Georgetown | Lombardi
COMPREHENSIVE CANCER CENTER

Phase I Study of Proton Therapy in Adjuvant Pancreatic Cancer (PROTON-PANC)

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TABLE OF CONTENTS PAGE

FIGURES, TABLES, AND ABBREVIATIONS PAGE

Figures

Tables

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

5-FU	5-fluorouracil
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
β-hCG	β-human chorionic gonadotropin
BTC	Biliary tract cancer
BUN	Blood urea nitrogen
CBC	Complete blood count
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CT	Computed tomography
CYP	Cytochrome P450
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DSMC	Data and safety monitoring review committee
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
FDA	US Food and Drug Administration
FdUMP	5-Fluoro-2′-deoxyuridine 5′-monophosphate
FOLFIRI	Leucovorin, fluorouracil, and irinotecan
FOLFIRINOX	Leucovorin, fluorouracil, irinotecan, and oxaliplatin (FFX)
FOLFOX	Leucovorin, fluorouracil, and oxaliplatin
FUTP	5-fluorouridine 5'-triphosphate
GEM	Gemcitabine
GGT	Gamma-glutamyl transpeptidase
HIV	Human immunodeficiency virus
HR	Hazard ratio
IFL	Irinotecan, fluorouracil (bolus), and leucovorin
IHC	Immunohistochemistry
IND	Investigational new drug
INR	International normalized ratio
IV	Intravenously
LCCC	Lombardi Comprehensive Cancer Center
LD	Longest diameter
LFT	Liver profile
LLN	Lower limit of normal
LV	Leucovorin
MRI	Magnetic resonance imaging
mOS	Median overall survival
mPFS	Median progression-free survival
NGS	Next-generation Sequencing
ORR	Overall response rate
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progression of disease
PI	Principal investigator
PK	Pharmacokinetics

PO	By mouth
PR	Partial response
PRT	Proton Radiation Therapy
PS	Performance Status
PT	Prothrombin time
PTT	Partial thromboplastin time
QD	Once daily
RECIST	Response Evaluation Criteria in Solid Tumors
RFS	Recurrence-free survival
RNA	Ribonucleic acid
RP2D	Recommended Phase II Dose
RR	Response rate
SAE	Significant adverse event
SD	Stable disease
TS	Thymidylate synthase
UGT1A1	UDP glucuronosyltransferase family 1 member A1
ULN	Upper limit of normal

STUDY SYNOPSIS

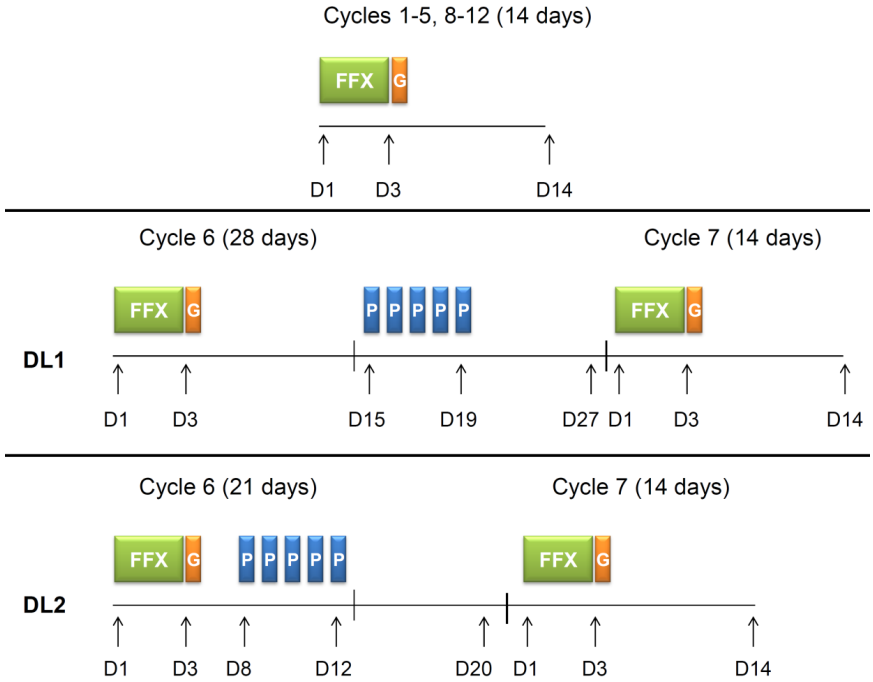
Title	Phase I Study of Proton Therapy in Adjuvant Pancreatic Cancer (PROTON-PANC)
Short Title	Proton Therapy in Adjuvant Pancreatic Cancer
Protocol Number	2018-1021
Clinicaltrials.gov number:	pending
Phase	Phase I
Investigational Agents	1) Proton Beam Therapy
Indication	Resected adenocarcinoma of the pancreatic head
Concept and Scientific Rationale	Pancreatic Cancer In 2018, it is estimated that 55,440 new cases of pancreatic ductal adenocarcinoma (PDAC) will be diagnosed and 44,330 people will die of PDAC in the United States.[1] Importantly, PDAC incidence is increasing and is estimated to overtake colorectal cancer as the 2nd-leading cause of cancer-related death in the United States by 2030.[2] Most patients with PDAC have either metastatic or unresectable locally advanced disease at the time of diagnosis and are unable to have a potentially curative surgical resection. For the 10-20% of patients who are able to undergo a surgical resection, outcomes are still relatively poor. The optimal treatment strategy for resectable pancreatic cancer remains under investigation. Subsets of patients with resectable disease appear to benefit from neoadjuvant therapy; however, many patients with resectable disease will receive upfront surgery. Although distant recurrence predominates after resection, up to 30% of patients have only local disease as the first site of recurrence.[3,4] Adjuvant Chemotherapy While the role of adjuvant chemoradiation is debated, systemic chemotherapy is the standard adjuvant therapy. Adjuvant chemotherapy options have historically involved either single-agent gemcitabine (GEM) or 5-fluorouracil (5-FU) with leucovorin (LV). Both agents had similar median overall survival (mOS) when compared head-to-head in the ESPAC-3 trial (23.6 months with GEM and 23.0 months with 5-FU, P = 0.39), with GEM favored due to a better toxicity profile.[5] The ESPAC-4 trial changed the adjuvant treatment paradigm, demonstrating that GEM plus capecitabine (CAPE, oral 5-FU) had a longer mOS than GEM alone (28.0 vs. 25.5 months, P = 0.032).[6] The PRODIGE 24 trial revolutionized the standard of care for fit patients, demonstrating that mFOLFIRINOX (FFX: LV, 5-FU, irinotecan, and oxaliplatin) was superior to GEM in terms of mOS (54.4 vs. 35.0 months, P = 0.003).[7] Thus, FFX is the new standard adjuvant regimen for fit patients. There is also an ongoing trial of GEM/nab-paclitaxel vs. GEM as an adjuvant treatment option.[8] Adjuvant Chemoradiation Chemoradiation typically consists of 5-FU or CAPE administered concurrently with radiation. The ESPAC-1 study suggested that patients who received chemoradiation had inferior mOS (13.9 months) compared to patients who received chemotherapy alone (21.6 months), chemoradiation followed by chemotherapy (19.9 months), or observation alone (16.9 months), although the

	study was not adequately powered to compare the 4 arms independently.[9] These results suggest that upfront administration of adjuvant systemic chemotherapy is paramount over other treatment modalities. The results of the RTOG 0848 trial will hopefully elucidate the role of adjuvant chemoradiation timed at the end of adjuvant chemotherapy.[10] In the RTOG 0848 trial, patients with no evidence of disease recurrence after 5 cycles of adjuvant GEM are randomized to 1 more cycle of GEM or chemoradiation with 5-FU or CAPE. <u>Proton Therapy and Targeted Radiation Therapy for Pancreatic Cancer</u> Proton-based radiotherapy (PRT) is an exciting novel treatment option for the treatment of PDAC. Conventional radiation therapy techniques typically require 25 to 28 fractions delivered over 5 to 6 weeks. However, because of the precision of proton therapy, it is feasible to complete treatment using a short course of only 5 sessions. Prior work has shown that concomitant CAPE and PRT is associated with a low rate of gastrointestinal toxicity.[11] In a phase I/II study, Hong and colleagues demonstrated the safety of short-course proton-based chemoradiation with CAPE in the neoadjuvant setting for patients with resectable PDAC.[12] The recommended phase II dose was 5 daily doses of 5 GyE. The MGH group attempted to deliver the same 5 fraction treatment using IMRT, however the toxicities were unacceptable.[13] For resected PDAC, photon-based stereotactic body radiation therapy delivered in 5 fractions (33 Gy) can be safely integrated with FFX chemotherapy in the adjuvant setting.[14] Nichols and colleagues compared treatment plans using protons to conventional photon intensity-modulation radiotherapy (IMRT) and found that proton-based postoperative chemoradiation decreases off-target small bowel and stomach exposure.[15] Thus, proton-based chemoradiation should cause fewer acute and long-term toxicities than conventional photon-based IMRT. Additionally, we hypothesize that delivery of radiation therapy earlier after resection (as opposed to following the completion of adjuvant chemotherapy) will increase its effectiveness while not disrupting adjuvant chemotherapy**.** Therefore, we propose a phaseI study to assess the safety and feasibility of short-course PRT with adjuvant FFX.
Study Duration	12 months
Study Centers	1) Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC
Objectives	<u>Primary Objective:</u> To determine the recommended phase II dose and schedule (RP2D) of short-course PRT integrated within adjuvant FFX (radiation 12 days following chemotherapy or 5 days following chemotherapy). The co-primary objectives are to demonstrate the safety and feasibility of short-course PRT within systemic adjuvant chemotherapy with FFX, including the number of cycles received and relative chemotherapy dose-intensity. <u>Exploratory Objectives:</u> To determine the median recurrence-free survival (mRFS) and median overall survival (mOS) in patients treated with adjuvant FFX and proton radiation.
Number of Subjects	A minimum of 2 and a maximum of 12 evaluable patients

Diagnosis and Main Inclusion and Exclusion Criteria	Key Inclusion Criteria
	• Pathologically-confirmed pancreatic adenocarcinoma of the pancreatic head
	• Undergone pancreaticoduodenectomy with curative intent
	• Completed 2 cycles of adjuvant chemotherapy composed of 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan
	• Complete resection (R0) or resection with microscopic positive magins (R1)
	• Adequate healing post-operatively
	• Adequate hepatic, renal, and bone marrow function
	• Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0-1
	• Prior neoadjuvant chemotherapy is alllowed
	
	Key Exclusion Criteria
	• Ampullary adenocarcinoma
	• Woman who are pregnant or breastfeeding
	• Macroscopic positive margins (R2) or evidence of residual local or metastatic disease
	• Resection not including pancreaticoduodenectomy
	• Known allergy or intolerance to leucovorin, 5-fluorouracil, oxaliplatin, or irinotecan
	• Prior radiation to the upper abdomen
	• Inability to swallow pills or bowel obstruction
	• Any invasive cancer in the previous 3 years requiring chemotherapy or radiation or anticancer therapy following surgery
	• Insurance unwilling to pre-authorize PRT, FFX, and pegfilgrastim
	• Clinically significant liver disease
	  ○ Patients with resolved hepatitis B infection are eligible if HBsAg testing is negative
	  ○ Patients with resolved hepatitis C infection are eligible if viral RNA PCR is negative
	• Uncontrolled HIV infection (CD4 count must be at least 200 and viral load undetectable on a stable antiretroviral regimen)
	• Major surgery within 4 weeks prior to enrollment

Study Design	We hypothesize that resected pancreatic cancer patients will benefit from enhanced local control with the addition of radiation therapy to adjuvant FFX. The recently reported PRODIGE 24 study, demonstrated that 12 cycles of adjuvant FFX without radiation therapy significantly improved survival and time to metastatic failure rates as compared to GEM alone. Excessive distant failures rates using prior adjuvant systemic therapies, may have limited the impact of radiation therapy; therefore, improvements in systemic control can increase the benefit of local control.

Figure 1. Study Schema



DL = dose level, FFX = mFOLFIRINOX, G = pegfilgrastim on-body injector (optional), P = proton radiation (5 GyE).

In this study, we utilize 5 fraction PRT, delivered over 1 week, during adjuvant FFX (between cycles 6 and 7) to minimize the interruptions in chemotherapy as well as to reduce the length of time from surgical resection to initiating adjuvant radiation therapy. Conventional radiation therapy is typically delivered over 5 weeks and is commonly given after the completion of adjuvant chemotherapy. Conventional radiation therapy cannot be given concurrently with FFX due to the synergistic toxicities. In contrast, PRT significantly reduces the exposure of normal tissues to the effects of radiation therapy and has been safely delivered using a 5 fraction schedule with chemotherapy, as previously discussed.

Chemotherapy will consist of mFOLFIRINOX in 14-day cycles x 12 as used in the PRODIGE 24 study:

- Irinotecan 150 mg/m^2 IV day 1
- Oxaliplatin 85 mg/m^2 IV day 1
- Leucovorin 400 mg/m^2 IV day 1
- 5-fluorouracil 2,400 mg/m^2 IV days 1-3 (no bolus)
- Pegfilgrastim 6 mg SC on-body injector day 3 (optional, up to investigator's discretion, can alternatively do day 4 without on-body injector)
- Suggested supportive care medications: fosaprepitant 150 mg IV day 1, dexamethasone 12 mg IV day 1, ondansetron 16 mg IV day 1, dexamethasone 4 mg PO q AM days 2-3, ondansetron 8 mg PO BID days 2-3.
- Dose adjustments will be permitted at the discretion of the treating oncologist based on patients' prior tolerability to FFX

	• Proton radiation will consistent of 5 daily doses of 5 GyE total, ideally administered Monday through Friday but can be administered within 7 business days, between cycles 6 and 7
Statistical Design, Feasibility, and Trial Duration	This study will use a 3+3 dose-escalation design to determine the safety and feasibility of combining 5 fraction adjuvant PRT with FFX. While there is limited literature on the combination of short course PRT and FFX, there are analogous experiences using 5 fraction SBRT or IMRT following FFX in routine clinical practice. The ongoing Alliance 021501 trial of preoperative chemotherapy vs. chemotherapy plus radiation (IMRT using 5 Gy X 5 or SBRT 6.6 X 5) in borderline resectable pancreatic cancer mandates that radiation starts 5 days or more following the last dose of FFX.[16] Additionally, at LCCC we routinely combine 5 fraction SBRT after a 10-14 day interval from FFX.[17] Thus dose level 1 uses a 12 day interval and dose level 2 uses a 5 day interval. Our proposed trial in the postoperative setting aims to integrate PRT between cycles of adjuvant FFX using different gaps in time between chemotherapy and radiation, which will serve as basis for future trial designs. No competing adjuvant PDAC trials exist at LCCC. Approximately 30 new patients with resected PDAC are seen annually at LCCC. We hypothesize that 24 patients will be eligible annually and 50% of these patients will enroll in the trial (12 evaluable patients maximum).

1.0 BACKGROUND AND JUSTIFICATION

1.1 Pancreatic Ductal Adenocarcinoma (PDAC)

In 2018, it is estimated that 55,440 new cases of pancreatic ductal adenocarcinoma (PDAC) will be diagnosed and 44,330 people will die of PDAC in the United States.[1] Importantly, PDAC incidence is increasing and is estimated to overtake colorectal cancer as the 2nd-leading cause of cancer-related death in the United States by 2030.[2] Most patients with PDAC have either metastatic or unresectable locally advanced disease at the time of diagnosis and are unable to have a potentially curative surgical resection. For the 10-20% of patients who are able to undergo a surgical resection, outcomes are still relatively poor. The optimal treatment strategy for resectable pancreatic cancer remains under investigation. Subsets of patients with resectable disease appear to benefit from neoadjuvant therapy; however, many patients with resectable disease will receive upfront surgery. Although distant recurrence predominates after resection, up to 30% of patients have only local disease as the first site of recurrence.

1.2 Adjuvant Chemotherapy

While the role of adjuvant chemoradiation is debated, systemic chemotherapy is the standard adjuvant therapy. Adjuvant chemotherapy options have historically involved either single-agent gemcitabine (GEM) or 5-fluorouracil (5-FU) with leucovorin (LV). Both agents had similar median overall survival (mOS) when compared head-to-head in the ESPAC-3 trial (23.6 months with GEM and 23.0 months with 5-FU, P = 0.39), with GEM favored due to a better toxicity profile.[5] The ESPAC-4 trial changed the adjuvant treatment paradigm, demonstrating that GEM plus capecitabine (CAPE, oral 5-FU) had a longer mOS than GEM alone (28.0 vs. 25.5 months, P = 0.032). [6] The PRODIGE 24 trial revolutionized the standard of care for fit patients, demonstrating that mFOLFIRINOX (FFX: LV, 5-FU, irinotecan, and oxaliplatin) was superior to GEM in terms of mOS (54.4 vs. 35.0 months, P = 0.003).[7] Thus, FFX is the new standard adjuvant regimen for fit patients. There is also an ongoing trial of GEM/nab-paclitaxel vs. GEM as an adjuvant treatment option.[8]

1.3 Adjuvant Chemoradiation

Chemoradiation typically consists of 5-FU or CAPE administered concurrently with radiation. The ESPAC-1 study suggested that patients who received chemoradiation had inferior mOS (13.9 months) compared to patients who received chemotherapy alone (21.6 months), chemoradiation followed by chemotherapy (19.9 months), or observation alone (16.9 months), although the study was not adequately powered to compare the 4 arms independently.[9] These results suggest that upfront administration of adjuvant systemic chemotherapy is paramount over other treatment modalities. The results of the RTOG 0848 trial will hopefully elucidate the role of adjuvant chemoradiation timed at the end of adjuvant chemotherapy.[10] In the RTOG 0848 trial, patients with no evidence of disease recurrence after 5 cycles of adjuvant GEM are randomized to 1 more cycle of GEM or chemoradiation with 5-FU or CAPE.

1.4 Proton Therapy and Targeted Radiation Therapy for Pancreatic Cancer

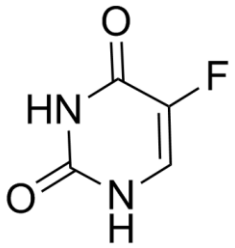
Proton-based radiotherapy (PRT) is an exciting novel treatment option for the treatment of PDAC. Conventional radiation therapy techniques typically require 25 to 28 fractions delivered over 5 to 6 weeks. However, because of the precision of proton therapy, it is feasible to complete treatment using a short course of only 5 sessions. Prior work has shown that concomitant CAPE and PRT is associated with a low rate of gastrointestinal toxicity.[11] In a phase I/II study, Hong and colleagues demonstrated the safety of short-course proton-based

chemoradiation with CAPE in the neoadjuvant setting for patients with resectable PDAC.[12] The recommended phase II dose was 5 daily doses of 5 GyE. The MGH group attempted to deliver the same 5 fraction treatment using IMRT, however the toxicities were unacceptable.[13].For resected PDAC, photon-based stereotactic body radiation therapy delivered in 5 fractions (33 Gy) can be safely integrated with FFX chemotherapy in the adjuvant setting.[14] Nichols and colleagues compared treatment plans using protons to conventional photon intensity-modulation radiotherapy (IMRT) and found that proton-based postoperative chemoradiation decreases off-target small bowel and stomach exposure.[15] Thus, proton-based chemoradiation should cause fewer acute and long-term toxicities than conventional photon-based IMRT. Additionally, we hypothesize that delivery of radiation therapy earlier after resection (as opposed to following the completion of adjuvant chemotherapy) will increase its effectiveness while not disrupting adjuvant chemotherapy**.** Although selected patients with borderline resectable and locally advanced PDAC undergo neoadjuvant therapy, the majority of patients with resectable disease in the US still receive surgery upfront. Therefore, we propose a phase I study to assess the safety and feasibility of short-course PRT with adjuvant FFX.

1.5 Fluorouracil and Leucovorin

Fluorouracil (5-FU) has been the backbone of chemotherapy regimens for gastrointestinal malignancies dating back to the 1950s. 5-FU is FDA-approved for use in colorectal, breast, gastric, and PDAC.[18]

Figure 2. Chemical Structure of Fluorouracil



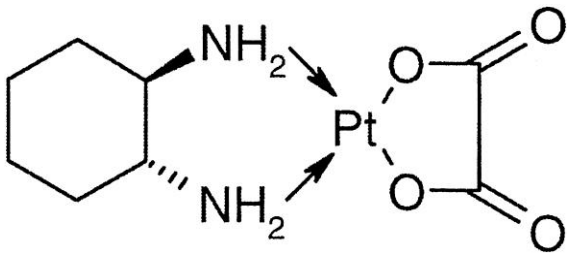
5-FU is a nucleoside metabolic inhibitor that is converted to FdUMP which inhibits thymidylate synthase (TS), disrupting DNA synthesis. Leucovorin (folinic acid) stabilizes the ternary complex of FdUMP, TS, and tetrahydrofolate, further potentiating TS inhibition.[19] The 5-FU metabolite FUTP is incorporated into RNA, and another, FdUTP, is incorporated into DNA, further disrupting RNA and DNA synthesis resulting in cell death in rapidly dividing cells.

5-FU must be permanently discontinued in patients with early onset or unusually severe toxicity which may indicate complete or near absence of dipyrimidine dehydrogenase (DPD) activity. Fluorouracil carries a risk of cardiotoxicity, hyperammonemic encephalopathy, neurologic toxicity, diarrhea, palmar-plantar erythrodyesthesia (hand-foot syndrome), myelosuppression, mucositis, increased risk of INR with warfarin, and embryofetal toxicity.

1.6 Oxaliplatin

Oxaliplatin is a platinum-based chemotherapy agent that induces inter- and intra-strand DNA crosslinking, halting DNA synthesis. It is FDA-approved[20] in combination with infusional 5-FU and LV for the management of adjuvant stage III colon cancer based on the MOSAIC trial,[21] and for the treatment of advanced colorectal cancer. [22] Oxaliplatin carries risks of allergic reactions, neuropathy, pulmonary toxicity, hepatotoxicity, and cytopenias.[20]

Figure 3. Chemical Structure of Oxaliplatin



1.7 Irinotecan

The active metabolite of irinotecan (SN-38) is a potent topoisomerase I inhibitor that induces DNA damage and cell death (see section 1.7.1.2). Irinotecan is FDA-approved for the first-line treatment of metastatic colorectal cancer (mCRC) and for treatment of mCRC following progression on or recurrence following 5-FU-based therapy.[23] Saltz and colleagues demonstrated that the addition of irinotecan 125 mg/m^2 IV in combination with 5-FU 425 mg/m^2 IV bolus and LV 20 mg/m^2 given weekly for 4 weeks every 6 weeks (IFL regimen) was superior to 5-FU and LV at the same doses given daily days 1-5 every 4 weeks in patient with mCRC.[24] André and colleagues also demonstrated the efficacy of bolus 5-FU 400 mg/m^2 IV, LV 400 mg/m^2 IV, irinotecan 180 mg/m^2 IV, and infusional 5-FU 2400 mg/m^2 IV over 46 hours every 2 weeks (FOLFIRI regimen).[25] Fuchs and colleagues later showed that irinotecan, LV, and infusional 5-FU (FOLFIRI) was superior to irinotecan, LV, and bolus 5-FU (IFL), both with and without bevacizumab.[26] FOLFIRI is an established regimen for mCRC in the first- or second-line settings.[27]

1.8 mFOLFIRINOX Regimen

The PRODIGE 4 ACCORD 11 trial established FFX (non-modified: LV 400 mg/m^2, 5-FU 400 mg/m^2 bolus, 5-FU 2400 mg/m^2 infusion, irinotecan 180 mg/m^2, and oxaliplatin 85 mg/m^2, every 2 weeks) as a standard-of-care for patients with advanced PDAC.[28] Patients were randomized 1:1 to FFX or GEM. Patients who received FFX had superior mOS (11.1 vs. 6.8 months; HR 0.57, 95% CI 0.45-0.73; P < 0.001) at the expense of more grade 3 or higher toxicities (neutropenia 46% vs. 21%, febrile neutropenia 5% vs. 1%, diarrhea 13% vs. 2%, sensory neuropathy 9% vs. 0%), although there was a quality of life benefit from FFX.

The PRODIGE 24 trial revolutionized the standard of care for fit patients in the adjuvant setting, demonstrating that FFX was superior to GEM in terms of mOS (54.4 vs. 35.0 months, P = 0.003).[7] Thus, FFX is the new standard adjuvant regimen for fit patients. In this trial, FFX was modified for tolerability: irinotecan was dropped to 150 mg/m^2 and no bolus 5-FU was included.

2.0 STUDY OBJECTIVES

2.1 Primary Objective:

To determine the recommended phase II dose and schedule (RP2D) of short-course PRT integrated within adjuvant FFX (radiation 12 days following chemotherapy or 5 days following chemotherapy) for resected PDAC. The co-primary objectives are to demonstrate the safety and

feasibility of short short-course proton radiation within systemic adjuvant chemotherapy with FFX, including the number of cycles received and relative chemotherapy dose-intensity.

2.2 Exploratory Objectives:

To determine, in patients with resected PDAC undergoing PRT integrated within adjuvant FFX:

2.2.1 Median recurrence-free survival (mPFS)

2.2.2 Median overall survival (mOS)

2.3 Primary Endpoint:

The primary endpoint is to determine the RP2D between the 2 proposed schedules. Using a 3+3 dose-escalation schema, 2-12 patients will be required to determine the RP2D.

Co-primary endpoints:

2.3.1 Safety: adverse event data will be collected and presented as descriptive statistics using the CTCAE version 5.0.

2.3.2 Feasibility: we will track the success rate in screening patients, completion of proton beam planning, completion of proton beam treatment, and completion of adjuvant therapy (including number of cycles completed and relative dose intensity).

2.4 Exploratory Endpoints:

2.4.1 Recurrence-free survival (RFS), defined as time from surgery until evidence of disease recurrence.

2.4.2 Overall survival (OS), defined as time from surgery until death from any cause or last follow-up.

2.5 Indication:

Patients with resected adenocarcinoma of the pancreatic head undergoing adjuvant FFX

3.0 SUBJECT POPULATION

3.1 Subject Population, Number of Subjects and Feasibility

3.1.1 Subject Population

Patients with resected pancreatic adenocarcinoma arising from the pancreatic head who have undergone pancreaticoduodenectomy with curative intent and are undergoing adjuvant FFX chemotherapy.

3.1.2 Number of Subjects

2-12 patients

3.1.3 Feasibility

No competing adjuvant PDAC trials exist at LCCC. Approximately 30 new patients with resected PDAC are seen annually at LCCC. We hypothesize that 24 patients will be eligible annually and 50% of these patients will enroll in the trial (12 evaluable patients maximum).

3.2 Inclusion Criteria

3.2.1 Undergone pancreaticoduodenectomy with curative intent

3.2.2 Pathologically-confirmed pancreatic adenocarcinoma of the pancreatic head (adenocarcinoma must be the predominant component of the histology)

3.2.3 Completed 2 cycles of adjuvant chemotherapy composed of 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan

3.2.4 Complete resection (R0) or resection with microscopic positive magins (R1)

3.2.5 Adequate healing post-operatively

3.2.6 Bone marrow function: absolute neutrophil count (ANC) ≥ 1,500/mm^3; Platelets ≥ 100 × $10^{9/}$L; hemoglobin ≥ 9.0 g/dL. Patients may have a transfusion of red blood cells to meet the hemoglobin requirement.

3.2.7 Renal function: serum creatinine ≤ 1.5 × upper normal limit of institution's normal range or creatinine clearance ≥ 30 mL/min for subjects with creatinine levels above institutional normal

3.2.8 Hepatic function: AST and ALT ≤ 3.0 × the upper normal limit of institution's normal range. Total bilirubin ≤ 1.5 × the upper normal limit of institution's normal range.

3.2.9 Partial Thromboplastin Time (PTT) must be ≤ 1.5 × upper normal limit of institution's normal range and INR (International Normalized Ratio) < 1.5. Subjects on anticoagulant (such as warfarin) will be permitted to enroll as long as the INR is in the acceptable therapeutic range as determined by the investigator.

3.2.10 Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0-1

3.2.11 Prior neoadjuvant chemotherapy is alllowed

3.2.12 Patients must have fully recovered from all effects of surgery. Patients must have had at least two weeks after minor surgery and four weeks after major surgery before starting therapy. Minor procedures requiring "Twilight" sedation such as endoscopies or

mediport placement may only require a 24-hour waiting period, but this must be discussed with an investigator.

3.2.13 Women of childbearing potential must have a negative serum pregnancy test within 14 days prior to initiation of treatment and/or postmenopausal women must be amenorrheic for at least 12 months to be considered of non-childbearing potential

3.2.14 Patient is capable of understanding and complying with parameters as outlined in the protocol and able to sign and date the informed consent, approved by the Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures

Table 1. ECOG Performance Status

Grade	ECOG
0	Fully Active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

3.3 Exclusion Criteria

3.3.1 Ampullary adenocarcinoma

3.3.2 Women who are pregnant or breastfeeding

3.3.3 Macroscopic positive margins (R2) or evidence of residual local or metastatic disease

3.3.4 Resection not including pancreaticoduodenectomy

3.3.5 Known allergy or intolerance to leucovorin, 5-fluorouracil, oxaliplatin, or irinotecan

3.3.6 Prior radiation to the upper abdomen

3.3.7 Inability to swallow pills or bowel obstruction

3.3.8 Any invasive cancer in the previous 3 years requiring chemotherapy, radiation, or anticancer therapy following surgery

3.3.9 Insurance unwilling to pre-authorize PRT, FFX, and (if necessary) pegfilgrastim

3.3.10 Clinically significant liver disease

3.3.10.1 Patients with resolved hepatitis B infection are eligible if HBsAg testing is negative

3.3.10.2 Patients with resolved hepatitis C infection are eligible if viral RNA PCR is negative

3.3.11 Uncontrolled HIV infection (CD4 count must be at least 200 and viral load undectable on a stable antiretroviral regimen to be eligible for enrollment)

3.3.12 Major surgery within 4 weeks prior to enrollment

3.4 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at Screening up to the Final Visit must be recorded in source documents and the case report forms (CRFs). The reason for use, date(s) of administration (including start and end dates), and dosage information (including dose and frequency) must be recorded. Any change in concomitant therapy during the study period must be similarly recorded. Questions regarding prior or concomitant therapy should be directed to one of the investigators.

3.4.1 Prior Anti-Cancer Therapy

For purposes of this protocol, anti-tumor treatment may be defined as, but is not limited to, anti-cancer agents (cytotoxic chemotherapy, immunotherapy, or biologic therapy), radiotherapy, and investigational agents. An investigational agent is any drug or therapy not currently approved for use in humans. No anti-cancer therapy is allowed while patients are on trial except for FFX and PRT. Prior neoadjuvant chemotherapy is allowed, but prior radiation to the upper abdomen is not.

3.4.2 Prior Surgery

Patients must have fully recovered from all effects of surgery. Patients must have had at least two weeks after minor surgery and four weeks after major surgery before starting therapy. Minor procedures requiring “Twilight” sedation such as endoscopies or mediport placement may only require a 24 hour waiting period, but this must be discussed with an investigator.

3.4.3 Supportive Care

Subjects should receive best supportive care and treatment of symptoms during the study as appropriate, including transfusion of blood and blood products, oxygen therapy, nutritional support, intravenous fluids, and treatment with appropriate medications (antibiotics, antiemetics, antidiarrheals, and analgesics, etc.). Medications, including steroids, which are given for supportive care, such as appetite stimulation, may be given concurrently.

3.4.3.1 Bisphosphonates and denosumab

Bisphosphonates and denosumab are permitted for the treatment of osteoporosis. Chronic concomitant bisphosphonate/denosumab therapy for the prevention of bone metastasis is not permitted.

3.4.3.2 Hematopoietic growth factors

Hematopoietic growth factors may be used according to ASCO guidelines. Pegfilgrastim is recommended as outlined in Section 5.0.

4.0 TRIAL DESIGN AND DETAILED STUDY PROCEDURES

4.1 Treatment Plan Overview

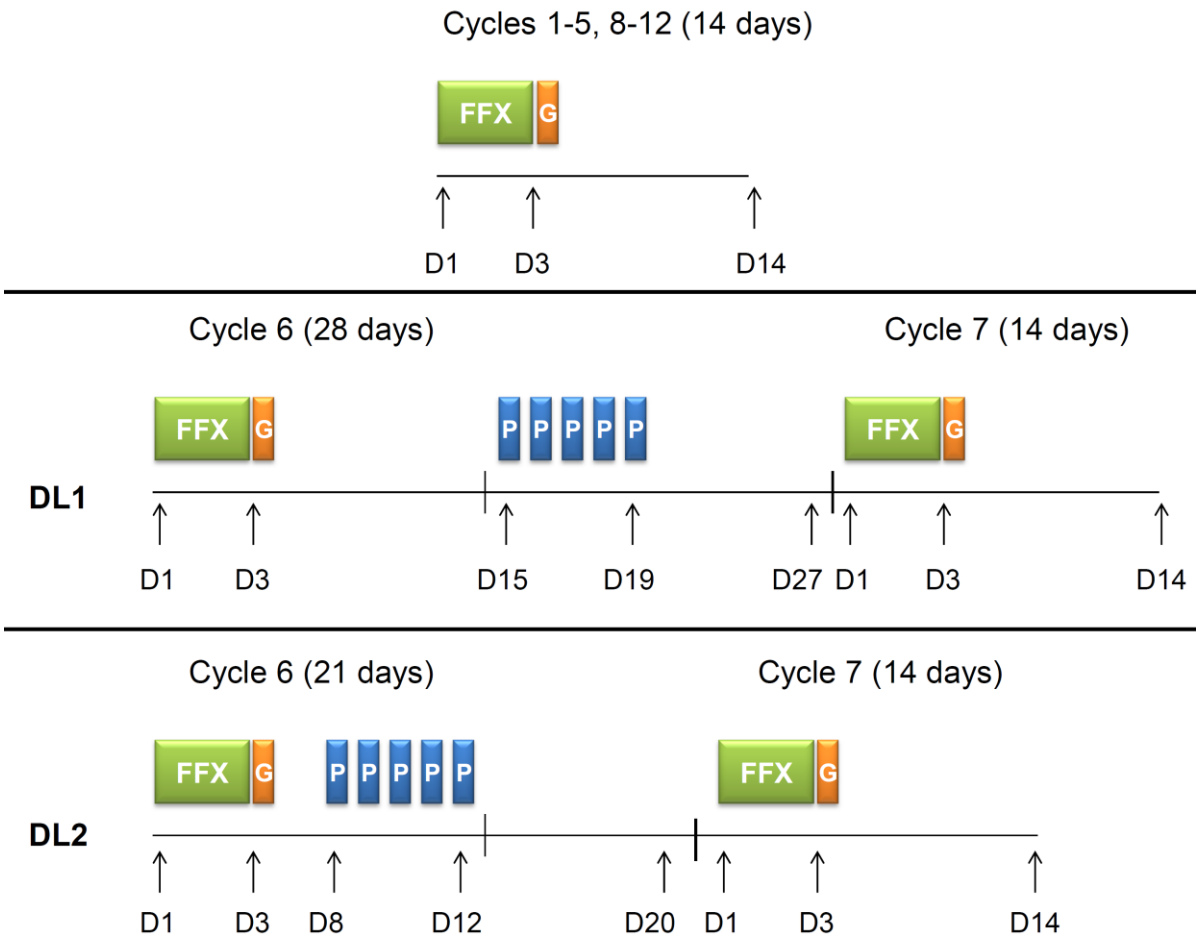
The study is a phase I, single-arm study to establish safety and feasibility of proton-based radiation therapy integrated within adjuvant FFX for patients with resected PDAC. Patients who have completed 2 cycles of FFX for resected pancreatic adenocarcinoma of the head of the pancreas will be eligible for enrollment. PRT will occur between cycles 6 and 7.

In dose level 1 (DL1), patients will complete cycle 6 chemotherapy (days 1-3) and then receive 5 days of daily 5 GyE proton therapy on days 15-19 (excluding weekend days) in a 28 day cycle, prior to starting cycle 7 (see Figure 1). In DL2, patients will complete cycle 6 chemotherapy (days 1-3) and then receive 5 days of daily 5 GyE proton therapy on days 8-12 (excluding weekend days) in a 21 day cycle, prior to starting cycle 7. A 3+3 dose-escalation schema will be used, requiring 3-12 patients to be enrolled.

Using a 3+3 dose-escalation design, if 0 of 3 patients experience a dose-limiting toxicity (DLT) at DL1, then 3 patients will then be enrolled in DL2. If 1 of 3 patients experiences a DLT at DL1, then 3 additional patients will be enrolled at DL1. If 2-3 of 3 patients experience a DLT at DL1, then the study is terminated. If 1 of 6 patients experiences a DLT at DL1, then 3 patients will be enrolled at DL2. If 0-1 of 3 patients experiences a DLT at DL2, then 3 additional patients will be enrolled at DL2. If 2-3 patients experience a DLT at DL2, treatment will continue at DL1 until 6 patients are enrolled at DL1. If 0-1 of 6 patients experiences a DLT at DL2, then DL2 is the recommended phase 2 dose and schedule (RP2D). Conversely, if 0-1 of 6 patients experiences a DLT at DL1 AND 2 or greater patients experience a DLT at DL2, then DL1 is the RP2D.
All cycles will be 14 days, except cycle 6 which is extended to 28 days in DL1, including the 5 daily doses of PRT on days 15-19 (excluding weekend days), and 21 days in DL2, including the 5 daily doses of PRT on days 8-12 (excluding weekend days, see Figure 1 below).

If a scheduled PRT dose falls on a weekend or holiday, then the next daily dose falls on the next business day. The 5 daily doses should be completed in the shortest possible time interval (e.g. 7 days total if 2 are weekend days).

Figure 1. Study Schema



DL = dose level, FFX = mFOLFIRINOX, G = pegfilgrastim on-body injector (optional), P = proton radiation (5 GyE).

4.2 Detailed Study Plan

4.2.1 Screening

Study activities are detailed in Tables 2 (DL1) and 3 (DL2), and a study activity checklist in Table 4. Screening will occur within 28 days prior to Cycle 6 Day 1 of FFX. Signed informed consent will be obtained from the subject or the subject's legally acceptable representative before any study-specific procedures are undertaken. For procedures performed at screening and repeated, the later procedure performed prior to dosing, will serve as a baseline for clinical assessment. A complete history and physical will be obtained at the screening visit. Additionally, labs will be reviewed/ordered during the screening visit, prior to the initiation of therapy.

Patients who pass screening will undergo PRT planning and a full evaluation on Cycle 6 Day 1, including a physical examination, vital signs, performance status, chemistry, hematology, medication review, and adverse event evaluation. If any abnormality is identified at subject assessment on Cycle 6 Day 1, the patient will be deemed a screen failure and will not start treatment.

All patients who start study treatment on cycle 6 day 1 will be eligible for the primary safety analysis. We will substitute patients who screen fail or screen and do not begin study treatment as above.

The screening procedures include the following listed below.

4.2.1.1 Informed Consent

Signed informed consent will be obtained from the subject or the subject's legally acceptable representative before any study-specific procedures are undertaken.

4.2.1.2 Medical History

The following information will be collected during the Screening Period:

1) Complete medical history, including documentation of any clinically significant medical conditions
2) History of tobacco and alcohol use
3) Presence and severity of any symptoms/conditions associated with metastatic pancreatic cancer
4) Detailed oncology history, including:
    a. Date of primary cancer diagnosis
    b. Pathology (histology or cytology) of primary tumor
    c. Surgical history
    d. Anti-cancer treatments administered (including dates and type of modality)
5) At each visit, the subject's medical history will be reviewed and any changes from baseline will be recorded in the case report form (CRF). On C6D1, any changes observed from the screening assessments, prior to dosing, will be recorded in the subject's medical history. All medications (prescription or over-the-counter, including vitamins and/or herbal supplements) will be recorded beginning with the screening visit and continuing up through the date of the off study visit.

4.2.1.3 Demographics

Age, gender, race and ethnicity will be recorded.

4.2.1.4 Review subject eligibility criteria

4.2.1.5 Review previous and concomitant medications

4.2.1.6 Physical exam including vital signs, height, and weight

A complete physical examination will be performed at the screening visit. Body weight will be recorded during every physical exam. The subject will wear lightweight clothing and no shoes during weighing. Height will be measured at the screening visit only; the subject will not wear shoes.

4.2.1.7 Vital sign determinations

Vital sign determinations of heart rate, blood pressure and body temperature will be obtained at the screening visit. If possible, blood pressure and heart rate measurements should not immediately follow scheduled blood collections.

4.2.1.8 Performance Status

Performance status will be evaluated prior to study entry according to Table 1.

4.2.1.9 Hematology

Hematology samples (CBC with differential) will be collected and assessed using a certified laboratory. The Investigator will review, initial and date all laboratory results. Any laboratory value outside the reference range stated in the inclusion criteria will preclude the patient from study participation.

4.2.1.10 Serum chemistries

Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT, AST, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin. Any laboratory value outside the reference range stated in the inclusion criteria will preclude the patient from study participation.

4.2.1.11 Pregnancy Test
For female subjects of childbearing potential, a serum pregnancy test will be performed at the screening visit within 28 days of C6D1 and a urine pregnancy test will be done at the C6D1 visit prior to the first dose of study drug. Subjects considered not of childbearing potential must be documented as being surgically sterile or post-menopausal (for at least 1 year). The test results must be reviewed and determined to be negative prior to dosing. If the urine pregnancy test is positive at C6D1, it should be confirmed by a serum pregnancy test. The test may be repeated at the discretion of the investigator at any time during the study. Should a female study subject become pregnant or suspect she is pregnant while participating in this study, she should inform the treating Investigator immediately.

4.2.1.12 Tumor assessment
Only patients with no evidence of local recurrence or metastatic disease will be eligible to enter onto the study. Patients with suspected disease recurrence will have to be evaluated to rule out disease recurrence prior to study enrollment.

4.3 Patient Study Number Assignment and Sample Labeling

4.3.1.1 Patient Study Number Assignment
Patients will be de-identified and assigned with a 3-digit study label (XXX).

4.4 Detailed Patient Assessments

Subject assessments (physical examinations, vital signs, performance status, chemistry, hematology, medication review, and adverse event evaluations) will be conducted at screening, C6D1, C6D15 (DL1) or C6D8 (DL2), and D1 of every subsequent cycle (every 14 days ± 3 days). Details are provided in Tables 2 and 3, and a checklist highlighting the important events for screening through the completion of the trial is provided below in Table 4. Patients will meet with the radiation oncologist during screening (prior to C6D1), during PRT, and at follow-up visits as outlined below.

4.4.1 Physical Examinations

A complete physical examination will be performed at the screening visit, on C6D1, C6D15 (DL1) or C6D8 (DL2), and D1 of every subsequent cycle (every 14 days ± 3 days). Any significant physical examination findings after the administration of the first doses PRT will be recorded as adverse events. Body weight will be recorded during every physical exam. The subject will wear lightweight clothing and no shoes during weighing. Weight will be measured on the same scale at each visit. Height will be measured at the screening visit and C6D1 only; the subject will not wear shoes.

4.4.2 Medical History

At each visit, the subject's medical history will be reviewed and any changes from baseline will be recorded as an adverse event. On C6D1, any changes observed from the screening assessments, prior to dosing, will be recorded in the subject's medical history. All medications (prescription or over-the-counter, including vitamins and/or herbal supplements) will be recorded beginning with the screening visit and continuing up through the date of the final visit.

4.4.3 Vital Signs

Vital sign determinations of body temperature (in degrees Celsius), heart rate, respiratory rate, blood pressure and pain (using a 0-10 Numeric Ranking Scale) will be obtained at the screening visit, on each day the subject is seen by the treating physician, and at the final visit. If possible, blood pressure and heart rate measurements should not immediately follow scheduled blood collections.

4.4.4 Clinical Laboratory Tests

All subjects will undergo the laboratory assessments outlined in Tables 2 and 3.

1) A complete blood count (CBC) with differential will be collected at the screening visit, on C6D1, C6D15 (DL1) or C6D8 (DL2), and D1 of every subsequent cycle (every 14 days ± 3 days).
2) Serum chemistries (total protein, albumin, total bilirubin, AST, ALT, alkaline phosphatase, sodium, potassium, chloride, bicarbonate, BUN, creatinine, and calcium) will be collected at the screening visit, on C6D1, C6D15 (DL1) or C6D8 (DL2), and D1 of every subsequent cycle (every 14 days ± 3 days).
3) PT/INR and aPTT will be collected at the screening visit (this may be repeated during the course of the study at the discretion of the investigator but is not required).

Laboratory samples for this study will be assessed using the certified laboratory at the investigators' institutions, or at a clinical laboratory such as Quest or LabCorp and these data will be used for all data analysis. The Principal Investigator or sub-investigator will review, initial and date all laboratory results. Any laboratory value outside the reference range that is considered clinically significant by the investigator will be followed as appropriate. Clinically significant laboratory values will be recorded as adverse events if they meet the criteria as specified in Section 6.0.

4.4.5 Adverse Event Evaluation

The Principal Investigator or sub-investigators will assess adverse events, laboratory data and vital signs throughout the study. Adverse events will be assessed by NCI CTCAE Version 5.0. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf. The investigators will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course, duration and outcome, relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events not considered "probably related" to study drug, the investigator will provide an "Other" cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded. All adverse events will be followed to a satisfactory conclusion.

4.4.6 Imaging and Evaluation

Patients will undergo a baseline tumor evaluation with imaging studies within 28 days prior to C6D1. Imaging studies should include a diagnostic CT scan of the chest, abdomen, and pelvis with PO and IV contrast (unless medically contraindicated). If a patient has an allergy to IV contrast, appropriate pre-medication can be given to prevent a contrast reaction. Patients may undergo other modalities such as an MRI instead of a CT scan at the treating physician's discretion if appropriate (such as severe allergy to CT contrast, extremity tumors, bone metastases requiring bone scans, etc.).

The first follow-up surveillance scan will occur within 14 days of the End of Treatment (EOT) visit which will be scheduled following completion of C12 or the last cycle of FFX administered. Follow-up visits including scans (CT or MRI) and blood work including CA19-9 will then occur every 3 months up to 24 months.

4.4.7 Removal of Subjects from Therapy or Assessment

4.4.10.1 Reasons for Removal of Subjects from Therapy or Assessment

Each subject has the right to withdraw from study treatment at any time. In addition, the investigator may discontinue a subject from the study treatment at any time for any reason if the investigator considers it necessary, including the occurrence of an adverse event or noncompliance with the protocol. Each subject will be withdrawn from the study if any of the following occur:

1) The subject experiences either clinical or radiographic progressive disease.
2) The subject requires other radiotherapy or alternate antineoplastic agents during the study period.
3) The investigator believes it is in the best interest of the subject.
4) Clinically significant deterioration of the subject's medical status as determined by the investigator.
5) Subject becomes pregnant or begins breastfeeding during the treatment portion of the study.
6) The subject or subject's legally acceptable representative decides to withdraw consent for any reason.
7) Any other medical reason that the study investigator deems appropriate.

4.4.10.2 Discontinuation of Individual Subjects

When a subject discontinuation from the study (without reaching a protocol-defined endpoint) is planned, the investigator will notify the PI as soon as possible (provided, in each case, subject care and safety are not compromised). When a subject discontinues the study, a final visit will be conducted (preferably prior to the initiation of another anticancer therapy). However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator feels are necessary to treat the subject's condition. Following discontinuation of the study drug, the subject will be treated in accordance with the investigator's best clinical judgment. At the final visit, the reason(s) for the discontinuation from the study will be recorded and a physical examination, body weight, vital signs measurement, laboratory analyses, performance status, tumor assessment, and an assessment of adverse events will be performed as soon as possible after discontinuation from the study. All subjects will have one final visit, which does not need to be performed for subjects who have had a visit greater than 30 days after discontinuation of the study drugs. If a subject is discontinued from the study with an ongoing adverse event or an unresolved clinically significant laboratory result, personnel will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory result or adverse event is achieved. In the event that a positive result is obtained on a pregnancy test for a subject during the study, the administration of study drug to that subject must be discontinued immediately.

4.4.10.3 Discontinuation of Entire Study

The investigators may terminate this study provided that written notice is submitted at a reasonable time in advance of the intended termination. The following procedures for discontinuation will be followed:

1) If the investigators have decided to prematurely discontinue the study, the investigators will promptly notify in writing the IRB of the decision and give detailed reasons for the discontinuation.
2) The PI must promptly notify enrolled subjects of the premature discontinuation and administer appropriate treatments such as replacement of protocol therapy by other appropriate regimens.

4.4.8 Protocol Deviations

The investigator should not implement any deviation from the protocol without prior review and agreement by the Sponsor and in accordance with the IRB and local regulations, except when necessary to eliminate an immediate hazard to study subjects.

Table 2. Study Activities – Dose Level 1

	Screening[a]	C6D1[b]	C6D2	C6D3	C6D15	C6D16	C6D17	C6D18	C6D19	D1 of C7[c]-C12	EOT[d]	F/U[e]
Informed Consent	X											
Demographics	X											
Medical History	X											
ECOG PS[f]	X	X			X					X	X	X
Concomitant Medications Collection	X	X			X					X	X	X
Adverse Events Assessment	X	X			X					X	X	X
Vital Signs	X	X			X					X	X	X
Height	X	X										
Weight	X	X			X					X	X	X
History and Physical Exam	X	X			X					X	X	X
CT or MRI Scan Tumor Evaluation and Assessment[g]	X										X[h]	X
β-hCG[i]	X	X										
CBC with differential	X	X			X					X	X	X
CMP[j]	X	X			X					X	X	X
PT/INR and aPTT	X											
CA19-9	X	X								X	X	X
mFOLFIRINOX		X	X	X						X		
Proton Beam Planning	X											
Proton Beam Therapy					X	X	X	X	X			
Survival		X			X					X	X	X

[a]Screening visit must occur within 28 days of C6D1 of mFOLFIRINOX
[b]This assumes proton therapy will be administered during C6 (may be delivered during C6-C11 if necessary)
[c]C6 is a 28 day cycle in dose level 1 (C7D1 = C6D29), all other cycles are 14 days in length
[d]End of treatment (D1 of last cycle of mFOLFIRINOX, typically C12)
[e]Follow-up assessments will be performed every 3 months for up to 24 months
[f]Eastern Cooperative Oncology Group Performance Status
[g]Screening scans should be done within 2 months of C6D1
[h]Can be performed within 14 days of the EOT visit
[i]Serum (screening) and urine (C6D1) pregnancy tests (for women of childbearing potential only)
[j]Comprehensive metabolic panel: sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, AST, ALT, alkaline phosphatase, total bilirubin, total protein, and albumin

Table 3. Study Activities – Dose Level 2

	Screening[a]	C6D1[b]	C6D2	C6D3	C6D8	C6D9	C6D10	C6D11	C6D12	D1 of C7[c]-C12	EOT[d]	F/U[e]
Informed Consent	X											
Demographics	X											
Medical History	X											
ECOG PS[f]	X	X			X					X	X	X
Concomitant Medications Collection	X	X			X					X	X	X
Adverse Events Assessment	X	X			X					X	X	X
Vital Signs	X	X			X					X	X	X
Height	X	X										
Weight	X	X			X					X	X	X
History and Physical Exam	X	X			X					X	X	X
CT or MRI Scan Tumor Evaluation and Assessment[g]	X										X[h]	X
β-hCG[i]	X	X										
CBC with differential	X	X			X					X	X	X
CMP[j]	X	X			X					X	X	X
PT/INR and aPTT	X											
CA19-9	X	X								X	X	X
mFOLFIRINOX		X	X	X						X		
Proton Beam Planning												
Proton Beam Therapy	X				X	X	X	X	X			
Survival		X			X					X	X	X

[a]Screening visit must occur within 28 days of C6D1 of mFOLFIRINOX
[b]This assumes proton therapy will be administered during C6 (may be delivered during C6-C11 if necessary)
[c]C6 is a 21 day cycle in dose level 1 (C7D1 = C6D15), all other cycles are 14 days in length
[d]End of treatment (D1 of last cycle of mFOLFIRINOX, typically C12)
[e]Follow-up assessments will be performed every 3 months for up to 24 months
[f]Eastern Cooperative Oncology Group Performance Status
[g]Screening scans should be done within 2 months of C6D1
[h]Can be performed within 14 days of the EOT visit
[i]Serum (screening) and urine (C6D1) pregnancy tests (for women of childbearing potential only)
[j]Comprehensive metabolic panel: sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, AST, ALT, alkaline phosphatase, total bilirubin, total protein, and albumin

Table 4. Study Activities Checklist

Screening

Informed Consent	_____
Demographics	_____
Medical History	_____
ECOG PS	_____
Concomitant Medications Collection	_____
Adverse Events Assessment	_____
Vital Signs	_____
Height	_____
Weight	_____
History and Physical Exam	_____
CT or MRI Scan	
Tumor Evaluation and Assessment	_____
β-hCG	_____
CBC with Differential	_____
Comprehensive Metabolic Panel	_____
PT/INR and aPTT	_____
CA19-9	_____
Proton Beam Planning	_____

Cycle 6 Day 1

ECOG PS	_____
Concomitant Medications Collection	_____
Adverse Events Assessment	_____
Vital Signs	_____
Height	_____
Weight	_____
History and Physical Exam	_____
β-hCG	_____
CBC with Differential	_____
Comprehensive Metabolic Panel	_____
CA19-9	_____
mFOLFIRINOX (Days 1-3)	_____
Survival	_____

Cycle 6 Day 15 (Dose Level 1) or Cycle 6 Day 8 (Dose Level 2)

ECOG PS	_____
Concomitant Medications Collection	_____
Adverse Events Assessment	_____
Vital Signs	_____
Weight	_____
History and Physical Exam	_____
CBC with Differential	_____
Comprehensive Metabolic Panel	_____
Proton Beam Therapy (Days 15-19 in Dose Level 1, Days 8-12 in Dose Level 2)	_____
Survival	_____

Day 1 of Subsequent Cycles (7-12)

ECOG PS	_____

Concomitant Medications Collection _____
Adverse Events Assessment _____
Vital Signs _____
Height _____
Weight _____
History and Physical Exam _____
CBC with Differential _____
Comprehensive Metabolic Panel _____
CA19-9 _____
mFOLFIRINOX (Days 1-3) _____
Survival _____

End of Treatment
ECOG PS _____
Concomitant Medications Collection _____
Adverse Events Assessment _____
Vital Signs _____
Height _____
Weight _____
History and Physical Exam _____
CBC with Differential _____
Comprehensive Metabolic Panel _____
CA19-9 _____
Survival _____

Follow-Up
ECOG PS _____
Concomitant Medications Collection _____
Adverse Events Assessment _____
Vital Signs _____
Height _____
Weight _____
History and Physical Exam _____
CBC with Differential _____
Comprehensive Metabolic Panel _____
CA19-9 _____
Survival _____

5.0 DOSAGES AND DISPENSATION OF DRUGS

5.1 FFX Administration

The study drugs are defined as 5-FU, LV, oxaliplatin, and irinotecan (FFX). Due to the infusional 5-FU, study drugs must be administered via central line (mediport, PICC, or other). Treatment cycles are every 14 days ± 3 days (except for C6 which is 28 days in DL1 and 21 days in DL2). The study drug dosages and administration are only recommended – dosages and supportive medication can be modified at the discretion of the investigator, taking into consideration dose modifications during cycles 1-5. Per the PRODIGE 24 trial, the 5-FU bolus is omitted and irinotecan is 150 mg/m^2. A research infusion nurse will access the patient's line. Treatment will then be administered in the following order (substitutions for prophylactic medications are allowed at the treating investigator's discretion):

Table 5. Drug Administration

Drug	Indication	Dose/Route	Duration
Fosaprepitant	Nausea prophylaxis	150 mg IV	30 minutes
Ondansetron	Nausea prophylaxis	16 mg IV	15 minutes
Dexamethasone	Nausea prophylaxis	10 mg IV	15 minutes
Leucovorin	Treatment	400 mg/m^2 IV	60 minutes
Oxaliplatin	Treatment	85 mg/m^2 IV	120 minutes (can be administered simultaneously with leucovorin via a Y-connector)
Atropine	Diarrhea prophylaxis	0.5 mg IV	IV push
Irinotecan	Treatment	150 mg/m^2 IV	90 minutes
5-fluorouracil	Treatment	2400 mg/m^2 IV	46 hours (continuous infusion)
Pegfilgrastim on-pro	Growth factor support	6 mg SC	Administered on day 3 (after 5-fluorouracil pump is unhooked)

The patient will return to the research infusion clinic after 46 hours for disconnection of the 5-FU infusional pump and administration of pegfilgrastim on-pro. Use of growth factor support is highly recommended but is at the discretion of the investigator. Alternatively, pegfilgrastrim 6 mg SC can be administered on day 4 (if not using on-pro administration).

5.2 Packaging, Labeling, Storage, and Handling of Chemotherapy

5-FU, LV, oxaliplatin,and irinotecan should be stored and handled as per their respective FDA labels and following protocols and guidelines of LCCC (see http://www.osha.gov/SLTC/hazardousdrugs/index.html).[18-20,23]

5.3 Proton Beam Therapy

PRT planning will commence following the screening visit with the radiation oncologist. PRT volumes will include a clinical target volume of the highest at risk nodal regions: celiac, SMA, and para-aortic regions. The porta hepatic nodes have been shown to be at significantly less risk for local recurrence and will not be included in the treatment.[29,30] The normal tissue constraints are as follows: stomach and small bowel: V30 < 0.1 cc, V20 < 5 cc, V15 < 10 cc, cord D_{max} < 25 Gy, liver V17 < 33%. Target volume coverage should be greater than 95%. Two posterior oblique beams or 1 posterior and 1 lateral beam are encouraged. The radiation oncology study chair will approve of all treatment plans.

If PRT has started and becomes unavailable, it will restart when available and the patient will resume the treatment schedule following this delay. If greater than 14 days elapse after PRT is held, PRT will not be completed and the patient will resume standard adjuvant mFOLFIRINOX for remainder of treatment.

6.0 SAFETY VARIABLES AND TOXICITY ASSESSMENT

The Principal Investigator or sub-investigators will assess adverse events, laboratory data and vital signs throughout the study. Adverse events will be assessed by NCI CTCAE Version 5.0: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

6.1 Adverse Event Assessment

The investigators will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course, duration and outcome, relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events not considered "probably related" to study drug, the investigator will provide an "Other" cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by personnel, or reported spontaneously by the subject will be recorded. All adverse events will be followed to a satisfactory conclusion.

6.2 Study Monitoring

6.2.1 Data Safety Monitoring Committee at Georgetown

The Georgetown Lombardi Comprehensive Cancer Center will be responsible for the data and safety monitoring of this multi-site trial. As this study is an investigator initiated study phase I study, it is considered a high-risk study which requires real-time monitoring by the PI and study team and review every 4 months by the LCCC Data and Safety Monitoring Committee (DSMC).

The Principal Investigator and the Co-Investigators will review the data including safety monitoring at their weekly institution based disease group meetings, on monthly disease group teleconferences, and monthly teleconferences between study sites.

All Severe Adverse Events (SAEs) are required to be reported to the IRB. Based on SAEs, the IRB retains the authority to suspend further accrual pending more detailed reporting and/or modifications to further reduce risk and maximize the safety of participating patients.

Progress on the trial and the toxicities experienced will be reviewed by the LCCC Data and Safety Monitoring Committee every 4 months from the time the first patient is enrolled on the study. Results of the DSMC meetings will be forwarded to the IRB with recommendations regarding need for study closure.

DSMC recommendations should be based not only on results for the trial being monitored as well as on data available to the DSMC from other studies. It is the responsibility of the PI to ensure that the DSMC is kept apprised of non-confidential results from related studies that become available. It is the responsibility of the DSMC to determine the extent to which this information is relevant to its decisions related to the specific trial being monitored.

A written copy of the DSMC recommendations will be given to the trial PI and the IRB. If the DSMC recommends a study change for patient safety or efficacy reasons the trial PI must act to implement the change as expeditiously as possible. In the unlikely event that the trial PI does not concur with the DSMC recommendations, then the LCCC Associate Director of Clinical Research must be informed of the reason for the disagreement. The trial PI, DSMC Chair, and the LCCC AD for Clinical Research will be responsible for reaching a mutually acceptable decision about the study and providing details of that decision to the IRB. Confidentiality must be preserved during these discussions. However, in some cases, relevant data may be shared

with other selected trial investigators and staff to seek advice to assist in reaching a mutually acceptable decision.

If a recommendation is made to change a trial for reasons other than patient safety or efficacy the DSMC will provide an adequate rationale for its decision. If the DSMC recommends that the trial be closed for any reason, the recommendation will be reviewed by the Associate Director for Clinical Research at G-LCCC. Authority to close a trial for safety reasons lies with the IRB, with the above described input from DSMC and the AD for Clinical Research.

6.3 Adverse Event and Toxicity Definitions

6.3.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product. Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

6.3.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to the DSMC as a serious adverse event (SAE) within 24 hours of the study personnel being made aware of the serious adverse event.

1) **Death of Subject** An event that results in the death of a subject.
2) **Life-Threatening** An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
3) **Hospitalization or**
4) **Prolongation of Hospitalization** An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
5) **Congenital Anomaly** An anomaly detected at or after birth, or any anomaly that results in fetal loss.
6) **Persistent or Significant Disability/Incapacity** An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
7) **Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome** An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may

jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8) **Spontaneous Abortion** Miscarriage experienced by study subject.
9) **Elective Abortion** Elective abortion performed on study subject.

6.3.3 Adverse Event Severity

The study investigator will rate the severity of each adverse event according to the NCI CTCAE Version 5.0. For adverse events not captured by the NCI CTCAE Version 5.0, the following should be used:

1) **Grade 1 (Mild)** The adverse event is transient and easily tolerated by the subject.
2) **Grade 2 (Moderate)** The adverse event causes the subject discomfort and interrupts the subject's usual activities.
3) **Grade 3-4 (Severe or Life Threatening)** The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.
4) **Grade 5 (Death)** The adverse event resulted in death of the subject.

6.3.4 Relationship to Study Drug

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

1) **Definitely Related** An adverse has a clear temporal relationship to study drug and/or recurs on re-challenge and an Other cause of event is extremely unlikely.
2) **Probably Related** An adverse event has a strong temporal relationship to study drug or recurs on re-challenge and an Other cause of event is unlikely or significantly less likely.
3) **Possibly Related** An adverse event has a strong temporal relationship to the study drug and an Other cause of event is equally or less likely compared to the potential relationship to study drug.
4) **Probably Not Related** An adverse event has little or no temporal relationship to the study drug and/or a more likely Other cause of event exists.
5) **Not Related** An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely Other cause of event).

If an investigator's opinion of possibly, probably not, or not related to study drug is given, an Other cause of event must be provided by the investigator for the serious adverse event.

6.4 Adverse Event Collection Period

All adverse events reported from the time of study drug administration until 30 days following discontinuation of study drug administration have elapsed will be collected, whether elicited or spontaneously reported by the subject. In addition, serious adverse events will be collected from the time the subject signed the study-specific informed consent.

6.5 Adverse Event Reporting

In the event of a serious adverse event, whether related to study drug, study procedure such as a biopsy, or even if not directly related to any study intervention, the investigator will notify the IRB within 72 hours of being made aware of the serious adverse event.

The SAE report should comprise a full written summary, detailing relevant aspects of the adverse events in question. Where applicable, information from relevant hospital case records and autopsy reports should be included.

6.6 Pregnancy

In the event of a positive pregnancy test result, study drugs will be immediately discontinued. The investigator must report the positive pregnancy test within 72 hours of the study personnel becoming aware of the pregnancy to the IRB. Patients should also notify the investigator if it is determined after completion of the study that they become pregnant either during the treatment phase of the study or within five days after the treatment period. Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected, and the status of the mother and child should be reported to the IRB after delivery. Pregnancy in a study subject is not considered an adverse event but does require discontinuation of the subject from the study. However, the medical outcome of an elective or a spontaneous abortion, stillbirth or congenital anomaly is considered a serious adverse event and must be reported to the IRB within 72 hours of study personnel becoming aware of the event. Male subjects should also notify the investigators if the subject's partner should become pregnant during the study, this should also be reported within 72 hours of study personnel awareness.

6.7 Toxicity Management and Dose Adjustments

6.7.1 Dose Reduction and Delays of FFX

As patients will enter the study already having completed 5 cycles of FFX, discretion is given to the investigator to continue patients at the same doses as cycle 5. Therefore, all dose modifications are recommended but left to the discretion of the investigator.

Table 6. Dose Levels for Modifications for FFX (Recommended)

Episode #	Irinotecan	Oxaliplatin	5-FU/LV
1st	Decrease to 120 mg/m^2	Decrease to 75 mg/m^2	Decrease to 1800 mg/m^2
2nd	Decrease to 90 mg/m^2	Decrease to 65 mg/m^2	Decrease to 1200 mg/m^2
3rd	Off Study	Off Study	Off Study

Table 7. Dose Modifications for FFX (Recommended)

Toxicity	Instruction
ANC < 1500/mm^3	Hold until ANC ≥ 1500/mm^3 and reduce one dose level as above
Platelets < 75000/mm^3	Hold until platelets ≥ 75000/mm^3 and reduce one dose level as above
Febrile neutropenia or Grade 4 neutropenia ≥ 7 days	Hold until afebrile and ANC ≥ 1500/mm^3, reduce one dose level as above
Grade 3-4 diarrhea	Initiate Imodium prn, hold until resolved to baseline or grade 1, reduce one dose level as above
Grade 3-4 peripheral neuropathy	Discontinue oxaliplatin

Other grade 3-4 toxicity	Hold until toxicity resolves to baseline or grade 1, reduce one dose level as above

6.8 Prohibited Concurrent Medications

The following medications must be discontinued at least 2 weeks prior to C6D1 (strong CYP3A4 inhibitors or inducers, strong UGT1A1 inhibitors):

Atazanavir, Atazanavir/ritonavir, boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, darunavir/ritonavir, elvitegravir/ritonavir, grapefruit juice, idelalisib, indinavir, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir,ombitasvir/paritaprevir/dasabuvir/ritonavir (VIEKIRA PAK), posaconazole, ritonavir, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycinvoriconazole, carbamazepine, enzalutamide, lumacaftor, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort (hypericum perforatum), adenine, propofol, indomethacin, nilotinib, pazopanib, regorafenib, flunitrazepam, erlotinib, sorafenib, enasidenib, pibrentasvir, glecaprevir, rucaparib, ertugliflozin, fostamatinib, dolutegravir, valproic acid, flurbiprofen, eltrombopag, silibinin A, and sodium aurothiomalate.

6.9 Dose Limiting Toxicities (DLTs)

Dose limiting toxicities (DLTs) are defined in Table 9 below. The DLT window will start with the first dose of PRT and continue for 28 days afterwards. Patients who receive at least one dose of PRT will be evaluable for DLT determination.

Table 9. Dose Limiting Toxicities (DLTs)

Toxicity
Delay in start of C7 (or whichever cycle follows PRT) of ≥ 14 days related to treatment AEs
Non-hematologic ≥ grade 3 AEs excluding grade 3-4 allergic reaction, grade 3 alopecia, grade 3 fatigue < 5 days, and except as listed below
Grade 3 nausea/vomiting ≥ 48 hours despite optimal anti-emetic therapy
Grade 3 diarrhea ≥ 48 hours despite optimal anti-diarrheal therapy
≥ Grade 3 colitis
≥ Grade 3 chest wall pain
≥ Grade 2 total bilirubin > 7 consecutive days
≥ Grade 3 total bilirubin, ≥ grade 2 ALT with a ≥ grade 2 total bilirubin elevation
≥ Grade 3 ALT lasting > 4 consecutive days
Grade 4 ALT or AST
Grade 4 serum alkaline phosphatase > 7 consecutive days
≥ Grade 3 serum creatinine
≥ Grade 3 constipation
≥ Grade 3 gastrointestinal obstruction
Grade 2 flatulence

7.0 EFFICACY ASSESMENT

7.1 Efficacy Variables

Disease recurrence will be assessed by a CT scan (or other appropriate modalities such by way of MRI consistent with the modality used prior to treatment) utilizing RECIST v1.1 criteria. Assessments will be performed within 2 months of C6D1, at EOT, and at follow-up visits.

We will track the success rate in screening patients, completion of PRT planning, completion of proton beam treatment, and completion of adjuvant therapy (including number of cycles completed and relative dose intensity).

7.2 RECIST v1.1 Criteria for Tumor Response

Changes in the measurable lesions over the course of therapy will be evaluated using the RECIST v1.1 criteria.

7.2.1 Definition of Lesions

7.2.1.1 Measurable Disease

The presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

7.2.1.2 Measurable Lesions

Lesions that can be accurately measured in at least one dimension with longest diameter ≥ 20 mm using conventional techniques or ≥ 10 mm with CT scan.

7.2.1.3 Non-measurable Lesions

All other lesions, including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with a CT scan), bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions and also abdominal masses that are suspicious though may or may not be confirmed and followed by imaging techniques.

All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 14 days before the beginning of the treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is required.

7.2.2 Methods of Measurement

CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. For accurate objective response evaluation, ultrasound should not be used to measure tumor lesions. However, ultrasound is a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination. Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

7.3 Definition of Disease Recurrence

Disease progression will be defined as:

1) Radiologic progression of disease by RECIST v1.1 criteria.
2) Clinical progression as determined by the investigator, which may be characterized as, but is not limited to:
    a. Increase of at least 2 points in ECOG performance status attributable to cancer progression.
    b. Requirement for radiation (beyond palliative radiation for bone pain relief as outlined in 3.4.3.3), chemotherapy or surgery.
3) Death from disease progression

8.0 STATISTICAL CONSIDERATIONS

8.1 Primary Objective:

To determine the recommended phase II dose and schedule (RP2D) of short-course PRT integrated within adjuvant FFX (radiation 12 days following chemotherapy or 5 days following chemotherapy) for resected PDAC. The co-primary objectives are to demonstrate the safety and feasibility of short short-course proton radiation within systemic adjuvant chemotherapy with FFX, including the number of cycles received and relative chemotherapy dose-intensity.

8.2 Exploratory Objectives:

To determine, in patients with resected PDAC undergoing PRT integrated within adjuvant FFX:

8.2.1 Median recurrence-free survival (mPFS)

8.2.2 Median overall survival (mOS)

8.3 Primary Endpoint:

The primary endpoint is to determine the RP2D between the 2 proposed schedules. Using a 3+3 dose-escalation schema, 2-12 patients will be required to determine the RP2D.

Co-primary endpoints:

8.3.1 Safety: adverse event data will be collected and presented as descriptive statistics using the CTCAE version 5.0.

8.3.2 Feasibility: we will track the success rate in screening patients, completion of proton beam planning, completion of proton beam treatment, and completion of adjuvant therapy (including number of cycles completed and relative dose intensity).

8.4 Exploratory Endpoints:

8.4.1 Recurrence-free survival (RFS), defined as time from surgery until evidence of disease recurrence.

8.4.2 Overall survival (OS), defined as time from surgery until death from any cause or last follow-up.

8.5 Study Design and Sample Size Calculation

The study is a phase I, single-arm study to establish safety and feasibility of proton-based radiation therapy integrated within adjuvant mFOLFIRINOX for patients with resected PDAC. Patients who have completed 2 cycles of mFOLFIRINOX for resected pancreatic adenocarcinoma will be eligible for enrollment. Proton therapy will occur between cycles 6 and 7.

In dose level 1 (DL1), patients will complete cycle 6 chemotherapy (days 1-3) and then receive 5 days of daily 5 GyE proton therapy on days 15-19 (excluding weekend days) in a 28 day cycle, prior to starting cycle 7 (see Figure 1). In DL2, patients will complete cycle 6 chemotherapy (days 1-3) and then receive 5 days of daily 5 GyE proton therapy on days 8-12 (excluding weekend days) in a 21 day cycle, prior to starting cycle 7. A 3+3 dose-escalation schema will be used, requiring 3-12 patients to be enrolled.

Using a 3+3 dose-escalation design, if 0 of 3 patients experience a dose-limiting toxicity (DLT) at DL1, then 3 patients will then be enrolled in DL2. If 1 of 3 patients experiences a DLT at DL1, then 3 additional patients will be enrolled at DL1. If 2-3 of 3 patients experience a DLT at DL1, then the study is terminated. If 1 of 6 patients experiences a DLT at DL1, then 3 patients will be enrolled at DL2. If 0-1 of 3 patients experiences a DLT at DL2, then 3 additional patients will be enrolled at DL2. If 2-3 patients experience a DLT at DL2, treatment will continue at DL1 until 6 patients are enrolled at DL1. If 0-1 of 6 patients experiences a DLT at DL2, then DL2 is the recommended phase 2 dose and schedule (RP2D). Conversely, if 0-1 of 6 patients experiences a DLT at DL1 AND 2 or greater patients experience a DLT at DL2, then DL1 is the RP2D.
All cycles will be 14 days, except cycle 6 which is extended to 28 days in DL1, including the 5 daily doses of PRT on days 15-19 (excluding weekend days), and 21 days in DL2, including the 5 daily doses of PRT on days 8-12 (excluding weekend days).

8.6 Analytic plan for explorary objectives

8.6.1 The nonparametric Kaplan-Meier method will be used to estimate median RFS.

8.6.2 The nonparametric Kaplan-Meier method will be used to estimate median OS.

8.7 Safety Assessments

8.7.1 The safety of FFX and PRT will be assessed by evaluating study drug exposure, adverse events, serious adverse events, oncology-related events, all deaths, as well as changes in laboratory determinations and vital sign parameters.

8.7.2 A summarization of the number of days and/or cycles subjects were exposed to FFX and PRT will be provided.

8.7.3 Analyses of adverse events (and serious adverse events) will include only "treatment-emergent" events, *i.e.*, those that have an onset on or after the day of the first dose of study drug. Analyses will not include those that have an onset greater than 30 days after the treatment. Treatment emergent adverse events will be summarized by system organ class and preferred term according to the MedDRA adverse event coding dictionary. The percentage of subjects experiencing an adverse event at a given severity, NCI CTCAE toxicity grade, and relationship to study drug will be provided.

8.7.4 The number of subject deaths will be summarized (1) for deaths occurring while the subject was still receiving study drug in this study, (2) for deaths occurring off treatment within 30 days after the last dose of study drug, and (3) for all deaths in this study regardless of the number of days after the last dose of study drug. The relatedness of the deaths to the study drugs will also be provided.

9.0 ETHICAL CONSIDERATIONS

9.1 Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IRB. IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to the study site. Any amendments to the protocol will require IRB approval prior to implementation of any changes made to the study design. Any serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to the IRB. During the conduct of the study, the investigator should promptly provide written reports to the IRB of any changes that affect the conduct of the study and/or increase the risk to subjects.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical Principals that have their origin in the Declaration of Helsinki.

9.3 Subject Information and Consent

Prior to the initiation of any screening or study-specific procedures, the investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding this study. A separate informed consent is also required from subjects who provide blood for genetic testing or fresh biopsy tissue samples for analyses. Each informed consent will be reviewed, signed and dated by the subject and the person who administered the informed consent. A copy of each informed consent will be given to the subject and each original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy. Tissue sample collection for analysis will only be performed if the subject has voluntarily consented to participate after the nature of the testing has been explained and the subject has had the opportunity to ask questions. If the subject does not consent to the tissue sample collection, it will not impact the subject's participation in the study.

9.4 Ethical Consideration for Enrollment

Only patients with advanced cancer, for whom no curative therapy exists, will be considered for enrollment. The only treatment options for these patients are enrollment in a Phase I clinical trial, or treatment off protocol, with a non-standard therapy. As described above, the combination of fluorouracil, leucovorin, and nanoliposomal irinotecan is a rational and promising combination for such patients

9.5 Protection of Patient Confidentiality

All patient records, questionnaires, and tissue specimens will be de-identified using a letter and number assigned to their case at the time of enrollment on study. No record or specimen will contain information which could identify the patient. The key which connects patient identifiable information with this assigned number will be held by the Principal investigator. For computer records, the key will be protected by a double password protection system. Any paper records will be contained in a locked cabinet within a locked office to ensure patient’s privacy is protected.

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