdomen (belly area) |
| Peripheral sensory neuropathy | Nervous system disorders | Numbness or tingling in your hands or feet |
| | Nervous system disorders | Problems with tasting food or drink |
| | Metabolism and nutrition disorders | Decreased appetite |
| | Skin and subcutaneous tissue disorders | Itchy skin |
| | Psychiatric disorders | Anxiety |
| | Psychiatric disorders | Sad or unhappy feelings |

Symptomatic adverse events reported by patients through PRO-CTCAE are not safety reporting and may be presented with other routine Adverse Event data.

### 9.2 Surgical Adverse Event Reporting

Specific toxicities related to pancreatic cancer surgery must be evaluated to best determine the adverse events of the protocol. The following events are collected at a single time point, which is 30 days after surgery:

| Event | Date to be Entered |
|---|---|
| Pancreatic fistula requiring drainage within 30 days of surgery | Yes/No |
| Abdominal abscess requiring drainage within 30 days of surgery | Yes/No |
| Patients with a hospitalization within 30 days of surgery: Length of hospital stay | Number of days |
| Reoperation for any reason within 30 days of surgery | Yes/No |

### 9.3 CTCAE Routine Reporting Requirements

In addition to the solicited adverse events listed in Section 9.1, the following table outlines the combinations of time points, grades and attributions of AEs that require routine reporting to the Alliance Statistics and Data Management Center. Questions about routine reporting should be directed to the Data Manager.

Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs)

| Attribution | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
|---|---|---|---|---|---|
| Unrelated | | | a | a | a |
| Unlikely | | | a | a | a |
| Possible | | a | a, b | a, b | a, b |
| Probable | | a | a, b | a, b | a, b |
| Definite | | a | a, b | a, b | a, b |

a) Adverse Events: Other CRF - Applies to AEs occurring between registration and within 30 days of the patient's last treatment date, or as part of the Clinical Follow-Up Phase.

b) Adverse Events: Late CRF - Applies to AEs occurring greater than 30 days after the patient's last treatment date.

### 9.4 Expedited Adverse Event Reporting (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. The CTCAE is identified and located on the CTEP website at: ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE. All reactions determined to be "reportable" in an expedited manner must be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to the Alliance by telephone at (773) 702-9171. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically by the original submitter at the site.

For further information on the NCI requirements for SAE reporting, please refer to the 'NCI Guidelines for Investigators: Adverse Event Reporting Requirements' document published by the NCI.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

#### 9.4.1 Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE ≤ 30 Days of the Last Administration of the Investigational Agent/Intervention [1]

**FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)**

**NOTE:** Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

**ALL SERIOUS** adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour;<br>5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

**Expedited AE reporting timelines are defined as:**

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS ≤ 24 hours of learning of the AE, followed by a complete expedited report ≤ 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted ≤ 10 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

**Expedited 24-hour notification followed by complete report ≤ 5 calendar days for:**

- All Grade 4, and Grade 5 AEs

**Expedited 10 calendar day reports for:**

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

### 9.4.2 Expedited AE Reporting Timelines Defined

"24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS ≤ 24 hours of learning of the event followed by a complete CTEP-AERS report ≤ 5 calendar days of the initial 24-hour report.

"10 calendar days" – A complete CTEP-AERS report on the AE must be submitted ≤ 10 calendar days of the investigator learning of the event.

Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions (see below).

Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent on this trial.

Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

### 9.4.3 Additional Instructions or Exclusions to CTEP-AERS Expedited Reporting Requirements

All adverse events reported via CTEP-AERS (i.e. serious adverse events) should also be forwarded to your local IRB.

Alliance A021806 uses a drug under an Alliance IND. The reporting requirements for investigational agents should be followed for all agents (any arm) in this trial.

Treatment expected adverse events include those listed in Section 10.0 and in the package insert.

CTEP-AERS reports should be submitted electronically.

**Exclusions**

Grade 1-3 nausea or vomiting and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting.

Grade 3 or 4 nausea or vomiting does not require AERS reporting, but should be reported via routine AE reporting

Grade 1-3 diarrhea and hospitalization resulting from such does not require AERS reporting, but should be reported via routine AE reporting

Grade 3 or 4 diarrhea does not require AERS reporting, but should be reported via routine AE reporting

Grade 1-3 mucositis and hospitalization resulting from such does not require AERS reporting, but should be reported via routine AE reporting

Grade 3 or 4 mucositis does not require AERS reporting, but should be reported via routine AE reporting

Grade 1-3 neuropathy and hospitalization resulting from such does not require AERS reporting, but should be reported via routine AE reporting.

Grade 3 neuropathy does not require AERS reporting, but should be reported via routine AE reporting

Grade 1-3 hand foot syndrome and hospitalization resulting from such does not require AERS reporting, but should be reported via routine AE reporting

Grade 3 hand foot syndrome does not require AERS reporting, but should be reported via routine AE reporting

Grade 1-4 hypersensitivity reaction and hospitalization resulting from such does not require AERS reporting, but should be reported via routine AE reporting

Grade 3 or 4 hypersensitivity reaction does not require AERS reporting, but should be reported via routine AE reporting

Grade 1-3 dehydration and hospitalization resulting from such does not require AERS reporting, but should be reported via routine AE reporting

Grade 3 dehydration does not require AERS reporting, but should be reported via routine AE reporting

Grade 1-3 fatigue and hospitalization resulting from such does not require AERS reporting, but should be reported via routine AE reporting.

Grade 3 or 4 fatigue does not require AERS reporting, but should be reported via routine AE reporting

Grade 1-4 hematosuppression (leukopenia, neutropenia, lymphopenia, anemia, and thrombocytopenia) and hospitalization resulting from such does not require AERS reporting, but should be reported via routine AE reporting

Grade 3 or 4 hematosuppression (leukopenia, neutropenia, lymphopenia, anemia, and thrombocytopenia) does not require AERs reporting, but should be reported via routine AE reporting

**Death**

Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (e.g. radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Any death occurring within 30 days of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

Any death occurring greater than 30 days after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours only if it is possibly, probably, or definitely related to the investigational agent/intervention.

**Pregnancy Loss and Neonatal Death**

Pregnancy loss is defined in CTCAE as "Death in utero." Any Pregnancy loss should be reported expeditiously, as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC. A Pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC.

**New Malignancies**

All new malignancies must be reported via CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e. solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome/acute myelogenous leukemia, and in situ tumors. In CTCAE version 5.0, the new malignancies (both second and secondary) may be reported as one of the following: (1) Leukemia secondary to oncology chemotherapy, (2) Myelodysplastic syndrome, (3) Treatment-related secondary malignancy, or (4) Neoplasms benign, malignant and unspecified-other.

Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.

New primary malignancies should be reported using the appropriate study Form in Rave.

**Secondary Malignancy**

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g. acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via Rave.

**Second Malignancy**

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting unless otherwise specified.

## 10.0 DRUG INFORMATION

### 10.1 General Considerations

Rounding the dose up or down to the nearest vial size as per institutional policy is allowed as long as the dose change is within 10%.

It is not necessary to change the doses of chemotherapy drugs due to changes in weight unless the calculated dose changes by ≥10%.

Chemotherapy may be administered at a non-registering institution.

If the Group credited for enrollment is a non-Alliance Group, then other requirements from the credited Group may apply.

### 10.2 5-Fluorouracil (5-FU, Efudex, Arucil, Carac, Fluroplex, NSC#19893)

For more information, please refer to the drug package insert.

***Procurement***

Commercial supplies. Institutional pharmacy shall obtain supplies from normal commercial supply chain or wholesaler.

***Formulation***

Commercially available as Intravenous Solution: 500 mg/10 mL (10 mL), 1 g/20 mL (20 mL), 2.5 g/50 mL (50 mL), and 5 g/100 mL (100 mL)

***Storage and Stability***

Store intact vials at room temperature and protect from light. A slight discoloration may occur with storage but usually does not denote decomposition. Solutions in 50 – 1000 mL 0.9% NaCl or D5W or undiluted solutions in syringes are stable for 72 hours at room temperature. Fluorouracil and leucovorin are compatible for 14 days at room temperature. Fluorouracil is compatible with vincristine, methotrexate, and cyclophosphamide.

***Preparation***

Dilute in 50 – 1000 mL of 0.9% NaCl or D5W. If exposed to cold, a precipitate may form; gentle heating to 60ºC will dissolve the precipitate without impairing the potency.

***Administration***

Fluorouracil may be given IV push, IV infusion. Refer to the treatment section for specific administration instructions. Avoid extravasation, may be an irritant.

Fluorouracil should not be coadministered with either diazepam, doxorubicin, daunorubicin, idarubicin, cisplatin, or cytarabine.

***Drug Interactions***

Fluorouracil may increase effects of warfarin. Avoid ethanol (due to GI irritation). Avoid black cohosh.

***Pharmacokinetics***

Distribution: Vd ~ 22% of total body water; penetrates extracellular fluid, CSF, and third space fluids (e.g. pleural effusions and ascitic fluid)

Metabolism: Hepatic (90%); via a dehydrogenase enzyme; Fluorouracil must be metabolized to be active.

Half-life elimination: Biphasic: Initial: 6-20 minutes; two metabolites, FdUMP and FUTP, have prolonged half-lives depending on the type of tissue.

Excretion: Lung (large amounts as $CO_2$); urine (5% as unchanged drug) in 6 hours.

***Adverse Events***

Consult the package insert for the most current and complete information.

<u>Common known potential toxicities, > 10%</u>:

Dermatologic: Dermatitis, pruritic maculopapular rash, alopecia.

Gastrointestinal (route and schedule dependent): Heartburn, nausea, vomiting, anorexia, stomatitis, esophagitis, anorexia, diarrhea. GI toxicity (anorexia, nausea, and vomiting) is generally more severe with continuous-infusion schedules.

Emetic potential: <1000 mg: Moderately low (10% to 30%) ≥ 1000 mg: Moderate (30% to 60%)

Hematologic: Leukopenia; Myelosuppressive (tends to be more pronounced in patients receiving bolus dosing of 5-FU). Decreased white blood cell count with increased risk of infection; decreased platelet count with increased risk of bleeding.

Local: Irritant chemotherapy.

Less common known potential toxicities, 1% - 10%:

Dermatologic: Dry skin

Gastrointestinal: GI ulceration

Rare known potential toxicities, <1% (Limited to important or life-threatening):

Cardiac enzyme abnormalities, chest pain, coagulopathy, dyspnea, ECG changes similar to ischemic changes, hepatotoxicity; hyperpigmentation of nail beds, face, hands, and veins used in infusion; hypotension, palmar-plantar syndrome (hand-foot syndrome), photosensitization. Cerebellar ataxia, headache, somnolence, ataxia are seen primarily in intracarotid arterial infusions for head and neck tumors.

***Nursing Guidelines***

Monitor complete blood count and platelet count. Instruct patient to report signs and symptoms of infection, unusual bruising or bleeding to the physician.

Administer antiemetics as indicated.

Diarrhea may be dose–limiting; encourage fluids and treat symptomatically.

Assess for stomatitis; oral care measures as indicated. May try vitamin E oil dabbed on sore, six times daily. Cryotherapy recommended with IV push administration.

Monitor for neurologic symptoms (headache, ataxia).

Inform patient of potential alopecia.

Those patients on continuous infusion may need instruction regarding central intravenous catheters and portable intravenous or IA infusion devices.

5FU–induced conjunctivitis is a common problem. Advise patient to report any eye soreness or redness to the healthcare team.

Photosensitivity may occur. Instruct patients to wear sun block when outdoors.

### 10.3 Leucovorin Calcium (NSC#3590)

For more information, please refer to the drug package insert.

***Procurement***

Commercial supplies. Institutional pharmacy shall obtain supplies from normal commercial supply chain or wholesaler.

***Formulation***

Commercially available as:

- Solution for Injection: 100 mg/10mL (10mL, 30 mL)
- Lyophilized Powder for Injection: 50 mg, 100 mg, 200 mg, 350 mg, and 500 mg

***Storage and Stability***

Solution for Injection: Prior to dilution, store vials under refrigeration at 2°C to 8°C (36°F to 46°F). Protect from light.

Powder for Injection: Store at room temperature of 25°C (77°F). Protect from light. Solutions reconstituted with bacteriostatic water for injection U.S.P. must be used within 7 days. Solutions reconstituted with SWFI must be used immediately. Parenteral admixture is stable for 24 hours stored at room temperature (25°C) and for 4 days when stored under refrigeration (4°C).

***Preparation***

Solution for Injection: Dilute in D5W or NS for infusion.

Powder for Injection: Reconstitute with SWFI or BWFI; dilute with D5W or NS for infusion. When doses >10 mg/$m^2$ are required, reconstitute using sterile water for injection, not a solution containing benzyl alcohol.

***Administration***

Combination therapy with Fluorouracil: Fluorouracil is usually given after, or at the midpoint, of the leucovorin infusion. Leucovorin is usually administered by IV bolus injection or short (10-120 minutes) IV infusion. Other administration schedules have been used; refer to individual protocols.

***Drug Interactions***

Capecitabine: Leucovorin Calcium-Levoleucovorin may enhance the adverse/toxic effect of Capecitabine. Risk C: Monitor therapy

Fluorouracil (Systemic): Leucovorin Calcium-Levoleucovorin may enhance the adverse/toxic effect of Fluorouracil (Systemic). This effect is associated with the ability of leucovorin or levoleucovorin to enhance the anticancer effects of fluorouracil. Risk C: Monitor therapy

Fluorouracil (Topical): Leucovorin Calcium-Levoleucovorin may enhance the adverse/toxic effect of Fluorouracil (Topical). Risk C: Monitor therapy

Fosphenytoin: Leucovorin Calcium-Levoleucovorin may decrease the serum concentration of Fosphenytoin. Risk C: Monitor therapy

PHENobarbital: Leucovorin Calcium-Levoleucovorin may decrease the serum concentration of PHENobarbital. Risk C: Monitor therapy

Phenytoin: Leucovorin Calcium-Levoleucovorin may decrease the serum concentration of Phenytoin. Risk C: Monitor therapy

Primidone: Leucovorin Calcium-Levoleucovorin may decrease the serum concentration of Primidone. Additionally, leucovorin/levoleucovorin may decrease concentrations of active metabolites of primidone (e.g., phenobarbital). Risk C: Monitor therapy

Raltitrexed: Leucovorin Calcium-Levoleucovorin may diminish the therapeutic effect of Raltitrexed. Risk X: Avoid combination

Tegafur: Leucovorin Calcium-Levoleucovorin may enhance the adverse/toxic effect of Tegafur. This effect is associated with the ability of leucovorin or levoleucovorin to enhance the anticancer effects of fluorouracil. Risk C: Monitor therapy

Trimethoprim: Leucovorin Calcium-Levoleucovorin may diminish the therapeutic effect of Trimethoprim. Management: Avoid concurrent use of leucovorin or levoleucovorin with trimethoprim (plus sulfamethoxazole) for Pneumocystis jiroveci pneumonia. If trimethoprim is used for another indication, monitor closely for reduced efficacy. Risk X: Avoid combination.

***Pharmacokinetics***

Absorption: Oral, IM: Well absorbed

Metabolism: Intestinal mucosa and hepatically to 5-methyl-tetrahydrofolate (5MTHF; active)

Bioavailability: Saturable at oral doses > 25 mg; 25 mg (97%), 50 mg (75%), 100 mg (37%)

Half-life elimination: ~ 4-8 hours

Time to peak: Oral: ~ 2 hours; IV: Total folates: 10 minutes; 5MTHF: ~ 1 hour

Excretion: Urine (primarily); feces

***Adverse Events***

Consult the package insert for the most current and complete information.

Dermatologic: Rash, pruritus, erythema, urticaria

Hematologic: Thrombocytosis

Respiratory: Wheezing

Miscellaneous: Allergic reactions, anaphylactoid reactions

***Nursing Guidelines***

Headache may occur. Advise patient that analgesics such as Tylenol may help. Instruct patient to report any headache that is unrelieved.

Observe for sensitization reaction (rash, hives, pruritus, facial flushing, and wheezing).

May potentiate the toxic effects of fluoropyrimidine (5-FU) therapy, resulting in increased hematologic and gastrointestinal (diarrhea, stomatitis) adverse effects. Monitor closely.

May cause mild nausea or upset stomach. Administer antiemetics if necessary and evaluate for their effectiveness.

### 10.4 Oxaliplatin (Eloxatin, NSC#266046)

For more information, please refer to the drug package insert.

***Procurement***

Commercial supplies. Institutional pharmacy shall obtain supplies from normal commercial supply chain or wholesaler.

***Formulation***

Commercially available as:

- Solution for Injection: 50 mg/10 mL (10 mL), 100 mg/20 mL (20 mL), and 200 mg/40 mL (40 mL)
- Lyophilized Powder for Injection: 50 mg and 100 mg

***Storage and Stability***

Store intact vials in original outer carton at room temperature and; do not freeze. According to the manufacturer, solutions diluted for infusion are stable up to 6 hours at room temperature or up to 24 hours under refrigeration. Oxaliplatin solution diluted with D5W to a final concentration of 0.7 mg/mL (polyolefin container) has been shown to retain >90% of its original concentration for up to 30 days when stored at room temperature or refrigerated; artificial light did not affect the concentration (Andre, 2007). As this study did not examine sterility, refrigeration would be preferred to limit microbial growth. Infusion solutions do not require protection from light.

***Preparation***

Dilution with D5W (250 or 500 mL) is required prior to administration. Do not prepare using a chloride-containing solution (e.g. NaCl). Refer to package insert for complete preparation and dispensing instructions.

***Administration***

Refer to the treatment section for specific administration instructions. Administer as IV infusion over 2-6 hours. Flush infusion line with D5W prior to administration of any concomitant medication. Patients should receive an antiemetic premedication regimen. Cold temperature may exacerbate acute neuropathy. Avoid mucositis prophylaxis with ice chips during oxaliplatin infusion.

***Drug Interactions***

Increased Effect/Toxicity: Nephrotoxic agents may increase oxaliplatin toxicity.

When administered as sequential infusions, observational studies indicate a potential for increased toxicity when platinum derivatives (carboplatin, cisplatin, oxaliplatin) are administered before taxane derivatives (docetaxel, paclitaxel).

Decreased Effect: Oxaliplatin may decrease plasma levels of digoxin

***Pharmacokinetics***

Distribution: Vd: 440 L

Protein binding: >90% primarily albumin and gamma globulin (irreversible binding to platinum)

Metabolism: Nonenzymatic (rapid and extensive), forms active and inactive derivatives

Phase: 16.8 hours

Excretion: Primarily urine (~54%); feces (~2%)

***Adverse Events***

Consult the package insert for the most current and complete information. Percentages reported with monotherapy.

<u>Common known potential toxicities, > 10%:</u>

Central nervous system: Fatigue, fever, pain, headache, insomnia

Gastrointestinal: Nausea, diarrhea, vomiting, abdominal pain, constipation, anorexia, stomatitis

Hematologic: Anemia, thrombocytopenia, leukopenia

Hepatic: Liver enzymes increased

Neuromuscular & skeletal: Back pain, peripheral neuropathy (may be dose limiting). The most commonly observed oxaliplatin toxicity is acute and cumulative neurotoxicity, observed in patients treated at doses above 100 mg/m$^2$/cycle. This neurotoxicity has included paresthesias and dysesthesias of the hands, feet, and perioral region as well as unusual laryngopharyngeal dysesthesias characterized by a loss of sensation of breathing without any objective evidence of respiratory distress (hypoxia, laryngospasm, or bronchospasm). Oxaliplatin neurotoxicity appears to be exacerbated by exposure to cold. Patients on this study will be counseled to avoid cold drinks and exposure to cold water or air. Should a patient develop laryngopharyngeal dysesthesia, their oxygen saturation should be evaluated via a pulse oximeter; if normal, an anxiolytic agent should be given and the patient observed in the clinic until the episode has resolved. Because this syndrome may be associated with the rapidity of oxaliplatin infusion, subsequent doses of oxaliplatin should be administered as a 6-hour infusion (instead of the normal 2-hour infusion).

Acute and cumulative neurotoxicities are dose limiting for oxaliplatin. The acute neurotoxicity is characterized by paresthesias and dysesthesias that may be triggered or exacerbated by exposure to cold. These symptoms occur within hours of exposure and are usually reversible over the following hours or days. Cumulative doses of oxaliplatin above 680 mg/m$^2$ may produce functional coordination; impairment is caused by sensory rather than motor changes.

The likelihood of experiencing neurotoxicity is directly related to the total cumulative dose of oxaliplatin administered. The relative risk of developing neurotoxicity was 10%, 50%, and 75% in patients who received total cumulative oxaliplatin doses of 780 mg/m$^2$, 1,170 mg/m$^2$, and 1,560 mg/m$^2$, respectively. Both acute and cumulative neurotoxicities due to oxaliplatin have lessened in 82% of patients within 4 to 6 months, and have completely disappeared by 6 to 8 months in 41% of patients. In addition, the likelihood that neurologic symptoms will regress has been shown to correlate inversely with cumulative dose.

Respiratory: Dyspnea, cough

<u>Less common known potential toxicities, 1% - 10%:</u>

Cardiovascular: Edema, chest pain, peripheral edema, flushing, thromboembolism

Central nervous system: Dizziness

Dermatologic: Rash, alopecia, hand-foot syndrome

Endocrine & metabolic: Dehydration, hypokalemia

Gastrointestinal: Dyspepsia, taste perversion, flatulence, mucositis, gastroesophageal reflux, dysphagia

Genitourinary: Dysuria

Hematologic: Neutropenia

Local: Injection site reaction

Neuromuscular & skeletal: Rigors, arthralgia

Ocular: Abnormal lacrimation

Renal: Serum creatinine increased

Respiratory: URI, rhinitis, epistaxis, pharyngitis, pharyngolaryngeal dysesthesia

Miscellaneous: Allergic reactions, hypersensitivity (includes urticaria, pruritus, facial flushing, shortness of breath, bronchospasm, diaphoresis, hypotension, syncope, hiccup

Rare known potential toxicities, <1% (Limited to important or life-threatening):

Gastrointestinal: Life threatening enteric sepsis secondary to neutropenia and diarrhea.

Hepatic: Veno-occlusive disease of the liver is a rare serious adverse event that has occurred in association with administration of oxaliplatin and fluorouracil.

Otic: Clinical ototoxicity occurs in less than 1% of patients following oxaliplatin administration, and sever ototoxicity has not been reported

***Nursing Guidelines***

GI toxicity similar to cisplatin occurs with doses above 30 mg/m$^2$. It can be almost constant and frequently severe, but not always dose-limiting. Monitor for nausea and vomiting and treat accordingly.

Dose-limiting side effect can be paresthesias of hands, fingers, toes, pharynx, and occasionally cramps which develops with a dose-related frequency (> 90 mg/m$^2$). Duration of symptoms tend to be brief (less than a week) with the first course, but longer with subsequent courses. Phase I patients have reported exacerbation of paresthesias by touching cold surfaces or exposure to cold. Advise patient of these possibilities and instruct patient to report these symptoms to the health care team. Also advise patient to refrain from operating dangerous machinery that requires fine sensory-motor coordination, if symptoms appear.

These sensory neuropathies developed after subsequent courses with increasing intensity (grade 3 toxicity after the fourth course) and with increasing duration. In 63% of the patients tested in phase I at high doses (135-200 mg/m$^2$), neuropathies became long-term with slow reversal over several months. Disabling walking and handwriting difficulties, as well as mouth and throat dysesthesias and laryngospasms were seen. Instruct patient to report any swallowing difficulties or gait changes.

Oxaliplatin is incompatible with NS. Flush lines with D5W prior to and following oxaliplatin infusion.

Low back pain is a common side effect, perhaps a form of hypersensitivity reaction. Instruct patient in good body mechanics, advise light massage, heat, etc.

Laryngopharyngeal dysesthesia (LPD) occurs in about 15% of patients and is acute, sporadic, and self-limited. It usually occurs within hours of infusion, is induced or exacerbated by exposure to cold, and presents with dyspnea and dysphagia. The incidence and severity appear to be reduced by prolonging infusion time. Instruct patient to avoid ice and cold drinks the day of infusion. If ≥ grade 2 laryngopharyngeal dysesthesia occurs during the administration of oxaliplatin, do the following:

- Stop oxaliplatin infusion
- Administer benzodiazepine and give patient reassurance
- Test oxygen saturation via a pulse oximeter
- At the discretion of the investigator, the infusion can be restarted at 1/3 the original rate of infusion.
- Rapid resolution is typical within minutes to a few hours. Can recur with retreatment.

**Comparison of the Symptoms and Treatment of Laryngopharyngeal Dysesthesias and Platinum Hypersensitivity Reactions**

| Clinical Symptoms | Laryngopharyngeal Dysesthesias | Platinum Hypersensitivity |
|---|---|---|
| Dyspnea | Present | Present |
| Bronchospasm | Absent | Present |
| Laryngospasm | Absent | Present |
| Anxiety | Present | Present |
| $O_2$ Saturated | Normal | Decreased |
| Difficult Swallowing | Present (Loss of Sensation) | Absent |
| Pruritus | Absent | Present |
| Urticaria/Rash | Absent | Present |
| Cold-induced Symptoms | Yes | No |
| BP | Normal or Increased | Normal or Decreased |
| **Treatment** | Anxiolytics, observation in a controlled clinical setting until symptoms abate or at the physicians' discretion | Oxygen, steroids, epinephrine, bronchodilators; fluids and vasopressors, if appropriate |

Alopecia is rare with oxaliplatin alone, but is seen with 5-FU-oxaliplatin combination. Advise patient.

Mild-moderate diarrhea has been seen - usually of short duration. Treat accordingly. See Section 8.0 for ancillary treatment.

Respiratory problems (i.e. pulmonary fibrosis, cough, dyspnea, rales, pulmonary infiltrates, hypoxia, air hunger and tachypnea) have been observed in patients administered oxaliplatin. In rare cases, death has occurred due to pulmonary fibrosis. Please monitor and instruct the patient to report any respiratory difficulties and hold oxaliplatin until interstitial lung disease is ruled out for cases of grade ≥ 3. If patient is experiencing shortness of breath, a chest x-ray and assessment of oxygenation via either finger oximetry or arterial blood gas evaluation are required to confirm the absence or presence of pulmonary infiltrates and/or hypoxia (treat accordingly: no intervention, steroids, diuretics, oxygen, or assisted ventilation).

Veno-occlusive disease (VOD) is a rare but serious complication that has been reported in patients receiving oxaliplatin in combination with 5-FU. This condition can lead to hepatomegaly, splenomegaly, portal hypertension and/or esophageal varices. Instruct patients to report any jaundice, ascites, or hematemesis to the MD immediately as these could be a sign of VOD or other serious condition.

Acute vein irritation can occur with infusion. Apply heat to arm of infusion if you are using a peripheral line. However, extravasation of drug can cause severe pain, redness, soreness, and exfoliation of the skin in the affected area with loss of affected vein for a long period. If a patient has a problem with pain or sclerosis when chemotherapy is given by a peripheral line, then placement of a central line should be considered.

Hemolytic uremic syndrome (HUS) may result in kidney damage. Oxaliplatin is to be discontinued in cases where hematocrit is <25%, thrombocytopenia <100,000, and creatinine ≥1.6 mg/dL.

Patients may experience sleep disturbances, specifically insomnia. Encourage good sleep hygiene, and instruct patient to report any problems with sleep to the MD, to assess for the potential use of sleeping aids.

Cold-induced transient visual abnormalities can be experienced by patients while receiving oxaliplatin, although the relationship to oxaliplatin has not been completely determined. Instruct patient to report any problems with vision to the MD.

Extrapyramidal side effects and/or involuntary limb movement has been seen with oxaliplatin administration. Patients may also experience restlessness. Instruct patient to report any of these side effects to the MD.

### 10.5 Irinotecan (Camptosar, NSC#616348)

For more information, please refer to the drug package insert.

***Procurement***

Commercial supplies. Institutional pharmacy shall obtain supplies from normal commercial supply chain or wholesaler.

***Formulation***

Commercially available as: injection 20 mg/mL (2 mL, 5 mL) [contains sorbitol 45 mg/mL; do not use in patients with hereditary fructose intolerance].

***Storage and Stability***

Store intact vials at room temperature and protect from light. Due to the relatively acidic pH, irinotecan appears to be more stable in D5W than 0.9% NaCl. Solutions diluted in D5W are stable for 24 hours at room temperature or 48 hours under refrigeration at 2ºC to 8ºC. Solutions diluted in 0.9% NaCl may precipitate if refrigerated. Do not freeze.

***Preparation***

Doses should be diluted in 250-500 mL D5W or 0.9% NaCl to a final concentration of 0.12-2.8 mg/mL. Refer to package insert for complete preparation and dispensing instructions.

***Administration***

Administer by IV infusion, usually over 90 minutes.

***Drug Interactions***

Cytochrome P450 Effect: Substrate (major) of CYP2B6, 3A4

Increased Effect/Toxicity: CYP2B6 and CYP3A4 inhibitors may increase the levels/effects of irinotecan. Bevacizumab may increase the adverse effects of irinotecan (e.g. diarrhea, neutropenia). Ketoconazole increases the levels/effects of irinotecan and active metabolite; discontinue ketoconazole 1 week prior to irinotecan therapy; concurrent use is contraindicated.

Decreased Effect: CYP2B6 and CYP3A4 inducers may decrease the levels/effects of irinotecan.

Ethanol/Nutrition/Herb Interactions Herb/Nutraceutical: St. John’s Wort decreases therapeutic effect of irinotecan; discontinue ≥ weeks prior to irinotecan therapy; concurrent use is contraindicated.

***Pharmacokinetics***

Distribution: Vd: 33-150 L/$m^2$

Protein binding, plasma: Predominantly albumin; Parent drug: 30% to 68%, SN-38 (active metabolite): ~95%

Metabolism: Primarily hepatic to SN-38 (active metabolite) by carboxylesterase enzymes; SN-38 undergoes conjugation by UDP- glucuronosyl transferase 1A1 (UGT1A1) to form a glucuronide metabolite. Conversion of irinotecan to SN-38 is decreased and glucuronidation of SN-38 is increased in patients who smoke cigarettes, resulting in lower levels of the metabolite and overall decreased systemic exposure. SN-38 is increased by UGT1A1*28 polymorphism (10% of North Americans are homozygous for UGT1A1*28 allele). Patients homozygous for the UGT1A1*28 allele are at increased risk of neutropenia; initial one-level dose reduction should be considered for both single-agent and combination regimens. The lactones of both Irinotecan and SN-38 undergo hydrolysis to inactive hydroxyl acid forms.

Half-life elimination: SN-38: Mean terminal: 10-20 hours

Time to peak: SN-38: Following 90-minute infusion: ~1 hour

Excretion: Within 24 hours: urine: Irinotecan (11% to 20%), metabolites (SN-38 < 1%, SN-38 glucuronide, 3%)

***Adverse Events***

Consult the package insert for the most current and complete information including U.S. Boxed Warnings pertaining to severe diarrhea and severe myelosuppression.

Common known potential toxicities, > 10%:

Cardiovascular: Vasodilation

Central nervous system: Cholinergic toxicity (includes rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing and intestinal hyperperistalsis); fever, pain, dizziness, insomnia, headache, chills

Dermatologic: Alopecia, rash

Endocrine & metabolic: Dehydration

Gastrointestinal: Late onset diarrhea, early onset diarrhea, nausea, abdominal pain, vomiting, cramps, anorexia, constipation, mucositis, weight loss, flatulence, stomatitis

Hematologic: Anemia, leukopenia, thrombocytopenia, neutropenia

Hepatic: Bilirubin increased, alkaline phosphatase increased

Neuromuscular & skeletal: Weakness, back pain

Respiratory: Dyspnea, cough, rhinitis

Miscellaneous: Diaphoresis, infection

Less common known potential toxicities, 1% - 10%:

Cardiovascular: Edema, hypotension, thromboembolic events

Central nervous system: Somnolence, confusion

Gastrointestinal: Abdominal fullness, dyspepsia

Hematologic: Neutropenic fever, hemorrhage, neutropenic infection

Hepatic: AST increased, ascites and/or jaundice

Respiratory: Pneumonia

Rare known potential toxicities, <1% (Limited to important or life-threatening):

ALT increased, amylase increased, anaphylactoid reaction, anaphylaxis, angina, arterial thrombosis, bleeding, Bradycardia, cardiac arrest, cerebral infarct, cerebrovascular accident, circulatory failure, colitis, deep thrombophlebitis, dysrhythmia, embolus, gastrointestinal bleeding, gastrointestinal obstruction, hepatomegaly, hiccups, hyperglycemia, hypersensitivity, hyponatremia, ileus, interstitial lung disease, intestinal perforation, ischemic colitis, lipase increased, lymphocytopenia, megacolon, MI, muscle cramps, myocardial ischemia, pancreatitis, paresthesia, peripheral vascular disorder, pulmonary embolus, pulmonary toxicity (dyspnea, fever, reticulonodular infiltrates on chest x-ray), renal failure (acute), renal impairment, syncope, thrombophlebitis, thrombosis, typhlitis, ulceration, ulcerative colitis, vertigo

***Nursing Guidelines***

If possible, check for any history of hypersensitivity reaction to any previous drug formulated with polysorbate 80.

Cholinergic symptoms of lacrimation, nasal congestion, diaphoresis, flushing, ABD cramping, and diarrhea can occur at the beginning, during, or immediately after the CPT-11 infusion. It is suggested that the patient remain in the treatment area for a minimum of one hour following the completion of the very first CPT-11 infusion. If diarrhea occurs within one hour of infusion, refer to Section 8.1 for management.

Patient education is extremely important. Impress on the patient the importance of compliance with treatment of diarrhea management. Stress the need for prompt recognition and early intervention. Motivate the patient to report any complications immediately. The cholera-like syndrome can be unresponsive to conventional antidiarrheals and can result in severe dehydration.

Ondansetron and diphenhydramine should provide good relief from the nausea/vomiting/cramping. Avoid prochlorperazine on the day of treatment due to its association with akathisia (motor restlessness). Prochlorperazine may be taken between treatments.

Advise avoidance of excess caffeine, a GI stimulant. Avoid magnesium-based antacids such as Mylanta, Maalox, Rolaids, MOM, Mag-Ox 400, and Tylenol with antacid.

The pulmonary toxicity seen is usually manifested by dyspnea beginning 42-175 days after treatment and occurs at a cumulative dose ranging from 400-1000 mg/m$^2$ (median 750). Instruct patient to report any cough or SOB.

Patients are at risk for developing eosinophilia and will improve on steroid therapy.

Hepatic enzyme elevations have been transient and did not require intervention.

Monitor CBC closely. Leukopenia occurs primarily as neutropenia but can be severe and dose limiting. The simultaneous occurrence of grade 4 diarrhea and grade 4 neutropenia is rare but may render the patient more susceptible to polymicrobial sepsis and potentially death.

Advise patients of probable hair loss.

## 11.0 MEASUREMENT OF EFFECT

For Arm 1 patients prior to surgical resection only, response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1) [20]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline.

For both Arm 1 and Arm 2 patients after surgical resection, the disease status (e.g. local and/or distant recurrence) will be evaluated as specified in Section 11.8.

## 11.1 Schedule of Evaluations

Restaging cross sectional imaging studies are performed as scheduled throughout the study timeline:

- Prior to treatment (includes real-time central review),
- Following 4 cycles of neoadjuvant chemotherapy (Arm 1)
- Following either 8 cycles of neoadjuvant chemotherapy or before surgery (Arm 1)
- Following surgery but prior to post-operative chemotherapy (both Arm 1 and Arm 2)
- Following 4 cycles of adjuvant chemotherapy (both Arm 1 and Arm 2)
- Following 8 cycles of adjuvant chemotherapy (Arm 2)
- Following 12 cycles of adjuvant chemotherapy (Arm 2)

Surveillance is per the schedule outlined in the Study Calendar in Section 5.0.

Supporting documentation of radiological, surgical, and pathologic response, progression, and recurrence should be submitted per Section 6.1.3.

## 11.2 Definitions of Measurable and Non-measurable Disease

### 11.2.1 Measurable Disease

A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥2.0 cm with chest X-ray, or as ≥ 1.0 cm with CT scan or MRI.

A superficial non-nodal lesion is measurable if its longest diameter is ≥ 1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

A malignant lymph node is considered measurable if its short axis is > 1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

### 11.2.2 Non-measurable Disease

All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥ 1.0 to < 1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.

Note: 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis < 1.0 cm are considered non-pathological (i.e. normal) and should not be recorded or followed.

## 11.3 Guidelines for Evaluation of Measurable Disease

### 11.3.1 Measurement Methods:

- All measurements should be recorded in metric notation (i.e. decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during neoadjuvant chemotherapy (Arm 1). For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre-treatment and restaging tumor assessments during neoadjuvant chemotherapy (Arm 1).
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

### 11.3.2 Acceptable Modalities for Measurable Disease:

- Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 3 mm or less.
- As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

### 11.3.3 Measurement at Restaging during Neoadjuvant Chemotherapy (Arm 1):

- The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.
- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g. residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

## 11.4 Measurement of Treatment/Intervention Effect (Prior to Surgical Resection)

### 11.4.1 Target Lesions & Target Lymph Nodes

- Measurable lesions (as defined in Section 11.2.1) up to a maximum of 3 lesions, representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. These lesions can be non-nodal or nodal (as defined in Section 11.2.1), where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.
- Note: If fewer than 3 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.
- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case

that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.

- **Baseline Sum of Dimensions (BSD):** A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.
- **Post-baseline Sum of the Dimensions (PBSD):** A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.
- The minimum sum of the dimensions (MSD) is the minimum of the BSD and the PBSD.

### 11.4.2 Non-target Lesions & Non-target Lymph Nodes

Non-measurable sites of disease (Section 11.2.2) are classified as non-target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be evaluated in accordance with Section 11.4.3.

### 11.4.3 Response Criteria

All target lesions and target lymph nodes followed by CT/MRI/physical examination must be measured on re-evaluation at the evaluation time points specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

Evaluation of Target Lesions

**Complete Response (CR):** All of the following must be true:

a. Disappearance of all target lesions.

b. Each target lymph node must have reduction in short axis to < 1.0 cm.

**Partial Response (PR):** At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (see Section 11.4.1).

**Progression (PD):** At least one of the following must be true:

a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.

b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.4.1). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.

**Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

Evaluation of Non-target Lesions & Non-target Lymph Nodes

**Complete Response (CR):** All of the following must be true:

a. Disappearance of all non-target lesions.

b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.

**Non-CR/Non-PD:** Persistence of one or more non-target lesions or non-target lymph nodes.

**Progression (PD):** At least one of the following must be true:

a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.

b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)

#### 11.4.3.1 Evaluation of Elevated CA19-9 Levels (When Present)

Note: this evaluation will be done for each patient for descriptive purposes only and will not be used to evaluate the secondary endpoint of progression free survival. Decision making for the efficacy of therapy and for relapse or progression must be based on imaging. Biochemical progression without the demonstration of objective progression of target or non-target lesion will not be sufficient indication to remove the patient from the study (refer to Section 13.1).

Biochemical Response (B-RESP): Reduction in elevated CA 19-9 level by at least 50% of normalization of an elevated value, confirmed with 2 successive measures.

Biochemical Progression (B-PROG): Increase in elevated CA 19-9 level by 50%, confirmed with 2 successive measures. If patient has had biochemical response as defined above, then subsequent biochemical progression is defined as >50% increase from the lowest recorded level while on study.

Biochemical Stability (B-STAB): Elevated CA 19-9 level does not change enough to qualify as response or progression.

### 11.4.4 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following tables:

| For Patients with Measurable Disease | | | |
|---|---|---|---|
| **Target Lesions & Target Lymph Nodes** | **Non-target Lesions & Non-target Lymph Nodes** | **New Sites of Disease** | **Overall Objective Status** |
| CR | CR | No | CR |
| CR | Non-CR/Non-PD | No | PR |
| PR | CR<br>Non-CR/Non-PD | No | PR |
| CR/PR | Not All Evaluated* | No | PR** |
| SD | CR<br>Non-CR/Non-PD<br>Not All Evaluated* | No | SD |
| Not all Evaluated | CR<br>Non-CR/Non-PD<br>Not All Evaluated* | No | Not Evaluated (NE) |
| PD | Unequivocal PD<br>CR<br>Non-CR/Non-PD<br>Not All Evaluated* | Yes or No | PD |
| CR/PR/SD/PD/Not all Evaluated | Unequivocal PD | Yes or No | PD |
| CR/PR/SD/PD/Not all Evaluated | CR<br>Non-CR/Non-PD<br>Not All Evaluated* | Yes | PD |

* See Section 11.4.3

| For Patients with Non-measurable Disease Only | | |
|---|---|---|
| **Non-target Lesions & Non-target Lymph Nodes** | **New Sites of Disease** | **Overall Objective Status** |
| CR | No | CR |
| Non-CR/Non-PD | No | Non-CR/Non-PD |
| Not All Evaluated* | No | Not Evaluated (NE) |
| Unequivocal PD | Yes or No | PD |
| Any | Yes | PD |

* See Section 11.4.3

### 11.4.5 Symptomatic Deterioration

Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration.

### 11.5 Definitions of Analysis Variables

Formal definitions of variables used in analyses can be found in the Statistical Considerations section of the protocol.

### 11.6 Surgical Pathologic Determination of Treatment Response (Arm 1)

Pathologic response to neoadjuvant therapy will be documented at the site by using the information from the local operative report and local pathology report. This will be utilized at the site for individual patient care. See Section 11.7 for further information.

In addition, there will be a retrospective central pathology review that documents the pathologic response to neoadjuvant therapy, but will NOT be utilized for the management of the individual patient.

Histopathologic response to pre-operative therapy will be determined by analysis of the resected surgical specimen by the pathologist (see Section 7.2). The following grades will be used to semi-quantitatively characterize treatment response:

- I - 0% residual tumor cells in the specimen (pCR)
- II - 1 to < 5% residual tumor cells in the specimen
- III - ≥ 5% residual tumor cells in the specimen

### 11.7 Histopathologic Determination of R-status

#### 11.7.1 "Macroscopic disease" is assessed by surgeon and "microscopic disease" is assessed by the histopathologist.

#### 11.7.2 Margins to be assessed in this trial include: 1) common bile duct, 2) SMA margin, 3) pancreatic neck as described in pathology section:

- R0- Macroscopically complete tumor removal with negative microscopic surgical margins.
- R1- Macroscopically complete tumor removal with positive microscopic margins (any or all).
- R2- Macroscopically incomplete tumor removal with known or suspected residual gross disease.

### 11.8 Treatment Evaluation after Completion of Surgery, during Post-operative Chemotherapy, and after Completion of Post-operative Chemotherapy

#### 11.8.1 The term "recurrence" is used if cancer returns either in the locoregional area of the primary tumor or at distant sites following R0 or R1 resection.

#### 11.8.2 Recurrence is determined radiographically and biopsy need not be performed except as detailed below or when CT findings are equivocal in the determination of the enrolling physician.

Locoregional Recurrence: identified by a new soft-tissue mass around the mesenteric vasculature or regional lymph nodes. Note that soft-tissue in this location on early post-operative scans may be benign and due to post-operative changes. Such findings may be difficult to distinguish from early tumor progression. In cases in which the diagnosis is ambiguous, discussion with the PI should occur. Performance of tissue biopsy should be considered prior to assigning a diagnosis of locoregional recurrent disease.

Distant Recurrence: identified by a new hypodensity in the liver or nodule(s) in the lungs or peritoneum. Other sites of presumptive distant recurrence (adrenal, brain) should require prompt biopsy confirmation. New ascites should be interrogated with aspiration and cytology if it is an isolated finding and should not necessarily be taken to indicate carcinomatosis, particularly following the performance of resection and reconstruction of the mesenteric vein(s).

## 12.0 END OF TREATMENT/INTERVENTION

### 12.1 Duration of Protocol Treatment

Protocol treatment is to continue for duration outlined in the treatment section or until disease progression. Please see the Study Calendar (Section 5.0) and the treatment section (Section 7.0) for treatment and follow-up time periods.

### 12.2 Criteria for Discontinuation of Protocol Treatment/Intervention

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

- Disease recurrence after resection
- Metastatic disease identified on imaging studies
- Local determination of disease progression via RECIST v1.1; the treating investigator should decide whether continuing protocol treatment is in the best interest of the patient
- Presence of locally advanced disease on pre-surgical restaging imaging studies
- Decline in performance status in the absence of radiographic evidence for disease progression if performance status cannot be recovered (symptomatic deterioration)
- Metastatic disease identified intraoperatively and biopsy-proven
- Unresectable disease identified intraoperatively (e.g. locally infiltrative disease without metastases for which the surgeon does not feel resection is safe)
- R2 surgical resection
- Nontherapeutic (aborted) operation for any other reason
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Patient non-compliance
- Pregnancy (if applicable)
    - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.
    - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by sponsor

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

## 12.3 Follow-up

### 12.3.1 Duration of Follow-up

All patients will be followed for survival for up to 6 years after registration.

### 12.3.2 Follow-up for Patients who Stop Study Treatment Early

Patients who are removed from protocol therapy will be followed per Section 5.0, post-treatment follow-up. Protocol treatment will be discontinued and further treatment is at the discretion of the treating physician.

## 12.4 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on data forms.
- Follow the patient for protocol endpoints as required by the Study Calendar.

## 12.5 Managing Ineligible Patients and Registered Patients Who Never Receive Protocol Intervention

**Definition of ineligible patient**

A study participant who is registered to the trial but does not meet all of the eligibility criteria is deemed to be ineligible.

**Follow-up for ineligible patients who continue with protocol treatment**

Patients who are deemed ineligible after registering may continue protocol treatment, provided the treating physician, study chair, and executive officer agree there are no safety concerns if the patient continues protocol treatment. All scans, tests, and data submission are to continue as if the patient were eligible. Notification of the local IRB may be necessary per local IRB policies.

**Follow-up for ineligible patients who discontinue protocol treatment**

For patients who are deemed ineligible after registering to the trial, who start treatment, but then discontinue study treatment, the same data submission requirements are to be followed as for those patients who are eligible and who discontinue study treatment.

**Follow-up for patients who are registered, but who never start study treatment**

For all study participants who are registered to the trial but who never receive study intervention (regardless of eligibility), the follow-up requirements are specified below.

Baseline, off treatment, and post-treatment follow-up (i.e., relapse, progression, and survival) data submission required. See the Data Submission Schedule accompanying the All Forms Packet.

# 13.0 STATISTICAL CONSIDERATIONS

## 13.1 Study Endpoints

Primary Endpoint

- Overall Survival (OS): The primary endpoint of this study is OS defined as the time from the date of randomization to the date of death due to all causes.

Secondary Endpoints

- Disease-free Survival (DFS): DFS is defined as the time from the date of randomization to the date of progression prior to surgery, metastases detected during surgery, recurrence (locoregional and/or distant) after resection, and death due to all causes, whichever occurs first.
- Time to Locoregional Recurrence (TLR): TLR is defined as the time from the date of randomization to the date of, locoregional recurrence after resection.
- Time to Distant Metastases (TDM): TLR is defined as the time from the date of randomization to the date of, metastases prior to surgery, metastases detected during surgery, or distant recurrence after resection.
- R0 Resection Rate: R0 resection rate is defined as the proportion of patients in whom an R0 resection was achieved during surgery (see Section 11.7).
- Rate of Unresectability: Rate of unresectability is defined as the proportion of patients who cannot undergo surgery due to adverse events, progressive disease, death, poor performance, or patient/physician decision, are deemed unresectable before surgery, or resection was not performed during surgery.
- Pathologic Complete Response (pCR) Rate: pCR rate is defined as the proportion of patients in whom a pCR was confirmed by histopathologic review of the surgical specimen (see Section 11.6).
- Adverse Events (AE): AEs and the maximum grade for each type of adverse events will be summarized for each patient separately for the following three periods:
    - During perioperative chemotherapy
    - Surgical complications during surgery and post-operative period for 30 days
    - During adjuvant chemotherapy
- mFOLFIRINOX Dose Intensity Delivered and Number of Cycles Received: Dose intensity delivered per agent in mFOLFIRINOX is defined as the total cumulative dose (both perioperative and adjuvant for Arm 1, and adjuvant for Arm 2) the patient received divided by total dose planned per protocol, times 100%. Number of cycles received is defined as the total number of cycles that the patient received at least one dose of any agent in mFOLFIRINOX.

## 13.2 Sample Size

We anticipate enrolling a maximum of 352 patients (176 per arm). We estimate 80% of patients who are pre-registered for central review will be randomized to therapy. We anticipate an actual rate of 80 patients per year. Thus, we expect to pre-register 460 patients to reach the targeted accrual of 352 patients. The accrual period of this study is estimated to be 4.4 years.

### 13.3 Power Justification

This randomized phase III trial is designed to primarily compare OS in patients with resectable pancreatic adenocarcinoma treated with perioperative mFOLFIRINOX and surgery versus up-front surgery followed by adjuvant mFOLFIRINOX. The randomization ratio is 1:1. This study implements a group sequential design with a single interim analysis for both futility and efficacy evaluation, adopting Rho family (Rho=3.2) beta spending function and Rho family (Rho=4.0) alpha spending function for controlling overall type I and type II error rate, respectively.

Table 1 summarizes the studies which reported R0 resection rates and 2-year OS rates among patients who received neoadjuvant mFOLFIRINOX. Most of these studies enrolled or studied borderline resectable or locally advanced patients. It is anticipated that OS will be greater in patients with resectable disease in comparison to the patients in these trials. Therefore, we hypothesize that the 2-year OS rate in the perioperative mFOLFIRINOX arm will be at least 50%.

**Table 1: Outcomes of patients who received neoadjuvant mFOLFIRINOX**

| Trial/ Reference | Design | N | Planned Total Cycles Neoadjuvant | R0 Rate | 2-year OS Rate |
|---|---|---|---|---|---|
| **Mix of Resectable and Borderline Resectable Patients** | | | | | |
| Janssen ASCO 2018 | Meta-analysis | 779 (304 BR PDAC) | Median of 4.5 cycles | 87% | ~22-53%* |
| **Borderline Resectable Patients** | | | | | |
| Murphy 2018 | Single-arm phase II (single site) | 48 | 8 + ChemoRT | 65% | 56% |
| Katz 2016 | Pilot (multi-site) | 22 | 4 + ChemoRT | 64% | 36% |
| **Locally Advanced Patients** | | | | | |
| Chllamma 2016 | Retrospective (single site) | 36 | Median of 6 cycles | 14% | ~48%* |
| Stein 2016 | Single-arm phase II (multi-site) | 29 | Median of 8 cycles | NR | ~53%$ |

* 2-year rates were converted from median time assuming exponential survival distribution; $ from KMs

Table 2 summarizes the studies which reported R0 resection rates and 2-year OS rates among patients who received adjuvant mFOLFIRINOX or gemcitabine. The PRODIGE24/CCTG PA.6 study randomized patients after resection (i.e. the patients who underwent R0 or R1 resection). We would anticipate that randomizing patients prior to surgery would lead to a 2-year OS rate lower than the 74% reported in this study. The adjuvant chemotherapy used in the PREOPANC and Jiang2018 studies was gemcitabine based. We would expect these to have an inferior outcome compared with the adjuvant mFOLFIRINOX treatment. Thus, we hypothesize that the 2-year OS rate of adjuvant FOLFIRINOX will be 30 to 40%.

**Table 2: Outcomes of Patients Who Received Adjuvant Treatments**

| Trial/ Reference | Design | N | Population | Randomization | Adjuvant Treatment | Resection Rate | Median Cycles of | 2-year OS Rate |
|---|---|---|---|---|---|---|---|---|

| | | | | | | | **Adjuvant Treatment** | |
|---|---|---|---|---|---|---|---|---|
| PRODIGE 24/ CCTG PA.6 ASCO 2018 | RP III | 247 | R0 (60%)/ R1 (40%) | After resection | mFOLFIRINOX | 100% | 12 | ~74%* |
| PREOPANC ASCO 2018 | RP III | 127 | BR (46%)/ R (54%) | Before resection | Gemcitabine | 72% | NR | ~30%* |
| Jiang 2018 | RP II/III | 23 | BR | Before resection | ChemoRT → Gemcitabine | 78% | NR | 26% (ITT)/ 42% (PP) |

* 2-year rates were converted from median time assuming exponential survival distribution

The power and sample size calculation is based on the assumption that perioperative therapy arm will be more efficacious than adjuvant therapy. A total number of 248 events will provide an 88% power to detect a hazard ratio (HR) of 0.697 (2-year OS rate of 50% and 37% in perioperative therapy vs. adjuvant therapy arms, respectively) at a one-sided significance level of 0.05. This will require enrollment of a maximum of 352 patients (176 per arm), assuming an accrual rate of 80 patients per year, minimal follow-up of 18 months, and constant consent withdrawal rate of 5% in both arms. With the decision rules stated in Section 13.4, this design provides the following design operation characteristics:

| If the true 2-year OS rate is… | H1<br>Perioperative therapy: 50%<br>Adjuvant therapy 37% | H0<br>Perioperative therapy: 37%<br>Adjuvant therapy: 37% |
|---|---|---|
| **Final Analysis** | | |
| Then the probability of declaring that OS of the perioperative therapy arm is superior to the adjuvant therapy arm is… | 0.881 | 0.049 |
| **Interim Analysis** | | |
| Probability of early reporting at the interim analysis due to that OS of the perioperative therapy arm is superior to adjuvant therapy arm is… | 0.234 | 0.013 |
| Probability of early reporting at the interim analysis due to futility is… | 0.003 | 0.414 |

Probabilities are based on simulation study with 50,000 replicates.

## 13.4 Statistical Analysis Plan

### 13.4.1 Analysis Populations

- **Intent-to-Treat (ITT) Population:** ITT population includes all patients who are deemed eligible by central imaging review and are properly randomized, regardless of the actual treatment received. The treatment grouping will be according to the original assignment at randomization.

- **Per-Protocol (PP) Population:** PP population includes all patients who are deemed eligible by central imaging review and received mFOLFIRINOX as specified in the following:
    - PP Population 1
        - Arm 1: completed at least 4 cycles of pre-operative mFOLFIRINOX
        - Arm 2: completed at least 4 cycles of adjuvant mFOLFIRINOX
    - PP Population 2
        - Arm 1: completed at least 6 cycles of pre-operative mFOLFIRINOX
        - Arm 2: completed at least 6 cycles of adjuvant mFOLFIRINOX
    - PP Population 3
        - Arm 1: completed 8 cycles of pre-operative mFOLFIRINOX
        - Arm 2: completed at least 12 cycles of adjuvant mFOLFIRINOX
- **Safety Population:** Safety population includes all patients who received any dose of treatment defined by protocol.

### 13.4.2 Primary Endpoint

ITT Analysis of OS

The primary efficacy inference regarding OS endpoint will be conducted on the ITT population; see Section 13.4.1.

- **Interim Analysis Decision Rule:** An OS interim analysis will be performed when 50% of the events (124 events, estimated accrual of 258 to 277 and estimated time of 3.2 to 3.5 years after first patient is enrolled; reference: total accrual time will be 4.4 years if the study continues after interim analysis) are observed combining the two arms. Stratified Cox model will be conducted to compare OS in the perioperative therapy arm to OS in the adjuvant therapy arm with stratification factors as stratum. The estimated HR will be compared to the following decision boundaries:

| Interim analysis | Boundary in HR scale | Decisions to allow early reporting |
|---|---|---|
| Efficacy | < 0.612 | Reject H0: concluding OS of the perioperative therapy arm is superior to adjuvant therapy arm |
| Futility | > 1.040 | Reject H1: concluding there will not be statistically significant evidence |

| | | |
|---|---|---|
| | | that OS of the perioperative therapy arm would be superior to adjuvant therapy arm if the study reached full accrual |

- If neither of the efficacy nor futility boundaries is crossed, then the trial will continue accrual and patient follow-up per protocol. The trial will not be halted while performing the interim analysis.
- If one of the boundaries is crossed, discussions between the A021806 Study Team, Alliance DSMB, and NCI will be carried out for early reporting and subsequent trial conduct.

- **Final Analysis Decision Rule:** If the trial continues after the interim analysis, the final OS analysis will be performed with a total of 248 events observed combining the two arms. Stratified Cox model will be conducted to compare OS in the perioperative therapy arm to OS in the adjuvant therapy arm. If the one-sided p-value of the comparison is < 0.05, then we will conclude the OS of the perioperative therapy arm is superior to adjuvant therapy.

PP Analysis of OS

If study passes interim analysis and continues accrual, in addition to ITT analysis, the OS will be compared between two treatment arms based on PP populations (see Section 13.4.1) by stratified Cox. Assuming 2/3 of patients will complete all protocol-defined treatment, the current sample size can provide at least 80% power to detect a HR of range of 0.6 to 0.7 at one-sided alpha of 0.1.

### 13.4.3 Secondary Endpoints

The analyses of secondary endpoints will be conducted on ITT and PP population whenever it is applicable and plausible. Safety-related analyses will be performed on the safety population.

The distributions of time-to-event endpoints will be estimated, in each arm, using the method of Kaplan-Meier and compared by a stratified Cox regression model. The binary endpoints will be estimated, in each arm, and compared by chi-squared test or Fisher's exact test. Dose intensity and number of cycles will be summarized by mean, standard deviation, median, Q1, Q3, and range, in each arm, and compared by Wilcoxon Rank Sum test. The maximum grade for each type of adverse events that are possibly, probably, or definitely related to study treatments will be recorded for each patient. The frequency tables will be reviewed to determine the patterns. The overall adverse event rates for grade 4 or higher adverse events will be compared between two treatment groups using Chi-square test (or Fisher's exact test if the data in the contingency table is sparse).

PRO-CTCAE is not intended for expedited reporting, real time review or safety reporting. PRO-CTCAE data are exploratory and not currently intended for use in data safety monitoring or adverse event stopping rules.

## 13.5 Monitoring

### 13.5.1 Safety Monitoring

The safety monitoring rule specified below is based on the knowledge available at study development. We note that the Adverse Event Monitoring Rule may be adjusted in the event of either 1) the study re-opening to accrual or 2) at any time during the conduct of

the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation.

If at any time in either arm we observe at least one of the following, discussions between the A021806 Study Team, Alliance DSMB, and NCI are required to assess if any changes to the study are needed:

- The rate of on-study deaths during treatment, or within the first 30 days following off-protocol treatment, exceeds 6 or more in the first 30 patients or, after 30 patients enrolled, 20% or more of all treated patients.
- If 6 or more patients in the first 30 treated patients (or 20% of all patients after 30 are accrued) experience a grade 4 or higher non-hematologic adverse event deemed at least possibly related to study treatment (i.e. an adverse event with attribute specified as "possible," "probable," or "definite").

The Study Chair and the Study Statistician will review the study monthly to identify accrual, adverse event/safety, and any endpoint problems that might be developing.

### 13.5.2 Data Safety Monitoring Board

This study will be monitored by the Alliance Data and Safety Monitoring Board (DSMB), an NCI-approved functioning body. Reports containing efficacy, adverse event, and administrative information will be provided to the DSMB every six months as per NCI guidelines.

### 13.5.3 DMU Monitoring

This study has been assigned Demography monitoring.

Required submission of patient demographic data for this study will be submitted automatically via OPEN.

**Note:** Serious adverse events must be submitted via CTEP-AERS per protocol guidelines.

## 13.6 Descriptive Factors

- Age: ≤ 55 years versus > 55 years
- Gender: male versus female
- Albumin < LLN: yes versus no

## 13.7 Inclusion of Women and Minorities

This study will be available to all eligible patients, regardless of race, gender, or ethnic origin. There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

The geographical region served by the Alliance, has a population which includes approximately 18% minorities. Based on prior Alliance studies involving similar disease sites, we expect about 20% of patients will be classified as minorities by race and about 39% of patients will be women. Expected sizes of racial by gender subsets for patients registered randomized to this study are shown in the following table.

| **DOMESTIC PLANNED ENROLLMENT REPORT** | | | | | |
|---|---|---|---|---|---|
| **Racial Categories** | **Ethnic Categories** | | | | **Total** |
| | **Not Hispanic or Latino** | | **Hispanic or Latino** | | |
| | **Female** | **Male** | **Female** | **Male** | |
| American Indian/ Alaska Native | 4 | 5 | 0 | 1 | 10 |
| Asian | 9 | 17 | 0 | 0 | 26 |
| Native Hawaiian or Other Pacific Islander | 7 | 24 | 0 | 0 | 31 |
| Black or African American | 6 | 11 | 1 | 3 | 21 |
| White | 106 | 145 | 4 | 9 | 264 |
| More Than One Race | 0 | 0 | 0 | 0 | 0 |
| **Total** | 128 | 196 | 5 | 13 | 352 |

## 14.0 CORRELATIVE AND COMPANION STUDIES

There will be a mandatory retrospective histopathology review, three optional substudies, and optional biobanking for future correlative science studies, and all patients are encouraged (or required) to participate.

### 14.1 Quality of Life Study (Alliance A021806-HO1)

#### 14.1.1 Background

Quality of life (QOL) in this study will be assessed using the EORTC QLQ-C30 questionnaire. The EORTC QLQ-C30 questionnaire consists of 30 items in which are embedded five functional domains (physical, role, emotional, cognitive, and social), nine symptom domains (including fatigue, pain, nausea and vomiting, dyspnea, loss of appetite, insomnia, constipation, diarrhea, and financial impact), and a global QOL assessment. Thus, this questionnaire adequately covers the main problems and symptoms presented by patients with pancreatic cancer. The validity and reliability of this questionnaire have been studied by the EORTC Study Group on Quality of Life [21]. This tool was used in the pivotal phase III trial that established the superiority of FOLFIRINOX over single agent gemcitabine for patients with metastatic adenocarcinoma of the pancreas [7]. In this study, data from the EORTC QLQ-C30 questionnaire demonstrated the time until definitive deterioration of QOL was significantly longer for FOLFIRINOX compared with single agent gemcitabine.

This protocol is for localized disease with likely a more fit patient population than the aforementioned metastatic study. The overarching hypothesis of the trial is that patients who receive perioperative mFOLFIRINOX will have a higher 2-year OS rate in comparison to those treated with adjuvant mFOLFIRINOX. This hypothesis is based on prior studies in which the use of FOLFIRINOX in the neoadjuvant setting has shown promise. Neoadjuvant FOLFIRINOX decreased nodal positivity, increased margin-negative resection rates, and improved OS in a retrospective analysis of borderline resectable patients [8]. Similarly, a recent phase II trial from Massachusetts General Hospital demonstrated that neoadjuvant FOLFIRINOX in patients with borderline resectable disease was well tolerated and led to margin-negative resection rates in greater than 90% of patients who underwent resection [9].

One of the possible drivers of the overarching hypothesis is that perioperative mFOLFIRINOX will be more tolerable than upfront surgery followed by adjuvant mFOLFIRINOX therapy. This QOL study will provide data to directly assess the impact of therapy on patient functioning, symptoms, and health status/QOL which are key components of tolerability per the Friends of Cancer Research working definition (https://www.focr.org/publications/broadening-definition-tolerability-cancer-clinical-trials-better-measure-patient). If a survival benefit is shown, these data will assist in understating the mechanism of action for the downstream OS benefit. If a survival benefit is not show (i.e. if comparable survival outcomes are observed for both arms), these data will enable selection of the approach which optimizes patient functioning, symptoms, and QOL outcomes.

#### 14.1.2 Objectives

To compare physical functioning, nausea/vomiting, and diarrhea, as measured with the EORTC QLQ-C30 between patients with resectable pancreatic adenocarcinoma treated with perioperative mFOLFIRINOX and surgery versus up-front surgery followed by adjuvant mFOLFIRINOX.

The following primary and secondary hypotheses will be tested:

- **Primary Hypothesis:** Physical functioning will be superior on the perioperative mFOLFIRINOX arm after 4, 8, and 12 cycles as compared to after the same number of cycles of mFOLFIRINOX given adjuvantly.
- **Secondary Hypothesis:** Nausea/vomiting and diarrhea will be superior on the perioperative mFOLFIRINOX arm after 4, 8, and 12 cycles as compared to after the same number of cycles of mFOLFIRINOX given adjuvantly.

To explore other domains of quality of life (QOL) including role, emotional, cognitive, and social functioning, pain, dyspnea, loss of appetite, insomnia, constipation, financial impact, and health status/global QOL, as measured with the EORTC QLQ-C30 between patients with resectable pancreatic adenocarcinoma treated with perioperative mFOLFIRINOX and surgery versus up-front surgery followed by adjuvant mFOLFIRINOX. These analyses will be considered as exploratory.

### 14.1.3 Methods

For the Schedule of Assessments for this quality of life study, see Section 6.4. All participating institutions must ask patients during Step 1 registration for their consent to participate in this quality of life study, although patient participation is optional. QOL will be measured at baseline (prior to initiation of treatment/intervention) and at predetermined intervals on both arms of the study. On Arm 1: ≤ 14 days prior to initiation of treatment/intervention, prior to cycle 5, after end of cycle 8 (but prior to surgery), prior to cycle 9, and at the end of study treatment. On Arm 2: ≤ 14 days prior to initiation of treatment/intervention, prior to cycle 1 (but after surgery), prior to cycle 5, prior to cycle 9, and at the end of study treatment.

Paper booklets will be used for this study. For information regarding ordering the booklets, see Section 4.4. For all patients who consent to participate in this quality of life study (Alliance A021806-HO1), a booklet will be given to the patient to complete at the specified planned clinic visits before any procedures/tests are initiated at the site visit and prior to any discussion of their status with healthcare personnel at the site. The booklet contains 30 questions, and it is anticipated that the booklet will take approximately 5-10 minutes for the patient to complete at each administration time point. We anticipate having booklets available in English and French, though additional languages may be made available over the course of the study. Patients who consent to participate in this quality of life study (Alliance A021806-HO1) may decline to complete a booklet at any time. The primary reason for each missed booklet will be collected on a case report form.

### 14.1.4 Analysis

The EORTC QLQ-C30 will be scored according to the published scoring algorithm. The primary statistical analysis approach will employ mixed modeling consistent with Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data (SISAQOL) recommendations [22]. The primary analysis will involve a single mixed model for the EORTC QLQ-C30 physical function and will include the following three time points as outcomes from each arm: prior to cycle 5, prior to cycle 9, and end of study treatment. In addition to a randomized arm covariate, the model will include the "≤ 14 days prior to initiation of treatment/intervention" (i.e. baseline) EORTC QLQ-C30 physical function score as a continuous covariate, will use the planned assessment as the categorical time covariate, and will include a time-by-arm interaction effect. Compound covariance will initially be used, though alternative covariance

structures will be investigated with the final covariance structure selected based on minimization of the Akaike information criterion. A contrast statement will be constructed for each of the primary hypothesis tests, i.e., to compare mean "prior to cycle 5", "prior to cycle 9", and "end of study treatment" EORTC QLQ-C30 physical function scores between arms. A Bonferroni approach will be used to maintain an overall $\alpha$=0.05 across the three primary hypothesis tests. A variety of sensitivity analyses will be employed to assess the impact that surgery may have on the primary analysis. Specifically, the primary analysis will be repeated using the "prior to cycle 1 (but after surgery)" time point as the baseline for Arm 2 (instead of the "≤ 14 days prior to initiation of treatment/intervention" time point) and using the "after end of cycle 8 (but prior to surgery)" time point as the assessment after 8 cycles of chemotherapy for Arm 1 (instead of the "prior to cycle 9" time point). In all analyses, estimates and tests of differences between arms will also be carried out incorporating changes from baseline (instead of absolute differences) within the mixed model framework.

Secondary and exploratory analyses will be conducted in the same way as described for the primary analysis. The primary patient-reported outcome analysis will be conducted at the time that all consented patients have completed the end-of-study assessment (or are no longer being followed for QOL). Release of the data for presentation will be at the discretion of the DSMB. Patients will be analyzed according to the randomized treatment arm assignment. All patients who consent for participation in the A021806-HO1 component with at least one baseline EORTC QLQ-C30 physical function score and at least one EORTC QLQ-C30 physical function score post-randomization will be included in the primary analysis. In the primary analysis, all observations available will be used. See below for information regarding analyses to account for missing data.

Graphical procedures will include plots of mixed model means with 95% confidence intervals over time by arm for each EORTC QLQ-C30 scale. Recommendations from Snyder et al. will be applied [23].

For all statistical analyses other than the three primary hypothesis tests, p-values <0.05 will be considered statistically significant (though interpretation will take into consideration that the type I error is strictly controlled for the primary hypothesis tests only). The clinical meaningfulness of score changes and differences will be based on Musoro et al., Cocks et al., and King et al. [24-27].

Missing data will be handled in a number of ways, following the recommended SISAQOL handling and reporting guidelines. Missing items within a scale score will be handled according to the EORTC QLQ-C30's published scoring algorithm. Missing data at the scale score level will be handled as follows. Baseline patient/disease characteristics will be compared between patients who do and do not provide data for the primary analysis. We will also graphically explore patterns of missing data. All analyses will be completed using all available data using mixed modeling, followed by analyses completed using a range of imputation methods. Lastly, we will employ pattern mixture models for longitudinal analyses. Output from all analyses will be tabulated and descriptively compared to assess the degree to which missing data impacts study results.

Power: For the purpose of power estimation, we use Table 4 in Cocks et al. which suggests that medium effects for the EORTC QLQ-C30 physical function, nausea/vomiting, and diarrhea scales are 14 points (0.6 standard deviations), 8 points (0.5 standard deviations), and 7 points (0.4 standard deviations), respectively [25]. Enrollment of all patients in this substudy ensures adequate power for all primary and secondary outcomes.

Assuming that 344 patients are randomized, of which 326 consent to the A021806-HO1 substudy and complete a baseline booklet, of which and 139, 125, and 119 complete booklets on Arm 1 and 126, 117, and 108 complete booklets on Arm 2 at the "prior to cycle 5", "prior to cycle 9," and "end of study treatment" time points (i.e. taking into account compliance and likelihood of staying on treatment), this study has 99%, 99%, and 98% power to detect a 0.6 standard deviation (i.e. 14-point) difference in EORTC QLQ-C30 physical function scores at each of the key time points between arms using a two-sided alpha=0.0167 t-test.

For the secondary comparison of EORTC QLQ-C30 nausea/vomiting, this study has 98%, 97%, and 96% power to detect a 0.5 standard deviation (i.e. 8-point) difference in EORTC QLQ-C30 nausea/vomiting scores at each of the key time points between arms using a two-sided alpha=0.05 t-test. For the secondary comparison of EORTC QLQ-C30 diarrhea, this study has 90%, 87%, and 85% power to detect a 0.4 standard deviation (i.e. 7-point) difference in EORTC QLQ-C30 diarrhea scores at each of the key time points between arms using a two-sided alpha=0.05 t-test.

## 14.2 Diet and Lifestyle Study (Alliance A021806-HO2)

### 14.2.1 Background

Epidemiologic and scientific research indicates that diet and other lifestyle factors have a significant influence on the risk of developing pancreatic cancer. Diet quality, certain dietary patterns, obesity, diabetes, leisure time physical activity, and smoking have been associated with the risk of developing pancreatic cancer [28-32].

The association of these modifiable dietary and lifestyle factors have not been studied in pancreatic cancer patients and survivors. There are limited data that supplementation with omega-3 fatty acids has a favorable effect on short-term weight status, performance status, or related factors in pancreatic cancer patients [33]. In one study, compliance with the prescription of 1.5 cans of a protein and energy dense, oral nutrition supplement +/-n-3 fatty acids improved nutrition related outcomes in untreated pancreatic cancer patients [34].

Cachexia is a prevalent condition in patients with pancreatic cancer, with progressive weight loss and nutritional deterioration. An estimated 40-80% of newly diagnosed pancreatic cancer will have cachexia, defined as greater than 5% weight loss over 6 months [35]. Cachexia is a complex metabolic disorder that involves features of anorexia, anemia, and loss of adipose and skeletal muscle mass. In one study of 977 patients treated at Kaiser Permanente, 63% were identified with cachexia, which was prevalent across all stages of disease and BMI classes. Patients with cachexia had lower survival (median 4.3 months, IQR 1.7–10.0) compared to those without cachexia (median 5.2 months, IQR 2.0–10.6), log-rank P=0.03. In the multivariate Cox regression, cachexia was independently associated with decreased overall survival (HR 1.24, CI: 1.06–1.45, P=0.01). However, the effect of cachexia on survival outcomes was modified by receipt of chemotherapy. Cachectic patients who did not receive chemotherapy had a 40% increase in risk of death compared to non-cachectic patients (HR 1.40, CI: 1.12–1.75), while those receiving chemotherapy were unaffected by cachexia (HR 1.04, CI: 0.82–1.32, Pinteraction=0.01) [36].

Physical activity has been extensively studies in patients treated for cancer. A recent Consensus Statement from International Multidisciplinary Roundtable reported there is enough evidence to conclude that specific doses of aerobic, combined aerobic plus

resistance training, and/or resistance training could improve common cancer-related health outcomes, including anxiety, depressive symptoms, fatigue, physical functioning, and health-related quality of life [37]. Implications for other outcomes, such as peripheral neuropathy and cognitive functioning, remain uncertain.

In other cancers, particularly breast, colorectal, and prostate cancers, there are increasing data on the associations of diet, physical activity, maintaining healthy body weight, smoking and certain supplements (e.g. omega 3 fatty acids and vitamin D) and disease recurrence and/or survivors [38]. Given the consistent data demonstrating associations of these factors on development of pancreatic cancer, A021806 presents a unique opportunity to collect contemporary data on dietary intake, physical activity, and other modifiable factors to investigate the associations of these modifiable variables on clinical outcomes.

Dietary constituents may influence chemotherapy toxicity by several means, including the induction or inhibition of enzymes responsible for the biotransformation and metabolism of chemotherapeutic agents. Earlier studies suggested that a high-protein-low-carbohydrate diet was associated with reduced toxicity from 5-FU [39].

Irinotecan is metabolized by a series of enzymes that are potentially influenced by exogenous factors. The principal toxicities of the drug are diarrhea and neutropenia, although individual patient experience will vary. In fact, the interpatient coefficient of variability of metabolism for irinotecan is among the highest for chemotherapeutic agents. Such variability may reflect both genetic as well as environmental factors. Irinotecan can be converted to aminopentanecarboxylic acid (APC) by cytochrome P450 3A4 or it can be bioactivated by carboxylesterases to SN-38 [40]. SN-38 is eliminated mainly through conjugation by hepatic uridine glucuronosyltransferase (UGT). Deconjugation of SN-38 by enteric beta-glucuronidase may contribute to enterohepatic recirculation of SN-38 and delayed intestinal toxicity. Little is known regarding the influence of exogenous factors on carboxylesterase activity. Several factors have been shown to influence P450 enzyme activity. Diets high in protein, garlic, vitamin C, red meat, and ethanol appear to increase P450 activity whereas diets high in carbohydrate and flavonoids reduce activity [41]. In addition, cigarette smoking appears to induce P450 activity possibly mediated by heterocyclic amines.

Activity of hepatic uridine glucuronosyltransferase (UGT) can be markedly influenced by exogenous factors. Studies in animals and humans suggest that cruciferous vegetable, ascorbic acid, carotenoid, protein, and ethanol intake increase UGT activity [42, 43]. In addition, smoking and obesity have been reported to increase UGT activity [44].

Inhibitors of beta-glucuronidase reduce the incidence of irinotecan toxicity. Dietary constituents appear to affect beta-glucuronidase activity. Increased consumption of vegetables and fiber decrease beta-glucuronidase activity whereas higher fat intake increases beta-glucuronidase activity [45-48]. Such dietary patterns could influence the rate of irinotecan toxicity.

Oxaliplatin undergoes nonenzymatic conversion in physiological solutions to active derivatives via displacement of the labile oxalate ligand. Several transient reaction species are formed, including monaquo and diaquo DACH platinum, which covalently bind with macromolecules, resulting in inter- and intra-strand platinum-DNA crosslinks. Oxaliplatin can cause significant neurotoxicity, possibly by accumulation of platinum within the peripheral nervous system [49]. The effects of diet and supplementation may also affect the incidence and severity of peripheral neuropathy. Other toxicities associated with platinum drugs may be altered with diet. In mouse models, diets high in zinc increase the

therapeutic index of carboplatin, with reduced hematological toxicity [50]. In a small randomized trial, Pace and colleagues demonstrated that supplementation with vitamin E significantly reduced incidence of neurotoxicity among patients treated with cisplatin [51].

The primary objectives of the A021806 trial is to compare perioperative therapy approach to postoperative therapy. Determining how host factors are associated with the toxicities of therapy as well as associations with outcomes will further understanding of the biology of pancreatic cancer, potential interaction of best approach to treat patients with resectable pancreatic cancer (i.e. factors that reduce potential for cachexia may impact tolerance to therapy, tolerance to surgery, whether starting with surgery or chemotherapy is optimal).

### 14.2.2 Objectives

**14.2.2.1** To prospectively assess the influence of diet, body mass index, weight loss, physical activity, and other lifestyle habits on the disease-free survival and overall survival among patients with localized pancreatic cancer.

**14.2.2.2** To assess the influence of diet, obesity, physical activity, and other lifestyle habits on the risk of toxicity associated with chemotherapy.

**14.2.2.3** In addition, exploratory analyses will investigate the interaction of diet and molecular markers within tumors on the prognosis of patients with localized pancreatic cancer.

### 14.2.3 Methods

In this companion study, patients participating in the treatment trial will be asked to consent to complete a 131-item validated, food-frequency questionnaire at 2 time points – (1) after randomization and within 4 weeks of starting chemotherapy (Arm 1) or before surgery (Arm 2) , as well as (2) 1 year after randomization. The questionnaire, designed by Dr. Walter Willett and colleagues for the Nurses' Health Study, has been extensively validated among both health professional and lay populations, and provides comprehensive data on over 100 micro-nutrients, with and without supplement use. This questionnaire can be self-administered. Within the questionnaire, a series of questions about leisure-time physical activity, smoking habits, alcohol intake, and other habits that have also been validated in large populations will be included. Height and weight will also be obtained as part of the clinical trial. Similar companion studies have been successfully conducted in other NCTN colorectal trials (CALGB 89803, CALGB 80405, CALGB 80702); 65-75% of eligible patients completed the questionnaire(s).

Validation of the Semi-quantitative Food Frequency Questionnaire (SFFQ): The current version of the questionnaire consists of 131 food items plus vitamin and mineral supplement use that collectively account for over 90% of the intake of the nutrients assessed [52-56]. For each food, a commonly used unit or portion size (e.g. one egg or slice of bread) is specified, and participants are asked how often, on average over the past year, they consumed that amount of each food. There are nine possible responses which range from never to six or more times per day. The nutrient intakes will be computed by multiplying the frequency of consumption of each food by the nutrient content of the specified portions, using composition values from Department of Agriculture sources supplemented with other data, including the components of specific vitamins and breakfast cereals. All nutrients will be adjusted for total energy intake by the residuals method [57].

In 1980, the food frequency questionnaire was administered twice to 173 individuals at an interval of approximately one year, and four one-week diet records for each subject were collected during that period. Diet records probably are the best measures of current, short-term food intake. Since the seven-day record provides information for a relatively short period of time, four one-week diet records in different seasons were collected. The mean calorie adjusted intakes from the four one-week diet records and those from the questionnaire were well-correlated [54-56]. In the 1986 diet validation study, the correlation between folate calculated from the SFFQ and red cell folate level was 0.55 [58]. Nutrients calculated from the expanded SFFQ were correlated with other corresponding biochemical indicators: plasma beta-carotene (r = 0.30-0.42), plasma vitamin E (r = 0.41-0.53), adipose linoleic acid (r = 0.35-0.37), adipose trans fatty acid (r = 0.51), and adipose N-3 fatty acids (r = 0.48-0.49) [59-62]. To evaluate further the capability of the revised 131-item questionnaire to discriminate among subjects, Willett and colleagues asked 127 individuals to complete two weeks of diet records and the semi-quantitative food frequency questionnaire in 1986. The mean calorie adjusted intakes from the diet records and those from the questionnaire were well-correlated [54].

The validity of this 131-item SFFQ was be separately assessed in 200 patients with colorectal, breast, or neuroendocrine cancer undergoing treatment with cytotoxic chemotherapy [63]. The Pearson correlation coefficients for various carotenoids as measured by the questionnaire, with the corresponding measurements in plasma specimens, ranged from 0.33 to 0.44 (all $P < .001$), adjusted for total energy intake, body mass index, age, sex, smoking status, and total plasma cholesterol. Similarly, the adjusted correlation between self-reported total vitamin E intake and plasma alpha-tocopherol was 0.34 ($P < .001$). Correlations between questionnaire and plasma measurements of trans-fat, eicosapentaenoic acid, and docosahexaenoic acid were 0.55, 0.29, and 0.42 (all $P < .001$), respectively. These levels of correlation were consistent with those reported in similar studies of self-reported diet in otherwise healthy populations. Thus, among patients with cancer receiving cytotoxic chemotherapy, questionnaire-based measurements of various micronutrients and dietary factors appeared to predict meaningful differences in the corresponding measurements in plasma specimens.

These data indicate that the proposed self-administered dietary questionnaires provide highly informative and biologically relevant measurement of a wide variety of nutrients, thus allowing one to address the dietary hypotheses outlined in the specific aims.

In terms of other measures from the survey, Wolf et al. reported on a detailed validation study of the physical activity questionnaire among a sample of 325 participants in the Nurses' Health Study II (NHS II) (241 random cohort sample and 84 random sample of African American participants) [64]. Participants completed four 1-week activity recalls and four 7-day activity diaries over one year and then repeated the NHS II activity questionnaire. For the total activity score, the correlations of the last activity questionnaire with the diaries was 0.64 for the total cohort sample and 0.59 for the African American sample. Within the Health Professionals Follow-up Study, a parallel study of men, validity of the physical activity questionnaire was assessed among 238 randomly selected participants by comparisons with four 1-week activity diaries, four 1-week activity recalls, and resting and post exercise pulse rates [65]. Correlations with the activity diaries were 0.41 for inactivity (sitting) and 0.58 for vigorous physical activity. Vigorous activity assessed by the questionnaire was correlated with resting pulse (r = -0.45) and post-exercise pulse (r = -0.41).

The data collected from the questionnaires, as described above, will be sent using encrypted secure spreadsheets to the Alliance SDC A021806 Statistician to prepare analysis datasets in conjunction with the clinical/outcome data. The A021806 Statistician will then coordinate the analyses with the A021806 Diet and Lifestyle Study co-Chair, Dr. Jeffrey Meyerhardt. Analyses will be conducted using the analysis dataset used for the analysis of the clinical endpoints to ensure consistent data is reported for the primary and secondary endpoints (e.g. data associated with censoring, proper inclusion of crossover data, and data to be excluded in cases of consent withdrawals for follow-up and correlative studies).

### 14.2.4 Potential Hypotheses

The A021806 questionnaire will provide the opportunity to examine multiple host factors (diet, lifestyle, medication use, cancer family history) on efficacy outcome, treatment-related toxicities, and operative complications. Several illustrative hypotheses demonstrate the potential of the data collected from two questionnaires.

**14.2.4.1** Regular physical activity (during and after completion of therapy) and avoidance of obesity will improve disease-free survival and overall survival. Sedentary lifestyle and obesity are each associated with an increased risk of developing pancreatic cancer. Both factors appear to act late in the pathway of carcinogenesis. While multiple studies have shown improvements in survival outcomes for breast, colon and prostate cancer, no study has assessed the influence of sedentary lifestyle and obesity among patients with pancreatic cancer. Further, we will test association of physical activity and BMI with tolerance to chemotherapy and surgical outcomes.

**14.2.4.2** Cachexia will be associated with worse disease-free and overall survival and be associated with tolerance to treatment. In the first questionnaire, we ask subjects regarding weight at 5 time points (current, age 18, typical adult weight, 12 months prior to diagnosis and 6 months prior to diagnosis). These data will allow for determination of changes in weight at various time points. Unintentional weight loss in patients with pancreatic cancer is highly prevalent and contributes to low therapeutic tolerance, reduced quality of life, and overall mortality [66]. Further, by assessing weight after completion of therapy, we will evaluate association of change in weight from diagnosis to post treatment with outcomes.

**14.2.4.3** Protein intake will be associated with improved disease-free and overall survival and improved recovery from surgery. In a study of 164 patients with pancreatic cancer, adipose and muscle tissue were measured by computed tomography (CT) at diagnosis and 50 to 120 days later [67]. Compared with patients in the bottom quartile of muscle change per 30 days (average gain of 0.8 ± 2.0 cm2), those in the top quartile (average loss of 12.9 ± 4.9 cm2) had a hazard ratio (HR) for death of 2.01 [95% confidence interval (CI), 1.12-3.62]. Patients in the top quartile of muscle attenuation change (average decrease of 4.9 ± 2.4 Hounsfield units) had an HR of 2.19 (95% CI, 1.18-4.04) compared with those in the bottom quartile (average increase of 2.4 ± 1.6 Hounsfield units). Changes in

adipose tissue were not associated with survival. Protein intake is important to muscle mass.

**14.2.4.4** Certain dietary patterns and scores associated with hyperinsulinemia and inflammation will be associated with disease-free survival. The empirical diet index for hyperinsulinemia (EDIH) was created using data from the Nurse's Health Study by entering 39 FFQ-derived food groups in stepwise linear regression models to predict fasting plasma C-peptide [68]. The EDIH is comprised of 18 food groups; 13 were positively associated with fasting C-peptide and 5 were inversely associated. The EDIH has been associated with CRC survival (submitted manuscript. The empirical dietary inflammatory pattern (EDIP) score is a score for overall inflammatory potential of whole diets defined using food groups [69]. Briefly, 39 predefined food groups were entered into reduced-rank regression models followed by stepwise linear regression analyses to identify a dietary pattern most predictive of 3 plasma markers of inflammation: IL-6, CRP, and TNFRSF1B (TNF receptor superfamily 1B, so-called TNF-α receptor 2, or TNF-R2). The EDIP score is the weighted sum of 18 food groups and assesses the inflammatory potential of diet on a continuum from maximally anti-inflammatory to maximally proinflammatory. That is, lower (more negative) scores indicate anti-inflammatory diets and higher (more positive) scores indicate proinflammatory diets. EDIP has been associated risk of multiple cancer types [70, 71].

**14.2.4.5** Increased vitamin D is associated with improved disease-free survival and overall survival in pancreatic cancer. In models of pancreatic cancer, the biological properties of vitamin D and its receptor are well established [72-75]. The presence of a common genetic variant in vitamin D receptor (VDR) is associated with improved survival in two clinical studies. VDR codes for the receptor of the active form of vitamin D (i.e. 1,25-dihydroxyvitamin D3). Preclinical studies indicate that vitamin D analogs halt progression through the cell cycle, induce apoptosis, and stop or slow the growth of pancreatic cancer in vivo [76-79]. It also potentiates the antitumor activities of a number of cytotoxic agents including gemcitabine [18]. By both assessing vitamin D supplementation as well as deriving vitamin D prediction score, the association of vitamin D and outcomes in resectable pancreatic cancer can be determined [80].

### 14.2.5 Analysis

The primary efficacy variable for analyses will be overall survival (OS), consistent with the primary outcome in A021806. Secondary efficacy endpoint is disease-free survival (DFS). The toxicity endpoint is defined as the rate of patients experiencing at least one grade 3 or higher adverse events during the treatment.

Exposure Definitions: For all dietary exposures, intakes will be categorized into energy-adjusted quintiles, consistent with our previous studies. In addition, physical activity will be categorized into categories of MET-hours as previously defined in prior work. Body mass index (in $kg/m^2$) will be divided into World Health Organization categories of underweight, normal weight, overweight and obesity. The diet/lifestyle measures will be

compared between subgroups of patients defined by baseline disease and demographic characteristic by Wilcoxon Rank test and chi-squired tests for continuous (or count) and categorical variables, respectively. The distributions of OS and DFS within subpopulations defined by certain patterns of diet/lifestyle measures will be estimated by the Kaplan-Meier estimates, and compared by the log-rank test. Cox proportional hazards models will be used to control for multiple confounders. For binary outcomes (e.g. toxicity endpoint), odds ratios will be estimated for comparing the risk of experiencing toxicity between subpopulations defined by certain patterns of diet/lifestyle measures. Logistic regression model will be used to control multiple confounders. The two-tailed P value for the linear trend test across categories will be calculated using the exposure level as a continuous variable, consistent with prior studies. In secondary analyses, we will examine how the relationship between a specific exposure level and patient outcome is modified by relevant covariates such as ECOG performance status, treatment assignment, physical activity and body mass index, among others. Tests for statistical interaction will be performed by entering into the model the cross-product term of the exposure level as a continuous variable with the covariate as a continuous or binary variable.

### 14.2.6 Power Considerations

Based on the questionnaire response rates observed in previous studies, we estimate that about 70% of patients will complete the questionnaires (n = 246, anticipated number of deaths = 174).

We provide power calculations for test associations between OS and different types of diet/lifestyle exposure variables. With the anticipated number of patients who will complete the questionnaires and number of deaths, assuming the study will complete with full accrual and full length of follow-up of all patients, we indicate the minimal detectable effect size in terms of HR, with one-sided alpha of 0.05 and power of 80% below.

Exposure variables defined by highest vs. lowest quartiles: Assuming 1) increased risk of death as the exposure level increases, 2) the 2-year OS rate is 35% in highest quartile, 3) same number of patients in highest and lowest quartiles groups, then the minimal detectable HR is 1.87 for comparing OS between highest to lowest quartiles.

Binary exposure variables:

1) Cachexia: Assuming 1) 60% of patients will meet definition of cachexia, 2) the 2-year OS rate is 35% in patients with cachexia, then the minimal detectable HR is 1.47 for comparing OS in pts who meet the definition of cachexia to those without cachexia.
2) BMI: Assuming 20% BMI < 21, 25% BMI 21-25, 30% BMI 25-29, and 25% BMI > 30, 2) the 2-year OS rate is 35% in patients with BMI > 30, then the minimal detectable HR is 1.68 for comparing OS between patients with BMI > 30 to those with MBI 25-29, and 1.70 for comparing OS between patients with BMI > 30 to those with MBI 21-29.

We also provide power calculations for test associations between toxicity endpoint and different types of diet/lifestyle exposure variables. With the anticipated number of patients who will complete the questionnaires, we indicate the minimal detectable effect size in terms of OR with one-sided alpha of 0.05 and power of 80% below.

Exposure variables defined by highest vs. lowest quartiles: Assuming 1) increased risk of experiencing grade 3+ adverse events as the exposure level increases, 2) the toxicity rate

is 65% in highest quartile, 3) same number of patients in highest and lowest quartiles groups, then the minimal detectable OR is 2.84 for comparing toxicity rate between highest to lowest quartiles.

Binary exposure variables:

1) Cachexia: Assuming 1) 60% of patients will meet definition of cachexia, 2) the toxicity rate is 65% in patients with cachexia, then the minimal detectable OR is 1.93 for comparing toxicity rate in pts who meet the definition of cachexia to those without cachexia.

2) BMI: Assuming 20% BMI < 21, 25% BMI 21-25, 30% BMI 25-29, and 25% BMI > 30, 2) the toxicity rate is 65% in patients with BMI > 30, then the minimal detectable OR is 2.41 for comparing toxicity between patients with BMI > 30 to those with MBI 25-29, and 2.51 for comparing toxicity between patients with BMI > 30 to those with MBI 21-29.

## 14.3 Imaging Study (Alliance A021806-IM1)

### 14.3.1 Background

FOLFIRINOX had been shown to induce a dense fibrotic reaction in PDAC, replacing tumor mass with extracellular matrix. Response to neoadjuvant chemotherapy is currently dependent on post-resection histological review which is an invasive delayed outcome that can sometimes be subjective to inter-reader variations. Quantitative radiological features retrieved from standard-of-care CT imaging (collectively called radiomics) have been shown to be serve as a non-invasive image-based biomarkers exploring tumor microenvironment and tumor aggressiveness. Some of these radiomics features have been associated with response to therapy and ultimately survival outcomes. These associations have been demonstrated in several solid tumors including lung cancer, pancreatic cancer and melanoma. Discrimination of viable tumor from post-treatment fibrosis is a challenging task to the radiologist and may be vulnerable to inter-reader variability while textural radiomics represent a reproducible imaging probe that could potentially make that distinction and assess response to chemotherapy [81-94].

Several qualitative (attenuation, heterogeneity, spiculation, location, size, shape, margins, calcification, cavitation, etc.) and quantitative (shape, gray-level intensity, histogram, co-occurrence matrix texture, run-length matrix texture, wavelet decomposition, standardized uptake value statistics, etc.) image features will be used to characterize the pancreatic tumors. The baseline and pre-operative follow-up imaging scans will be used in the perioperative therapy arm and the baseline imaging scans will be used in the adjuvant therapy arm; see Section 6.3 for imaging submission details. All quantitative imaging features/radiomics' values will be adjusted/modulated at the feature extraction stage according to the CT tube electric current, voltage, image acquisition slice thickness, scanner model, and reconstruction algorithm used to create the image. This approach will be followed in order to improve the signal to noise ratio in radiomics resulting from using different scanning settings.

### 14.3.2 Objectives

In the perioperative arm, our objective is to evaluate the ability of CT-based radiomics in distinguishing post-NAC fibrosis from viable tumor. We hypothesize that changes in CT-based radiomics between baseline and follow-up pre-operative scan may act as a non-invasive tool to: 1) assess the proportion of peri-tumoral fibrosis (by comparing this

proportion to the gold-standard retrieved from post-resection histological assessment performed as part of standard of care to assess the pathological response grade to NAC), 2) predict response to NAC, defined by histological assessment, and 3) predict the ability to obtain an R0 resection.

In the adjuvant arm, we hypothesize that CT-based radiomics retrieved from baseline examination may act as non-invasive predictors of survival outcome.

### 14.3.3 Analysis

The Alliance Statistics and Data Center (SDC) A021806 Statistician to prepare analysis datasets in conjunction with clinical/outcome data. The A021806 Statistician will then coordinate the analyses of the images specified in Section 6.3 and Section 7.3 with the Alliance ICL and the A021806 Imaging Co-Chair, Dr. Firas Ahmed, and designated computational analysis teams at Columbia University. Analyses will be conducted using the analysis dataset used for the analysis of the clinical endpoints to ensure consistent data is reported for the primary and secondary endpoints (e.g. data associated with censoring, proper inclusion of crossover data, and data to be excluded in cases of consent withdrawals for follow-up and correlative studies).

After CT-based radiomics features generation of each pancreatic tumor using MatLab, the change in the radiomics feature values will be used to assess the proportion of tumor peri-tumor fibrosis. Comparison between the radiomics based tumor fibrosis proportion and the histological tumor fibrosis proportion will be tested using Spearman rank correlation.

All the radiomics features' associations with R0 and response to NAC will be assessed used logistic regression model, with Lasso approach. Multivariable Cox-regression model will be utilized to assess for the association of CT-based radiomics with PFS and OS while controlling for clinically important confounders, like patient's age, comorbidities, and ECOG status.

The Least Absolute Shrinkage and Selection Operator (LASSO) logistic regression model will be used for feature selection and radiomics model building for the prediction of peri-tumoral fibrosis, response to NAC, and R0. The regularization parameter ($\lambda$) for LASSO regression model will be selected using 10-fold cross-validation (CV). The optimal value of $\lambda$ is determined as the value that could minimize CV error plus one standard error (the 1 standard error criteria). After determining the optimal $\lambda$, radiomics features with nonzero coefficients in the LASSO logistic regression model are selected as predictive features and the corresponding LASSO model is selected as finial predictive radiomics model. The area under the receiver operating characteristic curve (AUC) is used as the metric to indicate the prediction performance of radiomics model.

Evaluation of the radiomics signatures' role as an imaging biomarker predictive of survival outcomes independent of clinical and pathological covariates will be performed in a multivariable Cox proportional hazards model after inclusion of important clinical and pathological variables (e.g. age, gender, patient's performance status, and peri-tumoral fibrosis). The backward step-down feature selection approach and the Akaike information criterion will be used to build the multivariable Cox proportional hazards model. The log-rank test will be used to test the overall significance of the Cox proportional hazards model and hazard ratios will be used to indicate the prognostic magnitude of each variable in the model.

### 14.4 A021806 Biobanking for Future Correlative Science Studies

NOTE: Testing of banked samples will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

Note: All laboratory correlates are classified as exploratory, and the specimens requested for submission in Section 6.2 will be collected for banking-only at this time.

Blood, tissue, and/or stool specimens will be collected and stored for future translational research for patients who consent to participate. Future studies may include, but are not limited to, immunologic and mutational studies.

## 15.0 GENERAL REGULATORY CONSIDERATIONS AND CREDENTIALING

### 15.1 Institutional Credentialing

#### 15.1.1 IROC Institutional Requirements

Prior to the enrollment of patients, institutions that have not previously been credentialed for any other Alliance trials must be credentialed to participate in the trial by the Imaging Core Laboratory at IROC Ohio. For institutions that have previously been credentialed by the Imaging Core Laboratory at IROC Ohio to participate in imaging studies, the ICL will provide a brief A021806 protocol refresher prior to patient enrollments. Institutions should contact the Alliance ICL directly to complete credentialing or a refresher for A021806.

Contact information for IROC Ohio can be found under protocol contacts near the title page.

## 16.0 MONITORING PLAN

Use standard Alliance monitoring procedures.

## 17.0 REFERENCES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## APPENDIX I QUALITY OF LIFE MEASURES

### Registration Fatigue/Uniscale Assessments

At patient registration, this form is to be administered by a nurse/CRA, completed by the patient, and entered into Medidata Rave® at the time of registration.

If needed, this appendix can be adapted to use as a source document. A booklet containing this assessment does not exist – please do not order this booklet.

How would you describe:

your level of fatigue, on the average in the past week including today?

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| No Fatigue | | | | | | | | | | Fatigue as bad as it can be |

your overall quality of life in the past week including today?

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| As bad as it can be | | | | | | | | | | As good as it can be |

**National Cancer Institute PRO-CTCAE**

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**You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' and the side effects you are experiencing as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.**

1. This booklet contains one set of questions:
    a. National Cancer Institute PRO-CTCAE (15 questions)
2. Please follow the directions at the top of this questionnaire.
3. You may choose not to answer any questions that make you feel uncomfortable.
4. Please complete the booklet during your scheduled clinical visit and return it to your nurse, physician, or research coordinator.

**Thank you for taking the time to help us.**

**NCI PRO-CTCAE™ ITEMS**
**Item Library Version 1.0 - English**

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an X in the one box that best describes your experiences over the past 7 days…

| | | | | | |
|---|---|---|---|---|---|
| 1. | In the last 7 days, what was the SEVERITY of your DRY MOUTH at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |

| | | | | | |
|---|---|---|---|---|---|
| 2. | In the last 7 days, what was the SEVERITY of your PROBLEMS WITH TASTING FOOD OR DRINK at their WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |

| | | | | | |
|---|---|---|---|---|---|
| 3. | In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| | In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

| | | | | | |
|---|---|---|---|---|---|
| 4. | In the last 7 days, how OFTEN did you have NAUSEA? | | | | |
| | ○ Never | ○ Rarely | ○ Occasionally | ○ Frequently | ○ Almost constantly |
| | In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |

| | | | | | |
|---|---|---|---|---|---|
| 5. | In the last 7 days, how OFTEN did you have VOMITING? | | | | |
| | ○ Never | ○ Rarely | ○ Occasionally | ○ Frequently | ○ Almost constantly |
| | In the last 7 days, what was the SEVERITY of your VOMITING at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |

| | | | | | |
|---|---|---|---|---|---|
| 6. | In the last 7 days, how OFTEN did you have HEARTBURN? | | | | |
| | ○ Never | ○ Rarely | ○ Occasionally | ○ Frequently | ○ Almost constantly |
| | In the last 7 days, what was the SEVERITY of your HEARTBURN at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |

| | | | | | |
|---|---|---|---|---|---|
| 7. | In the last 7 days, how OFTEN did you have BLOATING OF THE ABDOMEN (BELLY)? | | | | |
| | ○ Never | ○ Rarely | ○ Occasionally | ○ Frequently | ○ Almost constantly |
| | In the last 7 days, what was the SEVERITY of your BLOATING OF THE ABDOMEN (BELLY) at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |

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| | | | | | |
|---|---|---|---|---|---|
| 8. | In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)? | | | | |
| | ○ Never | ○ Rarely | ○ Occasionally | ○ Frequently | ○ Almost constantly |

| | | | | | |
|---|---|---|---|---|---|
| 9. | In the last 7 days, how OFTEN did you have PAIN IN THE ABDOMEN (BELLY AREA)? | | | | |
| | ○ Never | ○ Rarely | ○ Occasionally | ○ Frequently | ○ Almost constantly |
| | In the last 7 days, what was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY AREA) at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| | In the last 7 days, how much did PAIN IN THE ABDOMEN (BELLY AREA) INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

| | | | | | |
|---|---|---|---|---|---|
| 10. | In the last 7 days, what was the SEVERITY of your ITCHY SKIN at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |

| | | | | | |
|---|---|---|---|---|---|
| 11. | In the last 7 days, what was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| | In the last 7 days, how much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

| | | | | | |
|---|---|---|---|---|---|
| 12. | In the last 7 days, how OFTEN did you have PAIN? | | | | |
| | ○ Never | ○ Rarely | ○ Occasionally | ○ Frequently | ○ Almost constantly |
| | In the last 7 days, what was the SEVERITY of your PAIN at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| | In the last 7 days, how much did PAIN INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

| | | | | | |
|---|---|---|---|---|---|
| 13. | In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| | In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

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| | | | | | |
|---|---|---|---|---|---|
| 14. | In the last 7 days, how OFTEN did you feel ANXIETY? | | | | |
| | ○ Never | ○ Rarely | ○ Occasionally | ○ Frequently | ○ Almost constantly |
| | In the last 7 days, what was the SEVERITY of your ANXIETY at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| | In the last 7 days, how much did ANXIETY INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

| | | | | | |
|---|---|---|---|---|---|
| 15. | In the last 7 days, how OFTEN did you have SAD OR UNHAPPY FEELINGS? | | | | |
| | ○ Never | ○ Rarely | ○ Occasionally | ○ Frequently | ○ Almost constantly |
| | In the last 7 days, what was the SEVERITY of your SAD OR UNHAPPY FEELINGS at their WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| | In the last 7 days, how much did SAD OR UNHAPPY FEELINGS INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

| Do you have any other symptoms that you wish to report? | |
|---|---|
| ○ Yes | ○ No |

Please list any other symptoms:

| | | | | | |
|---|---|---|---|---|---|
| 1. | In the last 7 days, what was the SEVERITY of this symptom at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| 2. | In the last 7 days, what was the SEVERITY of this symptom at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| 3. | In the last 7 days, what was the SEVERITY of this symptom at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| 4. | In the last 7 days, what was the SEVERITY of this symptom at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| 5. | In the last 7 days, what was the SEVERITY of this symptom at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |

The PRO-CTCAE™ items and information herein were developed by the NATIONAL CANCER INSTITUTE at the NATIONAL INSTITUTES OF HEALTH, in Bethesda, Maryland, U.S.A. Use of the PRO-CTCAE™ is subject to NCI's Terms of Use.

## EORTC QLQ-C30

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**You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' and the side effects you are experiencing as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.**

1. This booklet contains one set of questions:
    a. EORTC QLQ-C30 (30 questions)
2. Please follow the directions at the top of this questionnaire.
3. You may choose not to answer any questions that make you feel uncomfortable.
4. Please complete the booklet during your scheduled clinical visit and return it to your nurse, physician, or research coordinator.

**Thank you for taking the time to help us.**

EORTC QLQ - C30 (Version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

| | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? | 1 | 2 | 3 | 4 |
| 2. Do you have any trouble taking a long walk? | 1 | 2 | 3 | 4 |
| 3. Do you have any trouble taking a short walk outside of the house? | 1 | 2 | 3 | 4 |
| 4. Do you need to stay in bed or a chair during the day? | 1 | 2 | 3 | 4 |
| 5. Do you need help with eating, dressing, washing yourself or using the toilet? | 1 | 2 | 3 | 4 |

| **During the past week:** | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 6. Were you limited in doing either your work or other daily activities? | 1 | 2 | 3 | 4 |
| 7. Were you limited in pursuing your hobbies or other leisure time activities? | 1 | 2 | 3 | 4 |
| 8. Were you short of breath? | 1 | 2 | 3 | 4 |
| 9. Have you had pain? | 1 | 2 | 3 | 4 |
| 10. Did you need to rest? | 1 | 2 | 3 | 4 |
| 11. Have you had trouble sleeping? | 1 | 2 | 3 | 4 |
| 12. Have you felt weak? | 1 | 2 | 3 | 4 |
| 13. Have you lacked appetite? | 1 | 2 | 3 | 4 |
| 14. Have you felt nauseated? | 1 | 2 | 3 | 4 |
| 15. Have you vomited? | 1 | 2 | 3 | 4 |

Please go on to the next page

EORTC QLQ - C30 (Version 3)

| **During the past week:** | **Not at All** | **A Little** | **Quite a Bit** | **Very Much** |
|---|---|---|---|---|
| 16. Have you been constipated? | 1 | 2 | 3 | 4 |
| 17. Have you had diarrhea? | 1 | 2 | 3 | 4 |
| 18. Were you tired? | 1 | 2 | 3 | 4 |
| 19. Did pain interfere with your daily activities? | 1 | 2 | 3 | 4 |
| 20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television? | 1 | 2 | 3 | 4 |
| 21. Did you feel tense? | 1 | 2 | 3 | 4 |
| 22. Did you worry? | 1 | 2 | 3 | 4 |
| 23. Did you feel irritable? | 1 | 2 | 3 | 4 |
| 24. Did you feel depressed? | 1 | 2 | 3 | 4 |
| 25. Have you had difficulty remembering things? | 1 | 2 | 3 | 4 |
| 26. Has your physical condition or medical treatment interfered with your family life? | 1 | 2 | 3 | 4 |
| 27. Has your physical condition or medical treatment interfered with your social activities? | 1 | 2 | 3 | 4 |
| 28. Has your physical condition or medical treatment caused you financial difficulties? | 1 | 2 | 3 | 4 |

**For the following questions please circle the number between 1 and 7 that best applies to you.**

29. How would you rate your overall health during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

30. How would you rate your overall quality of life during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |