Official Study Title:	NeoOPTIMIZE: an open-label, phase II trial to assess the efficacy of adaptive switching of FOLFIRINOX or Gemcitabine/nab-Paclitaxel as a neoadjuvant strategy for patients with resectable and borderline resectable/locally advanced unresectable pancreatic cancer.
Protocol Number:	STUDY00021614
ClinicalTrials.gov ID	NCT04539808
Investigational products:	FOLFIRINOX, Gemcitabine, nab-Paclitaxel, Losartan
Version Number:	**2.4**
Version Date:	20 September 2023
Replaces:	2.3
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SUMMARY OF CHANGES

Version	Section	Summary of Changes	Justification
2.0	4.1	Inclusion criteria #9 revised to allow for up to 1 month of prior chemotherapy for the treatment of their pancreatic cancer per standard of care.	This revision was added to account for logistical timing of consenting study participants and the planned start of their standard of care
2.0	8.3.2	Frequency of blood collection revised to allow for PI discretion to reduce or omit blood collections for each study participant.	This revision does provides logistical flexibility to the planned collection of blood samples.
2.0	Synopsis, 1.4, 2.3, 3.1, 4.1, 11.3	Addition of a locally-advanced, unresectable PDAC (LAPC) cohort. Revisions include adding exploratory objectives and endpoints for the LAPC cohort, eligibility definitions, and statistical population for analyses.	The impact of providing an early switch to GA in the neoadjuvant setting after failing FOLFIRNOX has not been sufficiently explored in patients with LAPC. This exploratory cohort will be used as a benchmark for future studies.
2.0	2, 9.5, 11	Corrections to endpoint definitions and timing of assessments	Corrections provided for clarification
2.1	8.11	Added footnote “E” “if screening CA19-9 or CEA falls outside of screening window, it is allowed per investigator discretion as long as a C1D1 CA19-9 is drawn” to CA19-9 and CEA.	Clarification
2.1	8.4.1.2	Height and weight will be collected within 45 days of C1D1.	To account for the use of heights from a port placement or other visit that may occur prior to screening
2.1	8.2.2	Updated lab analytes and added TUMOR MARKERS section.	To clarify and align with OHSU’s SOC comprehensive metabolic panel.
2.2	1.6	Addition of Correlative Studies Background	Addition of correlative
2.2	8.3.1	Addition of Wong Lab Address for shipping	To provide shipping instructions
2.3	3.1, 7.6	Multi-Disciplinary Tumor Board for restaging	Clarification
2.3	3.2	Study Agent	Clarification
2.3	4.1	Inclusion 5 – Baseline Imaging	Increase flexibility

2.3	4.1	Inclusion 11 – Baseline Labs	Increase flexibility
2.3	4.2	Exclusion 5 – Cardiac History Exclusion 9 – Study Agent	Increase flexibility
2.3	6.8.6, 8.1.8	Administration	To reflect study team actual practice
2.3	7.1.3	Losartan – ACE Inhibitor or ARB	Participants currently receiving ACE/ARB will remain eligible
2.3	Tables 7, 8, 9	Management of toxicity	Align with changes to flexibility
2.3	7.7	Supportive Care	To reflect study team actual practice
2.3	8.1.5, 9.6	Assessment window	Align with changes to flexibility
2.3	8.8, Tables 21, 24	End of Treatment visit timing	To reflect study team actual practice
2.4	4.2, 7.9	Revision to exclusion criteria #7 and prohibited medication in regards anti-cancer treatment.	Clarifies that concomitant supportive cancer care agents are permitted if participant is co-consented to another trial. Exclusion criteria #8 removed as it duplicative
2.4	8.11	Revisions to sample collection timing	Correction to frequency of sample collection
2.4	8.1.7, 10.1, 10.5	Revision of AE collection time frame to end of treatment visit	AE collection for standard of care treatment updated to end of treatment visit.
2.4	8.9	Revision of Follow-up visits and their timing	Clarification to follow-up visits to coincide with standard of care visits, and variation to schedule are not considered deviations.
2.4	8.1.5, 8.11	Revision to screening window	Clarification to screening window.
2.4		Revision to inclusion criteria #10 to specify triplicate ECG	Clarification to ECG as triplicate measure

SYNOPSIS

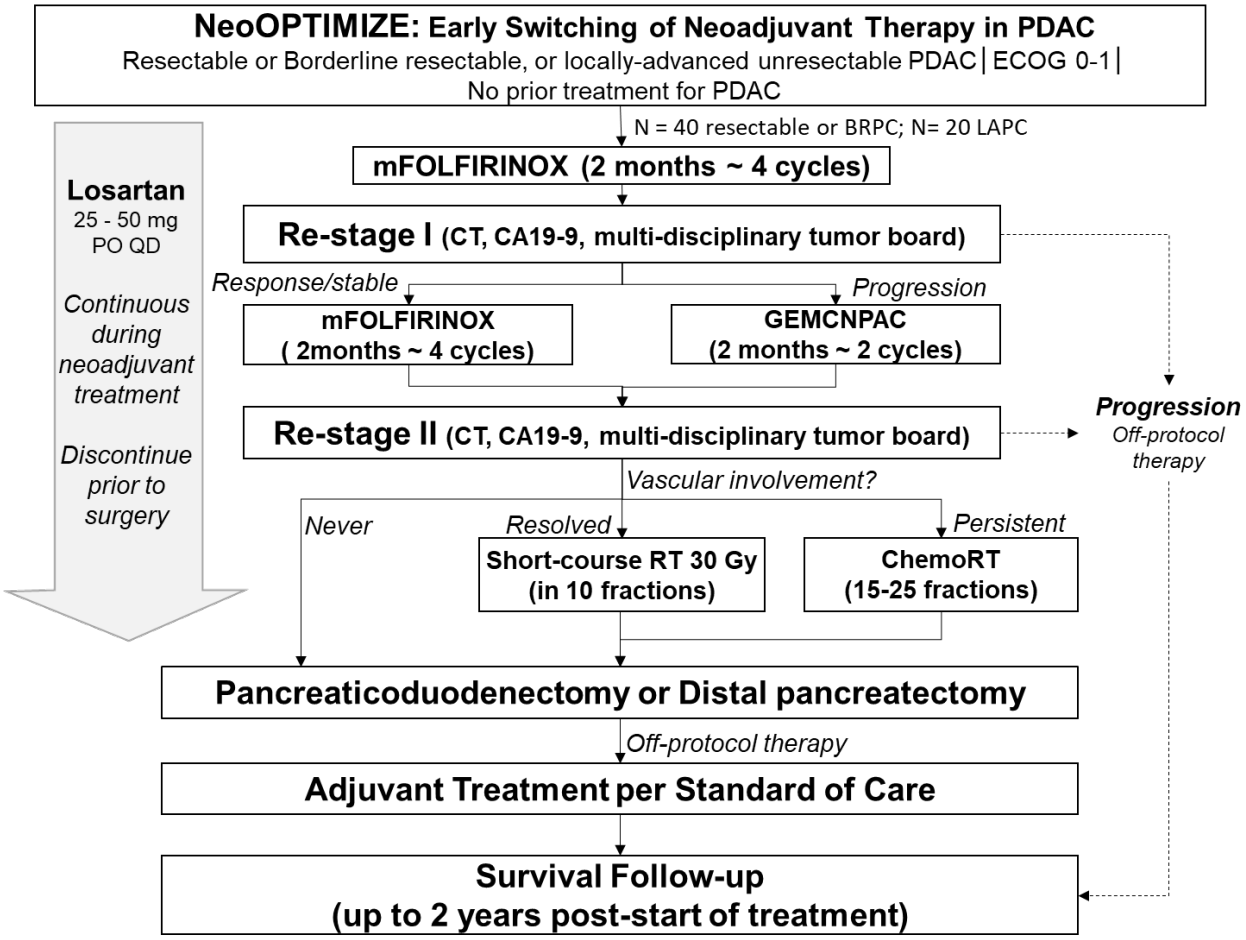
Study Title	NeoOPTIMIZE: an open-label, phase II trial to assess the efficacy of adaptive switching of FOLFIRINOX or Gemcitabine/nab-Paclitaxel as a neoadjuvant strategy for patients with resectable and borderline resectable, or locally-advanced unresectable pancreatic cancer
Protocol #	STUDY00021614
Coordinating Center	OHSU, Knight Cancer Comprehensive Center
Clinical Phase	Phase II
Study Description	Mounting evidence suggests that pre-operative chemotherapy and/or chemoradiation confers significant survival benefit in patients with resectable pancreatic ductal adenocarcinoma (PDAC); including the potential for improving compliance to chemotherapies, down-staging tumors, and increasing the rate of margin-negative resections. Either FOLFIRINOX or gemcitabine/nab-paclitaxel (GA) are currently used in the neoadjuvant setting; however, which of these is most optimal remains to be determined. There is preliminary evidence to suggest that for patients who do not respond to FOLFIRINOX, early switching to GA in the neoadjuvant setting has potential clinical benefit, but further studies are needed. The NeoOPTIMIZE trial described in this protocol intends to provide a flexible platform to provide early dynamic switching of neoadjuvant FOLFIRINOX to GA for patients with newly diagnosed resectable/borderline resectable, or locally-advanced unresectable PDAC (LAPC). The study will use standard of care imaging and clinical biomarker, CA19-9, as a strategy for determining early switch from FOLFIRINOX to GA in order to optimize curative therapy. Underlying this treatment platform is the continuous administration of losartan, an ARB suggested to improve vascular perfusion and increase delivery of chemotherapy agents to the pancreas.
Primary Objective	To determine the rate of margin-negative (R0) resection in participants with resectable or borderline resectable pancreatic cancer (BRPC) following treatment using NeoOPTIMIZE adaptive therapy
Secondary Objectives	1. To determine the progression free survival (PFS) of resectable or BRPC participants that received NeoOPTIMIZE adaptive therapy [i.e., FOLFIRINOX, or switch to GA] 2. To determine the PFS for the subset of resectable or BRPC participants that received NeoOPTIMIZE adaptive therapy plus preoperative radiation therapy [RT] 3. To determine the disease-free survival (DFS) of resectable or BRPC participants that received NeoOPTIMIZE adaptive therapy [i.e., FOLFIRINOX, or switch to GA] 4. To determine the DFS for the subset of resectable or BRPC participants that received NeoOPTIMIZE adaptive therapy plus preoperative RT 5. To determine the overall survival (OS) of resectable or BRPC participants that received NeoOPTIMIZE adaptive therapy 6. To determine the OS for the subset of resectable or BRPC participants that received NeoOPTIMIZE adaptive therapy plus

	preoperative RT 7. To assess the surgical complications of participants that undergo resection after receiving NeoOPTIMIZE adaptive therapy (i.e. all surgical resectable or BRPC participants) 8. To assess 30-day post-operative mortality that undergo surgical resection after receiving NeoOPTIMIZE adaptive therapy (i.e. all surgical resectable or BRPC participants) 9. To assess safety of NeoOPTIMIZE adaptive therapy (all participants)
Exploratory Objectives	1. To monitor changes in CA19-9 levels (all participants) 2. To determine the rate of margin-negative (R0) resection in participants with LAPC following treatment using NeoOPTIMIZE adaptive therapy 3. To determine the PFS of LAPC participants that received NeoOPTIMIZE adaptive therapy [i.e., FOLFIRINOX, or switch to GA] 4. To determine the PFS for the subset of LAPC participants that received NeoOPTIMIZE adaptive therapy plus preoperative radiation therapy [RT] 5. To determine the disease-free survival (DFS) of LAPC participants that received NeoOPTIMIZE adaptive therapy [i.e., FOLFIRINOX, or switch to GA] 6. To determine the DFS for the subset of LAPC participants that received NeoOPTIMIZE adaptive therapy plus preoperative RT 7. To determine the overall survival (OS) of LAPC participants that received NeoOPTIMIZE adaptive therapy 8. To determine the OS for the subset of LAPC participants that received NeoOPTIMIZE adaptive therapy plus preoperative RT 9. To assess the surgical complications of LAPC participants that undergo resection (i.e. all surgical LAPC participants) 10. To assess 30-day post-operative mortality for LAPC participants that undergo surgical resection (i.e. all surgical LAPC participants)
Primary Endpoint	1. Proportion of resectable or BRPC participants with R0 resection
Secondary Endpoints	1. $PFS_{NeoOPTMIZE}$ for resectable or BRPC cohort 2. $PFS_{NeoOPTMIZE + preop\text{-}RT}$ for resectable or BRPC subset with preoperative RT 3. $DFS_{NeoOPTMIZE}$ for resectable or BRPC cohort 4. $DFS_{NeoOPTMIZE+ preop\text{-}RT}$ for resectable or BRPC subset with preoperative RT 5. $OS_{NeoOPTMIZE}$ for resectable or BRPC cohort 6. $OS_{NeoOPTMIZE + preop\text{-}RT}$ for resectable or BRPC subset with preoperative RT 7. Proportion of surgical resectable or BRPC participants with peri- and post-operative complications [per the Clavien-Dindo classification system] 8. Proportion of surgical resectable or BRPC participants that die within 30 days of surgery 9. Incidence of grade ≥3 toxicities [per CTCAE v5.0]
Exploratory Endpoints	1. CA19-9 serum levels (U/ml) 2. Proportion of LAPC participants with R0 resection 3. $PFS_{NeoOPTMIZE}$ for LAPC cohort 4. $PFS_{NeoOPTMIZE + preop\text{-}RT}$ for LAPC subset with preoperative RT

	5. $DFS_{NeoOPTMIZE}$ for LAPC cohort 6. $DFS_{NeoOPTMIZE+\ preop\text{-}RT}$ for LAPC subset with preoperative RT 7. $OS_{NeoOPTMIZE}$ for LAPC cohort 8. $OS_{NeoOPTMIZE\ +\ preop\text{-}RT}$ for LAPC subset with preoperative RT 9. Proportion of surgical LAPC participants with peri- and post-operative complications [per the Clavien-Dindo classification system] 10. Proportion of surgical LAPC participants that die within 30 days of surgery
Key Inclusion Criteria	1. Cytologic or histologic proof pancreatic ductal carcinoma 2. No evidence of metastatic disease 3. Resectable, Borderline resectable, or local-advanced unresectable PDAC 4. No history of previous chemotherapy 5. Must have adequate organ function
Key Exclusion Criteria	1. Any other active malignancy or prior history of malignancy within 5 years except for successfully treated cervical carcinoma in situ, lobular carcinoma in situ of the breast, or non-melanoma skin cancer. 2. Medical co-morbidities that are deemed to make risk of surgery unacceptably high as determined by institutional standards. 3. Personal history of any of the following conditions: syncope of cardiovascular etiology, ventricular arrhythmia of pathological origin (including, but not limited to, ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest. 4. Recent major surgery (excluding laparoscopy) within 4 weeks prior to starting study treatment. Minor surgery within 2 weeks of starting study treatment. Patients must be recovered from effects of surgery. 5. Participants receiving any other study agents. 6. Judgment by the investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements.
Number of Participants	N =60; n = 40 resectable/BRPC cohort; n=20 LAPC cohort
Duration of Therapy	Up to 8 cycles of FOLFIRINOX and/or GA, followed by short- or long-course RT (1-8 weeks, per discretion of treating physician)
Duration of Follow Up	Up to 24 months from start of study treatment
Description of Study Intervention	FOLFIRINOX and/or GA, followed by short- or long-course RT
Statistical Analyses	This is an open-label, non-randomized, phase II trial to assess the efficacy of an adaptive treatment strategy that allows for early switching of neoadjuvant systemic chemotherapy in patients with resectable/borderline resectable or locally-advanced unresectable pancreatic cancer. The primary endpoint is to estimate the proportion of resectable or BRPC participants with R0 resection. Assuming that the proportion of R0 is 60%, a sample size of 32 participants will allow us to estimate the proportion with an exact 95% CI (0.41, 076); that is, a width of 0.35 for the 95%CI. To account for 20% lost to follow-up or ineligible for surgery, a total of 40 participants will be enrolled towards the primary endpoint of estimating the proportion of resectable or BRPC participants

	with R0 resection. A separate exploratory cohort of 20 participants with LAPC will be enrolled.

SCHEMATIC OF STUDY DESIGN



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LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
BRPC	Borderline resectable PDAC
BUN	Blood urea nitrogen
CBC	Complete blood cell (count)
CFR	United States Code of Federal Regulations
CRMS	Clinical research management system
CRQA	Clinical Research Quality & Administration
CRRC	Clinical Research Review Committee (OHSU)
CRF	Case report form
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
DFS	Disease-free survival
DLT	Dose limiting toxicity
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
eCRIS	Electronic Clinical Research Information System
EDC	Electronic data capture
FCBP	Female of childbearing potential
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
HIPPA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational new drug application
IRB	Institutional Review Board
IV	Intravenous
LAPC	Locally-advanced, unresectable PDAC
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
mOS	Median Overall Survival
MRI	Magnetic resonance imaging
N/A	Not applicable
NCI	National Cancer Institute
OHRP	Office for Human Research Protections
OHSU	Oregon Health & Science University
OS	Overall Survival
PDAC	Pancreatic adenocarcinoma
PET	Positron emission tomography
PI	Principle Investigator
PO	*Per os* (by mouth, orally)
RNI	Reportable new information
RT	Radiation therapy
SAE	Serious adverse event

TSMP	Trial Specific Monitoring Plan
ULN	Upper limit of normal
UP	Unanticipated problem

1. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 BACKGROUND

Pancreatic Ductal Adenocarcinoma (PDAC) is the most common cancer affecting the exocrine pancreas, with an estimated 56,770 new PDAC cases and 45,750 deaths expected the United States in 2019.[1] By the year 2030 PDAC is expected to be the second-leading cause of cancer-related death and highlights the need to improve treatment outcomes.[2,3] Surgical resection of the primary tumor followed by adjuvant therapy remains the current gold standard for a curative therapy; however, only 5-25% of patients have disease that is amendable to surgical intervention.[4] Even so, post-operative complications, worsening performance status, and disease progression results in only 55% of surgical patients receiving adjuvant chemotherapy.[5,6] Moreover, patients with R0 and microscopically residual PDAC disease (i.e., R1) that receive gemcitabine-based adjuvant chemotherapy have a median overall survival of 20 to 26 months, which is marginally improved to 28 months with the addition of capecitabine.[7,8] These dismal outcomes have given cause to rethink the treatment strategy of patients with borderline resectable pancreatic cancer (BRPC) or upfront resectable pancreatic cancer that emphasizes a neoadjuvant approach.

1.2 NEOADJUVANT THERAPY FOR (BORDERLINE) RESECTABLE PANCREATIC CANCER

Results from two separate phase III trials demonstrated substantial improvement in progression-free survival (PFS) and overall survival (OS) of patients with metastatic pancreatic cancer that received multi-agent chemotherapy regimens that combine 5-fluorouracil (5-FU), oxaliplatin, and irinotecan (FOLFIRINOX) or the combination of nab-paclitaxel and gemcitabine compared to standard gemcitabine.[9-11] Among those receiving FOLFIRINOX, median (m)PFS was 6.4 months compared to 3.3 months for those given gemcitabine monotherapy. Median (m)OS was also greatly improved (11.1 vs. 6.8 months).[11] Likewise, subjects receiving the combination of nab-paclitaxel plus gemcitabine (GA) had a mPFS of 5.5 and a mOS of 9.7 months, compared to 3.7 and 6.6 months, respectively, for those administered gemcitabine alone.[9] In addition to these studies, there is mounting evidence to suggest that gemcitabine-based regimens and multi-agent chemotherapy (i.e., FOLFIRINOX, FOLFOX) are promising therapies in the neoadjuvant setting.[12-17] As to which of these is the optimal neoadjuvant regimen remains unknown.

1.2.1 GEMCITABINE-BASED NEOADJUVANT REGIMENS

Sohal et al[18] reported on final results of the phase II trial, SWOG S1505 (NCT02562716), in which patients with resectable PDAC were randomized to receive either 12 weeks of perioperative FOLFIRINOX or GA. The primary outcome was 2-year OS. Among the 147 participants enrolled, 102 were evaluable for analysis, of which 55 received perioperative FOLFIRINOX and 47 received GA. The majority of participants, regardless of treatment assignment to FOLFIRINOX or GA, completed their perioperative chemotherapy (84% and 85%, respectively) and underwent surgical resection (73% and 70%, respectively). The authors observed no statistical difference in the 2-year survival rate (41.6% vs 48.8%) and median OS (22.4 vs. 23.6 months) for those treated with FOLFIRINOX or GA. Similarly, there was no statistical significance in the median disease-free survival (DFS) after resection between those given FOLFIRINOX or GA (10.9 vs. 14.2 months, p=0.87).

In the phase III PREOPANC trial, participants with resectable and borderline resectable PDAC that were randomized to receive neoadjuvant gemcitabine-based therapy for 6 cycles followed by surgery (Arm A) or perioperative treatment regimen consisting of 2 cycles of gemcitabine,

plus gemcitabine-based chemoradiation at a dose of 36 Gy/2.4 per fraction over 3 weeks, followed by surgery and 4 additional cycles of adjuvant gemcitabine (Arm B).[19] Compared to those receiving neoadjuvant gemcitabine alone, those receiving a perioperative treatment regimen had a nearly double OS benefit (Arm A, median OS = 16.8 months; Arm B, median OS = 29.9 months, p<0.001).

Jang et al[14] reported on results of a phase 2/3 trial in which 50 BRPC evaluable patients were randomized to receive a neoadjuvant gemcitabine-based chemoradiation regimen followed by surgery and adjuvant chemoradiation (n = 27), or upfront surgery followed by a chemoradiation approach (n = 23). Those in the neoadjuvant treatment group had a 2-year survival rate of 40.7% and a median survival of 21 months. In comparison, the 2-year survival rate and median survival among patients that received upfront surgery was 26.1% and 12 months, respectively. The rate of R0 resection was also significantly improved among patients in the neoadjuvant treatment group compared to those receiving upfront surgery (n = 14, 51.8% vs n = 6, 26.1%, P = 0.004). This significantly improved outcome in the neoadjuvant treatment group led to early study termination.

1.2.2 FOLFIRINOX NEOADJUVANT REGIMENS

Authors of a systematic review of 24 studies comprising 313 BRPC patients treated with FOLFIRINOX in the neoadjuvant setting reported a resection rate was 67.8% (95% confidence interval [CI], 60.1% to 74.6%), of which the R0-resection rate was 83.9% (95% CI, 76.8% to 89.1%). Treatment with neoadjuvant FOLFIRINOX ranged between 4 to 9 cycles, with mOS varying from 11.0 to 34.2 months. Further analysis across 20 studies containing patient-level data for 283 BRPC patients revealed that neoadjuvant FOLFIRINOX was associated with a mPFS of 18 months (95% CI, 14.5 to 21.5 months) and a mOS of 22.2 months (95% CI, 18.8 to 25.6 months). The authors found that the highest pooled event rates for grade III–IV adverse events (AEs) were for neutropenia (17.5 per 100 patients, 95% CI, 10.3% to 28.3%), diarrhea (11.1 per 100 patients, 95% CI, 8.6 to 14.3), and fatigue (10.8 per 100 patients, 95% CI, 8.1 to 14.2). No deaths were attributed to FOLFIRINOX across all reports includes in this study.

In a single site retrospective study of patients with unresectable locally-advanced pancreatic cancer (LPAC), Hosein et al[16] identified 18 BRPC and LAPC patients that were treated with neoadjuvant FOLFIRINOX with growth factor support. The authors found that following a median of 8 cycles per patient (range 3-17 cycles), 7 (39 %) patients were converted to resectable (per radiological criteria); 5 had R0 resections, 1 patient had an R1 resection, and 1 patient had unresectable disease. Of the 11 patients that remained unresectable, 3 patients achieved R0 resection following additional chemoradiation. Altogether, the authors reported an overall R0 resection rate of 44%. With a median follow-up of 13.4 months, the 1-year PFS rate was 83 % (95 % CI 59-96 %) and the 1-year OS rate was 100 % (95 % CI 85-100 %). The authors noted that neutropenia (22 %), neutropenic fever (17 %), thrombocytopenia (11 %), fatigue (11 %), and diarrhea (11 %) were common grade 3/4 chemotherapy-related toxicities.

In a similar single-site retrospective study, Blazer et al[17] reported on 43 patients (20 BRPC and 23 LAPC) that received modified (m) FOLFIRINOX (i.e., irinotecan at 165 mg/m2; oxaliplatin at 85 mg/m2; 5-fluorouracil (5FU) at 2,400 mg/m2 over 46 hours and pegfilgrastim on day 4 of each 2-week cycle). Patients also received gemcitabine-based chemoradiation (36 Gy in 15 fractions) if their best response was stable disease after 4 months of mFOLFIRINOX. Of the 19 evaluable patients with BRPC, treatment with neoadjuvant mFOLFIRINOX led to resection in 12 (63.2%) patients, of which 10 (53.6%) attained R0. Among those 20 evaluable patients with LAPC initially considered unresectable, resection was achieved in 9 (45%) patients, of which 8 (40%) were noted to be R0.

Murphy et al[20] reported on a single arm phase II trial in which 48 patients (27 male, 21 female) with newly diagnosed BRPC were given eight cycles of neoadjuvant FOLFIRINOX. Thirty-four (79%) of patients completed the planned 8 cycles, with 27 (56%) and 17 (35%) of patients receiving short-course or long-course chemoradiation, respectively. R0 resection was achieved in 31 of 48 patients (65%), and among those that underwent resection, the R0 resection rate was 97%. The authors observed a PFS of 14.5 months, and a 2-year PFS rate of 43%. The OS was 37.7 months, and the 2-year OS rate was 56%. Among those patients that underwent surgical resection, PFS was 48.6 months (95%CI, 14.4 to not reached), with 2-year PFS and 2-year OS rates reaching 55% and 72%, respectively.

1.2.3 IMPROVING DRUG DELIVERY IN PDAC

A desmoplastic-rich extracellular matrix is a common hallmark of pancreatic cancer. Dense deposits of extracellular collagen and hyaluronan create physical pressures that compress blood vessels thus limiting the ability for cytotoxic agents to reach cancer cells.[21] Coupled with diminished blood vessel density that is inherent to PDAC, drug delivery in these patients is largely ineffective and is a significant contributing factor to their poor survival outcomes.[22]

The renin-angiotensin system has an essential role in maintaining cardiovascular homeostasis, and uses a variety of signal effectors (e.g., angiotensin, renin, Angiotensin-converting enzyme [ACE]) to manage arterial blood pressure, and fluid and electrolyte balance. Preclinical and clinical studies also point to the renin-angiotensin system being dysregulated in numerous malignancies, including PDAC, where overexpression of several pathway components are associated with promoting cancer cell proliferation, as well as increasing invasiveness, angiogenesis, and metastases.[23,24] In fibroblasts, a dysregulated renin-angiotensin system elicits activation of the transforming growth factor β (TGF-β) pathway, which in turn increases tumor fibrosis and desmoplasia. Studies using PDAC mouse models have shown that vascular perfusion and consequently drug delivery can be improved with agents that modify the stroma by antagonizing the renin-angiotensin system.[25-28] Particularly, losartan, an angiotensin II receptor blocker (ARB), is capable of inhibiting TGF-β pathway activity and reduce the levels of collagen and hyaluronan in an orthotopic PDAC mouse models. This modification to the tumor stroma also increased the amount of 5-FU or doxil that perfused tumor vessels. Whereas, administration of 5FU, doxil, or losartan alone minimally impacted tumor growth, the combination of 5-FU or doxil with losartan resulted in significant tumor shrinkage.[27,28]

Building on the above findings, Murphy et al[29] recently reported on a phase II trial in which 49 patients with untreated locally advanced unresectable pancreatic cancer received 8-cycles of FOLFIRINOX along with losartan (up to 50 mg PO QD). A total of 39 (80%) patients completed all 8 planned cycles of FOLFIRINOX and losartan, while 10 patients received 1 to 7 cycles of the study regimen. Hypotension was observed in 3 patients, and toxicity noted in 2 patients. Of the 49 eligible patients, 45 (92%) proceeded to receive either short-course or long-course CRT. Seven (16%) patients received short-course chemoradiotherapy comprising of 25 GyE in 5 GyE per fraction proton treatment or 30 Gy in 10 fractions photon treatment, and capecitabine (825 mg/m^2 BID), given Monday through Friday for 2 weeks. Thirty-eight (84%) patients received long-course chemoradiotherapy consisting of 50.4 Gy in 28 fractions using intensity modulated radiotherapy, along with capecitabine (825 mg/m^2 BID) or 5-FU continuous infusion (225 mg/m^2/day) given Monday through Friday during the course of radiotherapy. Of the 49 evaluable patients, 34 (64%) underwent resection and 15 remained unresectable. Among the 34 patients that underwent surgery, 30 (88%) had an R0 resection, of which 5 required vessel resection with reconstruction. PFS overall and for those that underwent resection was 17.5 months (95% CI: 13.9-22.7) and 21.3 months (95% CI, 16.6-28.2), respectively. OS overall and for those that underwent surgery was 31.4 months (95% CI, 18.1-38.5) and 33.0 months (95% CI, 31.4 to not reached), respectively.

1.2.4 PREDICTIVE AND PROGNOSTIC BIOMARKERS IN PDAC

As ongoing clinical trials attempt to identify optimal neoadjuvant therapeutic regimen(s), there remains an equally unmet need to have effective biomarkers that can predict the clinical benefit of a given neoadjuvant treatment strategy. Several predictive markers including microsatellite instability, BRCA mutational status, secreted protein acidic and rich in cysteine (SPARC), human equilibrate nucleoside transporter 1 (hENT1), among others have been examined in clinical trials.[30] To date, only detection of BRCA mutation has gained approval from the Food and Drug Administration (FDA) for guiding treatment in PDAC. Specifically, PDAC patients who have inherited BRCA1 or BRCA2 genes mutations are eligible to receive olaparib, a poly-ADP-ribose polymerase (PARP) inhibitor, to treat those with metastatic pancreatic cancer that have completed at least 16 weeks of initial platinum-based chemotherapy without demonstrable disease progression.[31] This was based on results from the POLO trial, in which patients with BRCA mutation positive metastatic PDAC that received olaparib following standard chemotherapy had a mPFS of 7.4 months compared with a mPFS of 3.8 months for those who received a placebo after chemotherapy. No improvement in OS was observed among patients who received olaparib (olaparib = 18.9 months vs. placebo = 18.1 months). Moreover, the broader applicability of using this biomarker is unfortunately limited, as only 4-7% of PDAC patients have a BRCA mutation.

1.2.4.1 *CA19-9*

The most widely used biomarker for PDAC is carbohydrate antigen 19-9 (CA19-9). As a prognostic marker, higher median preoperative levels of CA19-9 are strongly associated more advanced stages of disease.[32-34] In a review of 1500 PDAC patients that underwent surgical resection, Hartwig et al.[34] observed that compared to patients with the low CA19-9 (<37 U/ml), those with high CA19-9 (≥4000 U/ml) had lower rates of resectability (80% vs 38%), as well as dramatically reduced OS (28.5 versus 14.4 months, respectively. Similarly, in the post-operative setting OS among those with low CA19-9 levels was 2.5-times greater than those with high CA19-9 levels (36.8 months vs. 14.6 months). In a separate study, Berardi et.al observed that high levels of CA 19-9 were an independent unfavorable prognostic factor as OS decreased from 18.49 months for those with CA19-9 ≤37 U/mL to 9.21 months for those with CA19-9 levels >37 U/mL.[32]

Although the above studies establish the prognostic value of CA19-9 in PDAC patients, its use as biomarker to guide multimodal therapies remains unclear. In a retrospective analysis, Wong et al[35] evaluated 75 patients with metastatic PDAC that received fixed-dose gemcitabine to determine if decreases in CA19-9 levels were surrogates for time-to-progression (TTP) and OS. Using a 50% decline in CA19-9 as the cut-off, the authors observed a significant correlation between the percent decline in CA19-9 levels and TTP (0-50% decline in CA19-9, TTP = 3.6 months; >50% decline in CA19-9, TTP = 6.2 months). The OS was 9.2 months for patients with more than a 50% decline in CA19-9, 6.8 months for those with 0% to 50% decline, and 3.5 months for those with no decline.

Tsai et al[36] conducted a retrospective analysis to assess CA19-9 levels among 131 patients with PDAC that received neoadjuvant therapy and surgery. The authors observed OS to be nearly double among patients that had normalized CA19-9 levels either pre- or post-operatively, compared to those that failed to normalize CA19-9 (preoperative = 46 vs. 24 months; postoperative 43 vs. 20 months). Compared with patients with normal preoperative CA19-9 levels, failure to normalize pre- or post-operative levels of CA19-9 was associated with a 2.77-fold and 4.03-fold increased risk of death, respectively ($P < 0.003$). Instead of relying on the magnitude of change of CA19-9 levels, these findings suggest that following neoadjuvant

therapy normalization of CA19-9 is a stronger prognostic marker of survival. Continued efforts to bolster the utility of CA19-9 include studies combining it with other biomarkers such as intercellular adhesion molecule 1, and osteoprotegerin, among others.[37]

1.3 STUDY RATIONALE

Mounting evidence suggests that pre-operative chemotherapy and/or chemoradiation confers significant survival benefit in the resectable PDAC population.[38-40] Benefits of an early treatment strategy includes the potential for improving compliance to chemotherapies, down-staging tumors, and increasing the rate of margin-negative resections.[38] Either FOLFIRINOX or gemcitabine plus nab-paclitaxel (GA) is currently used in the first-line treatment setting for advanced PDAC.[41,42] However, until more information is available, most clinical decisions involving the choice of one treatment over another will continue to be based on a factors such as patient comorbidities, performance status, and individual patient preference. Unfortunately, individual patients are often resistant or sensitive to one or both chemotherapy regimens; thus underscoring the significant clinical need to identify and validate biomarkers that can be used to optimize treatment regimens to individual cancer patients.

In single-institution retrospective cohort study, Vreeland et al[43] investigated the oncologic outcomes for patients with pancreatic cancer that underwent an early switch from FOLFIRINOX to GA in the neoadjuvant setting. Twenty-five patents were identified that underwent an early switch from FOLFIRINOX to GA citing failure to respond (16 [64%]), poor tolerance (6 [24%]), or both poor response and tolerance as reasons for the treatment change. The treatment change to GA was made after a median of 4 cycles of FOLFIRINOX, which coincided with initial re-staging. Of the 25 patients that underwent a switch to GA, 21 (84%) responded, of which 11 proceeded to undergo surgical resection. Of those underwent surgery, 9 (81.8%) had an R0 resection, and 3 (27.3%) were N0. At a median follow-up of 17.0 months, the estimated PFS was nearly double for patients that responded to GA and underwent resection (15.2 months), compared to those that responded to GA but did not undergo resection (6.5 months) or those that did not respond to GA (1.4 months). Barring the limitations of a retrospective study, these findings suggest that for patients who do not respond to FOLFIRINOX, early switching to GA in the neoadjuvant setting is warranted.

Altogether, the above findings strongly point to the need for early identification of possible resistance during the course neoadjuvant treatment of PDAC. The NeoOPTIMIZE trial described in this protocol intends to provide a flexible platform to provide dynamic switching of established neoadjuvant therapies for patients with newly diagnosed resectable/borderline resectable PDAC. Coupled with robust scientific correlative studies, the study aims to identify biomarker(s) that predict sensitivity of a given chemotherapy regimen. Specifically, the current study will use overall participant disposition, radiographic imaging, as well as changes in levels of the standard of care biomarker, CA19-9, as a means to enrich for patients that are responders to FOLFIRINOX or GA in order to optimize curative therapy. Underlying this treatment platform is the continuous administration of losartan, an ARB suggested to improve vascular perfusion and increase delivery of chemotherapy agents to the pancreas.[27,29]

1.4 EXPLORATORY STUDIES BACKGROUND

1.4.1 LOCALLY-ADVANCED UNRESECTABLE PDAC (LAPC) EXPLORATORY COHORT

The potential for systemic chemotherapy to downstage LAPC has been evaluated in several studies.[20,44-47] Notably, Murphy et al[29] reported that LAPC downstaging by total neoadjuvant therapy with FOLFIRINOX, losartan, and chemoradiotherapy achieved an R0 resection rate of 61%. However, for LAPC patients who do not respond to FOLFIRINOX, it is unclear if early

switching to GA in the neoadjuvant setting can confer similar clinical benefit. As such, the flexibility of the NeoOPTIMIZE trial platform will be used to separately examine patients with LAPC as part of an exploratory to cohort to assess if dynamic switching of established neoadjuvant therapies can improve clinical outcomes.

1.4.2 PDAC TUMOR BIOLOGY

The exploratory objectives of this study are to better understand the biological underpinnings of PDAC tumorigenesis and assess mechanisms of resistance following therapy. To this end, tumor biopsy and blood samples may be used to assess aberrant genomic, transcriptomic, proteomic, and metabolomic characteristics of PDAC, as well as dynamic interactions with the tumor and immune environment. These broad goals will be accomplished using a variety of cellular and molecular assays, and advanced imaging techniques described in Appendix C.

1.5 RISK/BENEFIT ASSESSMENT

1.5.1 KNOWN POTENTIAL RISKS

Systemic chemotherapy using FOLFIRINOX or GA has become routinely used in the neoadjuvant setting for patients with resectable and borderline-resectable PDAC. At OHSU, FOLFIRINOX or GA, followed by RT and surgery is a standard of care neoadjuvant approach to treating patients with resectable/borderline resectable PDAC. Even so, clear superiority of a neoadjuvant treatment regimen and alternating between two specific treatment modalities, has yet to be defined. A neoadjuvant treatment strategy carries the possible risk of over-treating patients with systemic chemotherapy and unnecessarily subjecting them to its associated toxicities. The associated risk of each chemotherapy regimen is well-defined, however.[1110,16] Another potential risk to utilizing a neoadjuvant treatment strategy in patients with clearly resectable disease is the possibility of missing the “window” for curative intent-resection in these patients.

1.5.2 KNOWN POTENTIAL BENEFITS

A neoadjuvant treatment strategy that provides dynamic switching between chemotherapy regimens based on CA19-9 profiling may provide access to a new treatment modality not previously available to patients with resectable PDAC. It cannot, however, be guaranteed that participants in this study will directly benefit from treatment during participation, as the clinical trial is designed to provide information about the safety and effectiveness of the investigational approach.

1.6 CORRELATIVE STUDIES BACKGROUND

The Wong research group has recently discovered that macrophages (MΦs) fuse with cancer cells to form a hybrid cancer cell that retains genotypes and phenotypes of both the parental cancer cell and MΦ.[39] The resulting tumor cell hybrid displays hallmarks of metastatic cancer cells but appears to have greater "stem cell"-like behavior. Interestingly, these cells represent a unique population of circulating tumor cells (CTCs) that are termed circulating hybrid cells (CHCs), which exist in blood at a log-fold higher than conventionally isolated CTCs in late stage disease. While enumeration of CHCs tracks with disease burden in CRC, the Wong group has also developed panels of antibodies that differentiate CHCs derived from inflamed tissue from cancer-derived CHCs. Based upon this novel biologic finding, an exploratory component of this study will evaluate and characterize CHCs as a potential measure of tumor response to therapeutic delivery and risk for recurrence or progression.

2. OBJECTIVES AND ENDPOINTS

2.1 PRIMARY OBJECTIVE AND ENDPOINT

Objective	Endpoint	Start	End
To determine the rate of margin-negative (R0) resection in participants with resectable or BRPC following treatment using NeoOPTIMIZE adaptive therapy [i.e., FOLFIRINOX alone, or switch to GA]	Proportion of resectable or BRPC participants with R0 resection	Start of neoadjuvant therapy [i.e., Day 1]	Time of Surgery

2.2 SECONDARY OBJECTIVES AND ENDPOINTS

Objective	Endpoint	Start	End
1. To determine the PFS of resectable or BRPC participants that received NeoOPTIMIZE adaptive therapy [i.e., FOLFIRINOX, or switch to GA]	1. $PFS_{NeoOPTMIZE}$ for resectable or BRPC cohort	Start of neoadjuvant therapy [i.e., Day 1]	Time of tumor progression, or death due to any cause [up to 24 months from start of study treatment]
2. To determine the PFS for the subset of resectable or BRPC participants that received NeoOPTIMIZE adaptive therapy plus preoperative radiation therapy [RT]	2. $PFS_{NeoOPTMIZE + preop\text{-}RT}$ for resectable or BRPC subset		
3. To determine the disease-free survival (DFS) of resectable or BRPC participants that received NeoOPTIMIZE adaptive therapy [i.e., FOLFIRINOX, or switch to GA]	3. $DFS_{NeoOPTMIZE}$ for resectable or BRPC cohort	Date of surgery	Time of tumor progression, or death due to any cause [up to 24 months from start of study treatment]

4. To determine the DFS for the subset of resectable or BRPC participants that received NeoOPTIMIZE adaptive therapy plus preoperative RT	4. $DFS_{NeoOPTMIZE + preop\text{-}RT}$ for resectable or BRPC subset		
5. To determine the OS of resectable or BRPC participants that received NeoOPTIMIZE adaptive therapy	5. $OS_{NeoOPTMIZE}$ for resectable or BRPC cohort	Start of neoadjuvant therapy [i.e., Day 1]	Death by any cause [up to 24 months from start of study treatment]
6. To determine the OS for the subset of resectable or BRPC participants that received NeoOPTIMIZE adaptive therapy plus preoperative RT	6. $OS_{NeoOPTMIZE + preop\text{-}RT}$ for resectable or BRPC subset		
7. To assess the surgical complications of resectable or BRPC participants that undergo surgical resection	7. Proportion of resectable or BRPC participants with peri- and post-operative complications [per the Clavien-Dindo classification system[48]]	Date of surgery	Within 30 days from date of surgery
8. To assess 30-day post-operative mortality of participants with resectable or BRPC that undergo surgical resection	8. Proportion of resectable or BRPC participants that die within 30 days of surgery	Date of surgery	30-days post surgery
9. To assess safety of NeoOPTIMIZE adaptive therapy (all participants)	9. Incidence of grade ≥3 toxicities [per CTCAE v5.0]	Start of neoadjuvant therapy [i.e. Day 1]	90 days after last dose of protocol-directed therapy

2.3 EXPLORATORY OBJECTIVES AND ENDPOINTS

Objective	Endpoint	Start	End
To monitor changes in CA19-9 levels (all participants)	CA19-9 serum levels (U/ml)	Day 0 [i.e., Baseline]	24 months after start of therapy

To determine the rate of margin-negative (R0) resection in patients with LAPC, following treatment using NeoOPTIMIZE adaptive therapy [i.e., FOLFIRINOX alone, or switch to GA]	Proportion of LAPC participants with R0 resection	Start of neoadjuvant therapy [i.e., Day 1]	Time of Surgery
To determine the PFS of LAPC participants that received NeoOPTIMIZE adaptive therapy [i.e., FOLFIRINOX, or switch to GA]	$PFS_{NeoOPTMIZE}$ for LAPC cohort	Start of neoadjuvant therapy [i.e., Day 1]	Time of tumor progression, or death due to any cause [up to 24 months from start of study treatment]
To determine the PFS for the subset of LAPC participants that received NeoOPTIMIZE adaptive therapy plus preoperative radiation therapy [RT]	$PFS_{NeoOPTMIZE + preop\text{-}RT}$ for LAPC subset		
To determine the disease-free survival (DFS) of LAPC participants that received NeoOPTIMIZE adaptive therapy [i.e., FOLFIRINOX, or switch to GA]	$DFS_{NeoOPTMIZE}$ for LAPC cohort	Date of surgery	Time of tumor progression, or death due to any cause [up to 24 months from start of study treatment]
To determine the DFS for the subset of LAPC participants that received NeoOPTIMIZE adaptive therapy plus preoperative RT	$DFS_{NeoOPTMIZE + preop\text{-}RT}$ for LAPC subset		
To determine the OS of LAPC participants that received NeoOPTIMIZE adaptive therapy	$OS_{NeoOPTMIZE}$ for LAPC cohort	Start of neoadjuvant therapy [i.e., Day 1]	Death due to any cause [up to 24 months from start of study treatment]
To determine the OS for the subset of LAPC participants that received NeoOPTIMIZE adaptive therapy plus preoperative RT	$OS_{NeoOPTMIZE + preop\text{-}RT}$ for LAPC subset		
To assess the surgical complications of LAPC participants that undergo surgical resection	Proportion of LAPC participants with peri- and post-operative complications [per the Clavien-Dindo classification system[48]]	Date of surgery	Within 30 days from date of surgery

To assess 30-day post-operative mortality of LAPC participants who undergo surgical resection	Proportion of LAPC participants who die within 30 days of surgery	Date of surgery	30-days post-surgery

3. STUDY DESIGN AND ENDPOINTS

3.1 DESCRIPTION OF THE STUDY DESIGN

Refer to Section 11*, Statistical Analysis for additional information regarding statistical methods used in this study.*

This is an open-label, non-randomized, phase II trial to assess the efficacy of an adaptive treatment strategy that allows for early switching of neoadjuvant systemic chemotherapy in patients with resectable and borderline resectable pancreatic cancer, or patients with locally-advanced, unresectable pancreatic cancer (LAPC). Participants must meet the inclusion criteria, have none of the exclusion criteria, and have provided written informed consent before the conduct of any screening tests not performed routinely in their treatment. Approximately 60 participants will be enrolled into this study. A total of 40 participants with resectable or BRPC will accrued towards the primary endpoint of estimating the proportion of individuals achieving R0 resection. A separate cohort comprised of 20 participants with LAPC will be enrolled to this study as part of an exploratory objective to similarly estimate the proportion of R0 resection that can be achieved using an early switching approach of neoadjuvant systemic chemotherapy.

Eligible participants enrolled into this study will initially receive approximately 2 months of preoperative mFOLFIRINOX (approximately 4 cycles) to be administered in accordance with institutional standards. Participants will then undergo disease restaging consistent with standard of care, including imaging (e.g., ultrasound, CT, MRI, PET-CT [per institutional standards]), CA19-9 serum levels, and performance status (i.e., Eastern Cooperative Group [ECOG]). Keeping with institutional standards, results of the disease reassessment (Re-Stage I) may be reviewed by the treating physician in conjunction with the investigator and institutional multi-disciplinary tumor board if warranted (comprised of radiologists, and medical, surgical, and radiation oncologists). A participant may be switched to GA from FOLFIRINOX prior to the imaging time point (and therefore prior to Restage 1 and the TB discussion); or a patient may be switched to GA from FOLFIRINOX after the imaging time point but without needing to be presented at a TB conference. The algorithm shown in **Table 1** should be used to aid in the decision of whether a participant will continue to receive mFOLFIRINOX or proceed with early switching to GA; however, the ultimate decision to continue or switch therapy is at the discretion of the treating physician in consultation with the multi-disciplinary tumor board. Treatment response at Re-Stage I will be defined as either radiographic or serologic:

i) a radiographic response is defined as “response” of any kind as noted in the radiology clinical report.
ii) a serological response is defined as any decrease in serum CA19-9 of at least 25% from baseline.
    a. Because serum CA19–9 levels may be influenced by elevations in bilirubin, consideration of changes in CA19-9 levels may be excluded from response assessment if, at the time of the CA19–9 assessment, the participants total bilirubin level is > 2.0 mg/dL (in the absence of stenting).

Table 1. Guidelines for mFOLFIRINOX to GA Switching
Continued mFOLFIRINOX at Re-Stage I will be based on the following considerations*:

1. If the participant is considered to have a radiographic response (per radiology clinical report), then they will proceed to receive an additional 2 months of mFOLFIRINOX (approximately 4 cycles). This treatment response may be considered independent of any possible increases in serum CA19-9 levels, or
2. In the absence of radiographic disease progression (per radiology clinical report), participants may continue to receive an additional 2 months of mFOLFIRINOX (approximately 4 cycles) if:
   a. serum CA19-9 levels have decreased ≥ 25% (from baseline), or
   b. serum CA19-9 levels remain unchanged (from baseline), or
   c. serum CA19-9 levels have increased <30% (from baseline)

Switch to GA at Re-stage I will be guided by the following considerations*:

1. Participants should be switched to receive up to 2 months of preoperative GA (approximately 2 cycles) if there is evidence of radiographic disease progression (per radiology clinical report), or
2. In the absence of radiographic disease progression (per radiology clinical report), participants may be switched to receive 2 months of preoperative GA (approximately 4 cycles) if serum CA19-9 levels have increased ≥30% (from baseline),
3. Participants responding to FOLFIRINOX but, per assessment of treating physician, are unlikely to physically tolerate additional courses, will also proceed to having treatment switched to GA.

*The decision to continue or switch therapy at Re-Stage I is at the discretion of the treating physician in consultation with the multi-disciplinary tumor board. There is no protocol deviation if the above algorithm is not explicitly followed. Reasons for alternate treatment decisions that are consistent with the general guidelines of the neoadjuvant treatment should be recorded.

After completing an additional 2 months of treatment with mFOLFIRINOX or GA participants will undergo disease restaging consistent with institutional standard of care (e.g., imaging, CA19-9 serum levels, and performance status). The results of the disease reassessment (Re-Stage II) will be reviewed by the treating physician in conjunction with the institutional multi-disciplinary tumor board. In the absence of disease progression, participants may undergo RT or planned surgery based on whether there was tumor involvement with pancreatic vasculature at baseline as follows:

1. If there was ***no vascular involvement*** *at the outset (i.e., no evidence of either arterial or venous tumor contact), then participants will proceed to planned surgical resection of their disease.*
2. If tumor involvement was present at baseline, but Re-stage II shows ***resolution*** of tumor contact with pancreatic vasculature, then participants will receive short-course RT (30 Gy/10 fractions), per institutional guidelines.
3. If tumor contact with pancreatic vasculature at baseline still ***persists*** at Re-stage II, then participants will undergo CRT (15-25 fraction) per institutional guidelines. The concurrent use of capecitabine or continuous infusion 5-fluorouracil (CIV-5-FU), per institutional guidelines, is permitted at the discretion of the treating physician.

Note that participants with any clinically-relevant condition that, in opinion of the treating physician, would contraindicate RT may proceed to undergo surgery (if eligible).

For participants that undergo RT, surgical resection should be performed 1 to 4 weeks after completing their RT regimen. For all participants that proceed to surgery, the tumor resection margins will be evaluated and scored. Following surgery, participants will considered off-protocol-directed therapy and will proceed to the follow-up portion of the trial. Throughout the

trial, any participant showing disease progression will discontinue study treatment, undergo surgery (if eligible), and proceed to longitudinal follow-up as described in Section 8.9. Subsequent management of the participant's disease will be in accordance with institutional standards.

Starting on Cycle 1 Day 1, all participants will initiate concurrent treatment with losartan. The administration of losartan will be continuous throughout the participant's chemotherapy (i.e., FOLFIRINOX or GA) and planned RT. Losartan administration will be discontinued after completion of the RT regimen.

3.2 JUSTIFICATION FOR RATIONALE OF STUDY DESIGN

There is clear evidence to show that pre-operative chemotherapy and/or chemoradiation confers significant survival benefit in the resectable PDAC population, including down-staging tumors, and increasing the rate of margin-negative resections.[38-40] Moreover, there is retrospective clinical data to show that early switching from mFOLFIRINOX to GA has clinical benefit for patients that failed initial mFOLFIRINOX treatment because of a lack of response, poor tolerability, or both.[43] However, a prospective study is needed to empirically evaluate the potential clinical benefit of early switching of neoadjuvant treatments. The NeoOPTIMIZE trial is designed to provide a flexible platform to allow for early switching of standard of care therapies by monitoring changes in both radiographic and serological response. Additionally, losartan is suggested to improve vascular perfusion and increase delivery of chemotherapy agents to the pancreas, and its continuous administration (if assigned) during the course of the study will also be assessed.[27,29] Participants currently receiving an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) will remain eligible for study participation. In such cases, losartan will not be assigned as part of the study intervention. These participants will continue to receive their ACE inhibitor or ARB per standard-of-care. The ACE inhibitor or ARB type should be recorded as a concomitant medication (including dose and frequency).

3.2.1 JUSTIFICATION FOR DOSE

The dosing regimens and schedules for both mFOLFIRINOX and GA are well established.[10,11] All systemic chemotherapy will be administered at doses consistent with institutional standard of care for the treatment of pancreatic cancer. Likewise, all RT will be administered at the discretion of treating radiation oncologist in accordance with institutional standards.

The administration of losartan in this study is based on a prior report of patients with locally advanced PDAC that received concomitant FOLFIRINOX and short-or long-course chemoradiotherapy (5 GyE x 5 protons).[29] In a previous trial, losartan was administered at a starting dose of 25 mg PO QD for the first 7 days of (i.e., Cycle 1, Day 1-7). Provided that the participants' systolic blood pressure is >100 mm Hg, then the losartan dose was increased to 50 mg PO QD for the remainder of the study in combination with FOLFIRINOX. Results from the study showed that of the 49 eligible patients, 39 (80%) received all 8 cycles of FOLFIRINOX and losartan. Of which only 3 patients experienced hypotension after losartan treatment, but all continued on the study. Based on these findings, the NeoOPTIMIZE trial will adapt a similar dosing strategy in which participants will receive losartan at a reduced dose 25 mg PO QD for the first 14 days, and if well-tolerated (i.e., maintain systolic BP > 100 mm Hg) then dose will increase to 50 mg PO QD.

3.3 END OF STUDY DEFINITION

A participant is considered to have completed the study they have completed all phases of the study including the last scheduled follow-up (i.e. up to 24 months after initiating study therapy).

4. STUDY POPULATION

4.1 PARTICIPANT INCLUSION CRITERIA

To be eligible to participate in this study, an individual must meet all of the following criteria:

1. Ability to understand and the willingness to sign a written informed consent document.
2. Age ≥ 18 years
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 (see Appendix A)
4. Cytologic or histologic proof pancreatic ductal carcinoma is required prior to study entry
   a. If a biopsy (e.g., EUS-guided FNA) is planned per standard of care, the participant may be asked to consent to the additional collection of tumor tissue for research.
5. No evidence of metastatic disease as determined by chest computed tomography (CT) scan, abdomen/pelvis Computed tomography (CT) scan (or magnetic resonance imaging [MRI] with gadolinium and/or manganese) within the 45-day window of study entry or prior to the one cycle of SOC administered before study entry, which is consistent with the standard of care.

   Note: On a case by case basis, for participants who enroll on trial after having received up to 1 month of Standard of Care chemotherapy per Investigator discretion, baseline radiographic imaging performed per institutional guidelines prior to SOC chemotherapy treatment may be used per investigator discretion to fulfill baseline radiographic imaging criteria even if performed >45 days prior to official study entry.
6. Diagnostic staging laparoscopy is not required for study eligibility.
   a. If staging laparoscopy is planned per standard of care, the participant may be asked to consent to the collection of tumor tissue for research.
7. At time of screening, per NCCN criteria, must have either:
   a. Resectable PDAC, defined as no arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]), or
   b. Node positive disease as defined by CT, MRI, or EUS imaging, or
   c. Borderline resectable PDAC, defined as:
      i. For tumors of the head or uncinate process:
         - Solid tumor contact with the SMV or portal vein of >180 degrees with contour irregularity of the vein or thrombosis of the vein, but with suitable vessel proximal and distal to the site of involvement, allowing for safe and complete resection and vein reconstruction.
         - Solid tumor contact with the inferior vena cava.
         - Solid tumor contact with the common hepatic artery without extension to the celiac axis or hepatic artery bifurcation, allowing for safe and complete resection and reconstruction.
         - Solid tumor contact with the SMA ≤180°.
         - Solid tumor contact with variable anatomy (e.g., accessory right hepatic artery,

replaced right hepatic artery, replaced common hepatic artery, and the origin of replaced or accessory artery), and the presence and degree of tumor contact should be noted if present, as it may affect surgical planning.

ii. For tumors of the body/tail:
- Solid tumor contact with the celiac axis of ≤180 degrees.
- Solid tumor contact with the celiac axis >180 degrees without involvement of the aorta and with an intact and uninvolved gastroduodenal artery, thereby permitting a modified Appleby procedure (although some members of the consensus committee preferred this criterion to be in the unresectable category).

d. Locally-advanced, unresectable disease as defined by NCCN guidelines as follows:

i. Tumors of the head with SMA ≥180°, or any celiac abutment, unreconstractable SMV or portal occlusion, or aortic invasion or encasement

ii. Tumors of the body with SMA or celiac encasement ≥180°, unreconstractable SMV or portal occlusion, or aortic invasion

iii. Tumors of the tail with SMA or celiac encasement ≥180°

iv. Irrespective of location, all tumors with evidence of nodal metastasis outside of the resection field that are considered unresectable.

8. Must be deemed fit to undergo planned curative resection as determined by institutional standards.
9. No history of previous chemotherapy for pancreatic cancer. At the discretion of the PI, patient that have received no more than 1 month of systemic chemotherapy (e.g., mFOLFIRINOX), per standard of care, for the treatment of their PDAC may be eligible to participate.
10. For participants who will get INV losartan, baseline systolic blood pressure (BP) > 100 mm Hg taken as the average of 3 blood pressure readings.
11. Must have adequate organ (as defined in **Table 2**) prior to the one month of standard of care chemotherapy allowed by the protocol or within 4 weeks of screening.

    Note: On a case by case basis, for participants who enroll on trial after having received up to 1 month of Standard of Care chemotherapy per Investigator discretion, labs prior to initiation of SOC chemotherapy treatment may be used per Investigator discretion to fulfill screening lab requirements even if performed >4 weeks prior to official study entry and/or there are more recent labs available from during chemotherapy treatment.

Table 2. Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Hemoglobin	> 9 g/dL with no blood transfusion within 28 days of starting treatment;
Absolute neutrophil count (ANC)[a]	≥1.0 x 10^9/L (> 1000 cells/mm^3);
Platelet count	≥100 x 10^9/L (>100,000 per mm^3);
Renal	
Creatinine **OR** Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 mg /dl, **OR** ≥30 mL/min/1.73m^2 for participants with creatinine levels >1.5 x institutional ULN

Hepatic	
Serum bilirubin	≤1.5 x institutional upper limit of normal (ULN); or ≤2 x ULN or 2 down-trending values for individuals who have undergone biliary stenting.
AST (SGOT) and ALT (SGPT)	≤ 2.5 x ULN, OR two consecutive down-trending values for individuals who have undergone biliary stenting.
[a] May be waived on a case-by-case basis for patient populations recognized to have normal baseline values below this level. [b] Creatinine clearance should be calculated per institutional standard. For participants with a baseline calculated creatinine clearance below normal institutional laboratory values, a measured baseline creatinine clearance should be determined. Individuals with higher values felt to be consistent with inborn errors of metabolism will be considered on a case-by-case basis.	

12. Female participants of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to initiating study therapy. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
13. Female participants of childbearing potential agree to use adequate methods of contraception (Appendix B) starting with the first dose of study therapy through 30 days after the last dose of study therapy.

    Participants of childbearing potential are those who have not been surgically sterilized or have not been free from menses for >1 year without an alternative medical cause.
14. Male participants must agree to use an adequate method of contraception (Appendix B) starting with the first dose of study therapy through 30 days after the last dose of study therapy.
15. Male patients must use a condom during treatment when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female partners of male participant should also use a highly effective form of contraception if they are of childbearing potential.
16. Participants currently receiving an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) will remain eligible for study participation. In such cases, losartan will not be assigned as part of the study intervention. These participants will continue to receive their ACE inhibitor or ARB per standard-of-care. The ACE inhibitor or ARB type should be recorded as a concomitant medication (including dose and frequency).

4.2 PARTICIPANT EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. History of previous chemotherapy, targeted/biologic therapy, or radiation therapy for the treatment of their PDAC.
2. Evidence of metastasis to distant organs (liver, peritoneum, lung, others).
3. Any other active malignancy or prior history of malignancy with less than a 90% cure rate in the judgement of the investigators.
4. Medical co-morbidities that are deemed to make risk of surgery unacceptably high as determined by institutional standards.
5. Personal history of any of the following conditions: syncope of cardiovascular etiology,

ventricular arrhythmia of pathological origin (including, but not limited to, ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest. Patients with cardiovascular conditions that are well-controlled in the clinical judgement of the treating oncologist are eligible to participate.

6. Recent major surgery (excluding laparoscopy) within 4 weeks prior to starting study treatment. Minor surgery within 2 weeks of starting study treatment. Patients must be recovered from effects of surgery.
7. Concomitant use of other anti-cancer therapy (chemotherapy, immunotherapy, hormonal therapy (Hormone replacement therapy is acceptable), not otherwise allowed in this study. Note: participation in other trials for supportive cancer care (e.g., cancer-related cachexia) interventions is permitted per PI discretion.
8. Participants with a history of hypersensitivity reactions to study agents or their excipients. In cases of losartan hypersensitivity, losartan will be omitted and patient may still be eligible to participate.
9. Participant is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 30 days after the last dose of trial therapy.
10. Psychiatric illness/social situations, or any condition that, in the opinion of the investigator, would: interfere with evaluation of study treatment or interpretation of participant safety or study results, or substantially increase risk of incurring AEs, or compromise the ability of the patient to give written informed consent.
11. Judgment by the investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements.

4.3 PARTICIPANT SCREENING AND ENROLLMENT

In order to participate in this study, signed informed consent must be obtained from the participant. The current Institutional Review Board (IRB) approved informed consent must be signed and dated by each participant prior to undergoing any study procedures or before any prohibited medications are withheld from the participant in order to participate in this study. The informed consent discussion must be documented in the participant's medical record and a copy of their signed IRB approved informed consent form must be scanned into their record.

Screening will begin once the participant has provided written informed consent to participate in the study and ends on Day 1 of the study. All screening and baseline evaluations will be performed during the screening phase (i.e., up to, but just before, start of treatment). Day 1 of the clinical trial will be when participants are started on the study intervention.

4.3.1 SCREEN FAILURES

Any participant that has signed the consent form but does not meet the study eligibility criteria, or meets study eligibility criteria but terminates their participation prior to receiving study treatment, will be considered a screen failure and not counted towards total number of planned enrollments. The reason for screen failure should be captured in the database for each participant failing to meet the eligibility criteria.

4.4 STRATEGIES FOR RECRUITMENT AND RETENTION

This study will be conducted in the United States. Participants for this study will primarily be recruited from hematology and oncology practices within OHSU and its affiliated community hematology and oncology (CHO) partners, but additional collaborative study sites may also be invited to participate in this trial. Participants may be identified and referred to this study by their primary treating physician from within OHSU/CHO, collaborating study sites, or from the outside community. Participants may be identified by a member of the participant's treatment team, the PI, research team, or medical and surgical oncology clinics part of OHSU/CHO or collaborating study sites. As a member of the treatment team, the investigator(s) will screen their participant's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Referral of potential participants to investigator(s) of this study is made as part of standard of care, with the referring physician seeking advice on the diagnosis, evaluation, and/or treatment of the participant's malignancy.

The investigator(s) may also screen the medical records of potential participants with whom the investigator does not have a treatment relationship. This will be done for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these potential individuals regarding the possibility of participating in the study. Participants may also initiate contact with the investigator through information of this study posted on the clinicaltrials.gov website.

4.4.1 ACCRUAL ESTIMATES

Up to 40 participants are planned for enrollment over approximately 36 months.

No OHSU Knight Comprehensive Cancer Center study will focus on any particular gender, racial or ethnic subset. No participant will be excluded from the study on the basis of gender, racial or ethnic origin. Male, female and minority volunteers will be recruited for this study from the general population and approximately 50% men and 50% women will be studied. Gender-nonconforming and gender-fluid individuals as members of the general population will also be recruited.

The projected gender, racial, and ethnic composition of the study will represent that of the state of Oregon.

Table 3. Population Demographics - Oregon (%)

Ethnic Category	**Sex/Gender**					
	Females		Males		Total	
	n	*%*	n	*%*	n	*%*
Hispanic or Latino	3	*6.7*	3	*6.6*	5	*13.3*
Not Hispanic or Latino	17	*43.7*	17	*43.0*	35	*86.7*
Ethnic Category: Total of all participants*	20		20		40	*100.0*
Racial Category						
American Indian or Alaskan Native	0	*0.9*	0	*0.9*	1	*1.8*
Asian	1	*2.4*	1	*2.4*	2	*4.8*
Black or African American	0	*1.1*	0	*1.1*	1	*2.2*
Native Hawaiian or other Pacific Islander	0	*0.3*	0	*0.2*	0	*0.5*

Table 3. Population Demographics - Oregon (%)

Ethnic Category	Sex/Gender					
	Females		Males		Total	
White	17	*43.6*	17	*43.0*	35	*86.6*
Two or more races	1	*2.0*	1	*1.9*	2	*3.9*
Racial Category: Total of all participants*	20	*50.4*	20	*49.6*	40	*100**
Source: Adapted from U.S. Census Bureau, 2019. *Totals may not equal 100 due to rounding.						

4.4.2 INCLUSION OF CHILDREN

This protocol does not include children as the number of children with this type of cancer is rare.

5. STUDY ENROLLMENT AND WITHDRAWAL

5.1 REGISTRATION PROCEDURES

5.1.1 OHSU REGISTRATION

Participants will be required to give written informed consent to participate in the study before any screening tests or evaluations are conducted that are not part of standard care. Registration from all consented participants must be entered into the OHSU electronic Clinical Research Management System (CRMS, e.g., eCRIS). At a minimum, registration of OHSU participants will include:

- Signed copies of the most recently IRB-approved, informed consent form and HIPAA authorization.
- Investigator validation (signature and date) on participant's inclusion and exclusion criteria

5.1.2 MULTICENTER REGISTRATION

The OHSU coordinating center study team will manage the participant registration process. Investigators, or study team designee, at participating sites will identify eligible participants and send source documents that support eligibility to OHSU for review and verification before the participating site may enroll and treat the participant.

The OHSU coordinating center team is responsible for verifying completeness of documents, entering registration information into the Knight CRMS, and assigning a study number/identifier for each individual participant. The OHSU coordinating center will send an email to the participating site to indicate whether or not a participant is eligible and will assign a participant number/identifier. Registration at participating research sites will include, at a minimum, signed copies of the most recent local IRB-approved, informed consent form and HIPAA authorization.

Each participating research site is expected to maintain a screening log of all participants who are approached for the study. The log documents an explanation for exclusion due to screen failure. This log should be submitted to the OHSU coordinating center on a regular basis. Participating sites are required to retain, in a confidential manner, sufficient information on each participant so that the participant may be contacted should the need arise

5.2 PARTICIPANT WITHDRAWAL OR DISCONTINUATION FROM THE STUDY

Participants are free to withdraw consent and discontinue participation in the study at any time and without prejudice to further treatment. If a participant no longer wants to receive investigational product, but is willing to come for follow-up appointments, the participant's request should be honored, if possible. If a participant withdraws consent, they will be specifically asked if they are withdrawing consent to:

- All further participation in the study including any further follow up (e.g., survival contact telephone calls)
- Withdrawal of consent to the use of their study generated data
- Withdrawal to the use of any biological samples

No further participant contact should be made if the participant withdraws consent for participation in the study. Information about the reason(s) for discontinuation and about any new or ongoing AEs should be collected at the time the participant withdraws consent.

A participant may also be withdrawn from investigational product/study by the Sponsor-Investigator, local IRB, or regulatory authorities. Reasons for a participant to discontinue the study intervention may include the following:

- Participant dies or is lost to follow-up
- Participant withdraws consent for any further participation
- The end of study is reached
- Pregnancy
  Note: In the event of a pregnancy, the study treatment will be permanently discontinued. Refer to Section 10.6.3 regarding reporting of pregnancy.
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive study drug for the intended duration of study treatment

5.3 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study funder, local IRB, and other regulatory agencies (as required). If the study is prematurely terminated or suspended, the Investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension. Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met

- Investigator(s) do not adhere to the study protocol, or applicable regulatory guidelines in conducting the study.
- Participant enrollment is unsatisfactory.
- Submission of knowingly false information from the study site to Sponsor or regulatory authorities.
- Upon instruction by local or other regulatory, or oversight authority.

The Study may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the Sponsor, IRB and/or FDA.

5.3.1 HANDLING PARTICIPANT DISCONTINUATION FROM STUDY

When an individual discontinues participation in the study, the reason the participant is no longer participating, the study name, IRB study number, and the date of discontinuation must be documented in the participant's medical record. The change in study status must be documented in the appropriate trial management system (e.g., eCRIS) within 24 hours from time of participant discontinuation. For all other reasons for discontinuation from the study treatment phase, the participant should return to the clinic for the end of treatment (EOT) visit according to Section 8.

5.3.1.1 *Participant replacement*

If after enrollment, any participant found to not fulfill any inclusion/exclusion criteria (per Sections 4.1 and 4.2), which could adversely affect safety or efficacy evaluation of that individual, may be replaced after discussion with the Principal Investigator. A participant who receives FOLFIRINOX for less than 80% of the days during their treatment cycle and discontinues the study during this initial stage of treatment will not be evaluable for efficacy, and will be replaced by another participant.

5.4 LOST TO FOLLOW-UP

Lost to follow-up is defined by the inability to reach the participant after a minimum of three (3) documented phone calls, faxes, emails, and/or a registered mail letter. The investigator should show "due diligence" by documenting in the source documents the steps taken to contact the participant. If it is determined that the participant has died, the site may use permissible local methods to obtain date and cause of death.

6. STUDY INTERVENTION

A list of the adverse events and potential risks associated with the study intervention administered in this study can be found in Section 10.4, Adverse Events.

6.1 FLUOROURACIL

Fluorouracil (5-fluorouracil; 5-FU; Adrucil™; Carac™; Efudex™, Efudix™) is a fluorinated pyrimidine antimetabolite that is metabolized intracellularly to its active form, fluorouridine monophosphate (FdUMP). The active form inhibits DNA synthesis by inhibiting thymidylate synthetase and the normal production of thymidine. Effects on RNA (incorporation into RNA and RNA inhibition) occur especially with bolus administration. Fluorouracil is cell cycle phase-specific (S-phase). Please refer to package insert for additional detail.

6.1.1 ACQUISITION

5-FU will be both supplied and prepared by OHSU pharmacy per manufacturer instructions.

6.1.2 FORMULATION

5-FU is provided as a sterile, non-pyrogenic injectable solution for intravenous administration (50 mg/ml vial).

6.1.3 STORAGE AND STABILITY

5-FU is stored at room temperature 15° to 30°C and protected from light. 5-FU IV admixtures (50 to 1000 mL NS or D5W) or (undiluted solutions in syringes) are stable for 72 hours at room temperature.

6.1.4 COMPATIBILITY

Broad compatibility. Please refer to package insert.

6.1.5 HANDLING

Appropriate care should be exercised in the handling and preparation of 5-FU infusion solutions.

6.1.6 PREPARATION

5-FU is supplied ready for injection.

6.1.7 ADMINISTRATION

5-FU is delivered by IV infusion per institutional standards.

6.1.8 SPECIAL CONSIDERATION FOR ADMINISTRATION

Injection should be administered only intravenously, using care to avoid extravasation.

6.2 **FOLINIC ACID**

Also known as calcium folinate, citrovorum factor, Leucovorin® (Pfizer).

Folinic acid is a reduced form of folic acid. As part of the FOLFIRINOX regimen, folinic acid is used to enhance the activity of 5-FU by binding to the enzyme thymidylate synthetase and decreasing intracellular levels of thymidylate. Please refer to package insert for additional details.

6.2.1 ACQUISITION

Folinic acid will be both supplied and prepared by OHSU pharmacy per manufacturer instructions.

6.2.2 FORMULATION

Folinic acid is supplied as lyophilized powder for injection in 50 mg, 100 mg, and 200 mg vials.

6.2.3 STORAGE AND STABILITY

Folinic acid injection, powder, lyophilized, for solution: Store vials at 20° to 25°C (68° to 77° F). Protect from light.
Folinic acid solution for injection: Store in refrigerator 2° to 8°C (36° to 46°F). Protect from light.

6.2.4 COMPATIBILITY

Can be diluted in D5W, lactated ringers, water (sterile or bacteriostatic).

6.2.5 HANDLING

No special handling required under conditions of normal product use. Follow institutional and manufacturer guidelines.

6.2.6 PREPARATION

Each 50, 100, and 200 mg vial of folinic acid for injection when reconstituted with 5, 10, and 20 mL, respectively, of sterile diluent yields a leucovorin concentration of 10 mg/ml. Folinic acid for Injection contains no preservative, inactive ingredient is Sodium Chloride, USP, added to adjust tonicity. Reconstitute the lyophilized vial products with Bacteriostatic Water for Injection, USP (benzyl alcohol preserved), or Sterile Water for Injection, USP. When reconstituted with Bacteriostatic Water for Injection, USP, the resulting solution must be used within 7 days. If the product is reconstituted with Sterile Water for Injection, USP, use immediately and discard any unused portion.

6.2.7 ADMINISTRATION

Administer immediately if reconstituted with sterile water for injection. Administer IV at maximum rate of 160 mg/min.

6.2.8 SPECIAL CONSIDERATION FOR ADMINISTRATION

Do not administer the injectable product intrathecally. Do not mix with 5-FU in the same infusion as a precipitate may form.

6.3 **IRINOTECAN**

Also known as camptothecin-11; CPT-11; U-101440E, or Camptosar® (Pfizer).

Irinotecan is a semi-synthetic derivative of camptothecin, an alkaloid extract from *Camptotheca acuminata*. Camptothecin and its analogue belong to the class of topoisomerase I inhibitors. Irinotecan is metabolized to its active form, SN38, in the presence of hepatic or gastrointestinal carboxylesterase. Irinotecan and its active metabolite, SN-38, bind to the topoisomerase DNA complex, preventing re-ligation of the single-strand breaks in the DNA molecule. The drug and its active metabolite exert their cytotoxic effects during the S-phase of cell cycle. Please see package insert for additional details.

6.3.1 ACQUISITION

Irinotecan will be both supplied and prepared by OHSU pharmacy per manufacturer instructions.

6.3.2 FORMULATION, APPEARANCE, PACKAGING AND LABELING

Irinotecan is provided as a sterile, IV solution (20 mg/ml).

6.3.3 PRODUCT STORAGE AND STABILITY

Solution is stable at room temperature and ambient fluorescent light for up to 24 hours. Solution diluted in D5W is stable for 48 hours when refrigerated and protected from light; use within 24 hours. Do not refrigerate solutions diluted with NS. Use within 4 hours if solution is kept at room temperature. Do not freeze reconstituted of diluted solutions. Use solution immediately after reconstitution if possible. Complete infusion within 12 hours (if kept at room temperature) or 24 hours (if kept refrigerated) if reconstitution and dilution are performed under strict aseptic conditions.

6.3.4 COMPATIBILITY

Compatible with D5W (D5W-Dextrose 5%).

6.3.5 HANDLING

Care should be exercised in the handling and preparation of infusion solutions prepared from irinotecan. The use of double gloves and gown is recommended. If a solution of irinotecan contacts the skin, wash the skin immediately and thoroughly with soap and water. If irinotecan contacts the mucous membranes, flush thoroughly with water.

6.3.6 PREPARATION

Irinotecan is supplied as a sterile, pale yellow, clear, aqueous solution, and can be reconstituted in 5% Dextrose Injection, USP, (preferred) or 0.9% Sodium Chloride Injection, USP, to a final concentration range of 0.12 mg/mL to 2.8 mg/mL.

6.3.7 ADMINISTRATION

Irinotecan is delivered by IV infusion per institutional standards.

6.3.8 SPECIAL CONSIDERATION FOR ADMINISTRATION

Contraindicated in patients with a known hypersensitivity to the drug or its excipients.

6.4 **OXALIPLATIN**

Oxaliplatin, also known as 1-OHP; L-OHP; oxalatoplatin; oxaliplatinum, or Eloxatin® (Sanofi Aventis).

Oxaliplatin is a platinum alkylating agent, containing platinum complexed to oxalate and diaminocyclohexane complex. Platinum complexes are formed intracellularly and inhibit

DNA synthesis through covalent binding of DNA molecules to form intra- and inter-strand DNA cross-links. Oxaliplatin-induced cytotoxicity is cell-cycle nonspecific, and considered a radiation-sensitizing agent. Please refer to package insert for additional details.

6.4.1 ACQUISITION

Oxaliplatin will be both supplied and prepared by OHSU pharmacy per manufacturer instructions.

6.4.2 FORMULATION, APPEARANCE, PACKAGING AND LABELING

Oxaliplatin is provided as a sterile, preservative-free lyophilized powder.

6.4.3 PRODUCT STORAGE AND STABILITY

After final dilution, the Oxaliplatin shelf life is 6 hours at room temperature [20° to 25°C] or up to 24 hours under refrigeration [2° to 8°C]. Unopened vials should be stored at 15-30°C, and protected from light.

6.4.4 COMPATIBILITY

Compatible with D5W (D5W-Dextrose 5%).

Oxaliplatin is incompatible in solution with alkaline medications or media (such as basic solutions of 5-fluorouracil) and must not be mixed with these or administered simultaneously through the same infusion line. The infusion line should be flushed with 5% Dextrose Injection, USP prior to administration of any concomitant medication. Oxaliplatin should always be administered before fluorouracil.

6.4.5 HANDLING

Care should be exercised in the handling and preparation of infusion solutions prepared from Oxaliplatin Injection. The use of gloves is recommended. If a solution of oxaliplatin contacts the skin, wash the skin immediately and thoroughly with soap and water. If oxaliplatin contacts the mucous membranes, flush thoroughly with water.

6.4.6 PREPARATION

Oxaliplatin reconstituted in water or 5% Dextrose.

6.4.7 ADMINISTRATION

Oxaliplatin is delivered by *IV* infusion per institutional standards.

6.4.8 SPECIAL CONSIDERATION FOR ADMINISTRATION

Increasing infusion time to 6 hours may decrease acute toxicity such as pharyngolaryngeal dysesthesia. Oxaliplatin may be administered at the same time as leucovorin.

6.5 GEMCITABINE

Gemcitabine is nucleoside analogue that replaces cytidine, during DNA replication. That process arrests tumor growth, as only one additional nucleoside can be attached to the "faulty" nucleoside, resulting in apoptosis. Please refer to package insert for additional detail.

6.5.1 ACQUISITION

Gemcitabine will be both supplied and prepared by OHSU pharmacy per manufacturer instructions.

6.5.2 FORMULATION, APPEARANCE, PACKAGING AND LABELING

Gemcitabine HCl is available as a solution for intravenous administration in several formats: 38 mg /1 ml, 100 mg /1 ml.

6.5.3 PRODUCT STORAGE AND STABILITY

Store unopened vials at a controlled room temperature between 20 and 25°C (68 and 77°F), with excursions permitted between 15 and 30 degrees C (59 and 86°F)

6.5.4 COMPATIBILITY

Gemcitabine is compatible with D5W (Dextrose 5% in water) or NS (Normal saline (Sodium chloride 0.9%)).

6.5.5 HANDLING

Use appropriate precautions for receiving, handling, administration, and disposal. Gloves (single) should be worn during receiving, unpacking, and placing in storage.

6.5.6 PREPARATION

May dilute reconstituted drug in normal saline for IV infusion, resulting in a minimum final concentration of at least 0.1 mg/mL.

6.5.7 ADMINISTRATION

Gemcitabine should be given by IV infusion according to institutional standards (approximately 30 -60 minutes).

6.6 NAB-PACLITAXEL

Paclitaxel is the active ingredient in the nanoparticle albumin-bound (nab) nab-paclitaxel. Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization, which interferes with the normal dynamic reorganization of the microtubule network required for interphase and mitotic functions. Please refer to package insert for additional detail.

6.6.1 ACQUISITION

Nab-paclitaxel will be both supplied and prepared by OHSU pharmacy per manufacturer instructions.

6.6.2 FORMULATION, APPEARANCE, PACKAGING AND LABELING

Nab-paclitaxel is presented in single-use vials containing 100 mg of paclitaxel, and are individually packaged in a carton.

6.6.3 PRODUCT STORAGE AND STABILITY

Store the vials in original cartons at 20°C to 25°C (68°F to 77°F). Retain in the original package to protect from bright light

6.6.4 COMPATIBILITY

Do not admix with other drugs.

6.6.5 HANDLING

Care should be exercised in the handling and preparation of infusion solutions prepared from nab-paclitaxel. The use of double gloves and gown is recommended. If a solution of nab-paclitaxel contacts the skin, wash the skin immediately and thoroughly with soap and water. If nab-paclitaxel contacts the mucous membranes, flush thoroughly with water.

6.6.6 PREPARATION

Nab-paclitaxel should be prepared according to manufacturer instructions. The drug agent can be reconstituted by slowly injecting 20 mL of 0.9% Sodium Chloride Injection, USP, over a minimum of 1 minute, using the sterile syringe to direct the solution flow onto the inside wall of the vial. Allow the vial to sit for a minimum of 5 minutes to ensure proper wetting of the lyophilized cake/powder. Gently swirl and/or invert the vial slowly for at least 2 minutes until complete dissolution of any cake/powder occurs. Avoid generation of foam. No further dilution is required after reconstitution. Transfer reconstituted drug to an empty, sterile IV PVC or non-PVC infusion bag.

6.6.7 ADMINISTRATION

Nab-paclitaxel should be IV infused according to institutional standards (approximately 30 – 40 minutes. When administered as part of a combination chemotherapy regimen with gemcitabine, nab-paclitaxel should be given first, followed immediately by gemcitabine.

6.6.8 SPECIAL CONSIDERATION FOR ADMINISTRATION

Do not substitute nab-paclitaxel for or with other paclitaxel formulations.

6.7 CAPECITABINE

Capecitabine is an orally available fluoropyrimidine carbamate with antineoplastic activity. The drug precursor, 5'-deoxy-5-fluorouridine (5'-DFUR), is converted to 5FU.

6.7.1 ACQUISITION

Capecitabine will be both supplied and prepared by OHSU pharmacy per manufacturer

instructions.

6.7.2 FORMULATION

Capecitabine is supplied as biconvex, oblong film-coated tablets for oral administration. Each light peach-colored tablet contains 150 mg capecitabine and each peach-colored tablet contains 500 mg capecitabine. The inactive ingredients in capecitabine include: anhydrous lactose, croscarmellose sodium, hydroxypropyl methylcellulose, microcrystalline cellulose, magnesium stearate and purified water. The peach or light peach film coating contains hydroxypropyl methylcellulose, talc, titanium dioxide, and synthetic yellow and red iron oxides.

6.7.3 STORAGE AND STABILITY

Store tightly closed at a controlled room temperature of 25°C (77°F), with excursions permitted between 15 and 30°C (59 and 86°F).

6.7.4 COMPATIBILITY

Capecitabine is a white to off-white crystalline powder with an aqueous solubility of 26 mg/mL at 20ºC.

6.7.5 HANDLING

Use appropriate precautions for receiving, handling, administration, and disposal. Gloves (single) should be worn during receiving, unpacking, and placing in storage.

6.7.6 PREPARATION

None.

6.7.7 ADMINISTRATION

Capecitabine will be self-administered by the participant and should be taken with water within approximately 30 minutes after a meal. The tablets should be swallowed whole and neither crushed or cut. Missed or vomited doses will not be made up.

6.8 LOSARTAN

Losartan is an angiotensin II receptor (type AT1) antagonist. Please refer to package insert for additional detail.

6.8.1 ACQUISITION

Losartan will be both supplied and dispensed by OHSU pharmacy.

6.8.2 FORMULATION, APPEARANCE, PACKAGING AND LABELING

Losartan potassium is a white to off-white free-flowing crystalline powder available as tablets for oral administration containing either 25 mg, 50 mg or 100 mg of losartan potassium and the following inactive ingredients: microcrystalline cellulose, lactose hydrous, pregelatinized starch, magnesium stearate, hydroxypropyl cellulose, hypromellose, and titanium dioxide.

6.8.3 PRODUCT STORAGE AND STABILITY

Tablets should be stored at 59°F to 86°F (15°C to 30°C), and kept in a tightly closed container that protects the medicine from light.

6.8.4 HANDLING

National Institute for Occupational Safety and Health (NIOSH) recommends the use of single gloves by anyone handling intact tablets or capsules or administering from a unit-dose package.

6.8.5 PREPARATION

None.

6.8.6 ADMINISTRATION

Losartan will be self-administered by the participant and may given with or without food. Missed or vomited doses will not be made up. Participants will receive instruction on how to administer the study drug from a physician, clinical research nurse, or other designated, qualified healthcare provider. At each visit the Investigators seeing the participants ask directly whether r not the participant has been taking the study agent as prescribed and if any doses have been missed. This is then documented in the participant's research note and added into the office visit note for that cycle.

6.9 ACCOUNTABILITY (ALL STUDY AGENTS)

Responsibility for drug accountability at the study site rests with the Investigator; however, the Investigator may assign some of the drug accountability duties to an appropriate pharmacist or designee. Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities or other oversight bodies

6.10 DESTRUCTION AND RETURN (ALL STUDY AGENTS)

At the end of each treatment, unused supplies of oxaliplatin should be destroyed according to institutional policies.

7. TREATMENT PLAN

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks associated with study therapies are described in Section 10.4. No other investigational agents or therapies other than those described herein may be administered with the intent to treat the participant's malignancy.

7.1 DOSAGE AND ADMINISTRATION

All systemic chemotherapy and radiation therapy will be administered in accordance with institutional standards. The mFOLFIRINOX (**Table 4**) and GA (**Table 5**) regimens described in this protocol are provided as a reference only, and the exact dosing and frequency is at the discretion of the treating oncologist. Recommended modifications to the mFOLFIRINOX and GA

dosing are described in Sections 7.2.1 and 7.2.2, respectively. The exact modifications to these treatment regimens are, however, at the discretion of the treating oncologist in accordance with intuitional standards. The actual number of mFOLFIRINOX and/or GA treatment cycles administered, along with associated dosing should be recorded for each participant.

7.1.1 MFOLFIRINOX

Starting on Cycle 1 Day 1, participants will initiate the mFOLFIRINOX as recommended in **Table 4**. Each course of mFOLFIRINOX is administered as a 14-day cycle. Participants are planned to receive approximately 2 months of mFOLFIRINOX (approximately 4 cycles) before disease restaging (Re-stage I). Absent disease progression or failure to respond to mFOLFIRINOX (as described in Section 3.1), participants will proceed to receive an additional 2 months of mFOLFIRINOX (approximately 4 cycles), for a total of approximately 4 months of mFOLFIRINOX (i.e., approximately 8 cycles), after which they will be undergo disease restaging (Re-stage II). A reduction or increase in the total number of planned mFOLFIRINOX treatment cycles is permitted at the discretion of the treating physician. The total number of mFOLFIRINOX cycles received must be recorded in the appropriate eCRF.

Table 4. Recommended mFOLFIRINOX Treatment regimen*			
Oxaliplatin	85 mg /m²	IV over ~2 hours	Day 1
Then,			
Folinic acid	400 mg /m²	IV over ~2 hours	Day 1
approximately 30 minutes after starting folinic acid, give:			
Irinotecan	150 mg /m²	IV over ~90 minutes, concurrently with folinic acid	Day 1
Then,			
Fluorouracil	2400 mg /m²	IV continuous infusion over ~46 hours	Start on Day 1
* The mFOLFIRINOX regimen is be administered *per* institutional standards. Per the treating physician, the individual dose and frequency of one (or more) drug agents comprising the mFOLFIRINOX regimen may be reduced or omitted if there is concern over toxicity or other warranting medical concerns.			

7.1.2 GEMCITABINE AND NAB-PACLITAXEL (GA)

Per criteria described in Section 3.1, if at Re-stage I, a switch in treatment from mFOLFIRINOX to GA is warranted, participants will start GA in a manner consistent with institutional standards (**Table 5**). Each GA treatment cycle is 28 days. Starting on Day 1, participants are planned to receive approximately 2 months of GA (approximately 2 cycles), after which they will be undergo disease restaging (Restage II). Treatment should only be initiated if a participant has an ANC ≥ 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L and other toxicities ≤ grade 2 or as described in Section 7.2.2. Reduced doses should not be escalated. Recommended GA dose modification guidelines to manage toxicities are described in Section 7.2.2.

In general, the switch to GA should occur after Re-stage I; however, treatment with GA may occur earlier if, per the discretion of the treating physician, a participant demonstrates toxicity or inability to tolerate mFOLFIRINOX without needing to be presented at a TB conference. In such cases, the GA treatment may be extended beyond the planned 2 months of therapy. The total number of GA cycles received must be recorded in the appropriate eCRF.

Table 5. GA Treatment regimen*			
nab-Paclitaxel	125 mg /m²	IV	Days 1, 8, 15

Do not substitute for or with other paclitaxel formulations.			
Gemcitabine	1000 mg /m²	IV	Days 1, 8, 15
* The GA regimen is be administered *per* institutional standards. Per the treating physician, the individual dose and frequency of one (or more) drug agents comprising the GA regimen may be reduced or omitted if there is concern over toxicity or other warranting medical concerns.			

7.1.3 LOSARTAN

Starting on Cycle 1, losartan may be administered at a starting dose of 25 mg PO QD for the first 2 weeks (i.e., Day 1 - 14) of initiating study intervention. Participants will have blood pressure monitored as shown in schedule of events. Participants currently receiving an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) will remain eligible for study participation. In such cases, losartan will not be assigned as part of the study intervention. These participants will continue to receive their ACE inhibitor or ARB per standard-of-care. The ACE inhibitor or ARB type should be recorded as a concomitant medication (including dose and frequency). Provided that by Cycle 2 Day 1, participants maintain a resting systolic BP >100 mm Hg, the dose of losartan will be increased to 50 mg PO QD. Losartan may be administered continuously throughout their assigned systemic chemotherapy as well as any RT that may be administered per the recommendation of the multi-disciplinary tumor board. Losartan will be discontinued at the completion of RT (or earlier if the RT is not recommended). In the event that losartan is not tolerated, the dose may be held or reduced as described in Section 7.2.5. Participants that discontinue losartan during the course of the study will remain eligible to continue on-study.

7.2 DOSING DELAYS AND MODIFICATIONS

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons (i.e., elective surgery, unrelated medical events, vacation, and holidays) not related to study therapy. Participants should be placed back on study therapy within 4 weeks of the scheduled interruption unless otherwise discussed with the investigator. The reason for interruption should be documented in the participant's study record.

7.2.1 RECOMMENDED MFOLFIRINOX TOXICITY MANAGEMENT

All toxicities observed during the course of mFOLFIRINOX treatment regimens will managed according to institutional standards. Supportive care measures are described in Section 7.7. The dosing levels described in **Table 6** are provided as general recommendations, but any changes to the FOLFIRINOX regimen is ultimately at the discretion of the treating physician. All mFOLFIRINOX dose interruptions or modification(s) should be recorded.

Table 6. Recommended mFOLFIRINOX Dose Levels			
Drug agent	**Starting Dose***	**1st Dose reduction**	**2nd Dose reduction)**
Irinotecan	150 mg/m^2	120 mg/m^2	--
Oxaliplatin	85 mg/m^2	60 mg/m^2	--
Fluorouracil infusion	2400 mg/m^2	75%	25%
*Lower starting doses for any individual drug agent are at the discretion of the treating physician in accordance with institutional standards.			

New cycles of mFOLFIRINOX should not be started until platelets ≥ 75 x 10^9/L and ANC ≥ 1.5 x 10^9/L, recovery from diarrhea (to baseline without antidiarrheal [e.g., loperamide] for at least 24 hours), and other non-hematologic toxicities have recovered to ≤ grade 2. Doses should be

adjusted based on the worst preceding toxicity.

The mFOLFIRINOX dose should not be re-escalated if reduced for toxicity, and the regimen may be discontinued if toxicity recurs after 2 dose reductions. Refer to **Table 7** for recommended management of mFOLFIRINOX toxicities.

Note: **Tables 7, 8 and 9**. Recommended Dose Modifications for mFOLFIRINOX Toxicities will be followed for the first protocol cycle, if SOC chemotherapy is administered prior to enrollment

Table 7. Recommended Dose Modifications for mFOLFIRINOX Toxicities

Toxicity	Occurrence	Irinotecan	Oxaliplatin	Flurouracil
Neutropenia				
Delayed Day 1 treatment delayed for ANC <1.5 x 10^9/L, *OR* Febrile neutropenia, *OR* grade 4 neutropenia >7 days	1st	Reduce to 1 dose level	No change	-
	2nd	Reduce to 1 dose level	Reduce to 1 dose level	-
	Discontinue treatment if no recovery after a 2-week delay, or if there is a third occurrence of ANC <1.5 x 10^9/L on day 1			
For grade 4 neutropenia >7 days **during** treatment, OR febrile neutropenia,	1st	-	Reduce to 1 dose level	Reduce to 75% of original dose
	2nd	Reduce to 1 dose level	-	Reduce to 75% of original dose
	3rd	Discontinue		
Thrombocytopenia				
Delay in Day 1 treatment for platelets < 75 x 10^9/L	1st	-	Reduce to 1 dose level	Reduce to 75% of original dose
	2nd	Reduce to 1 dose level	-	-
	Discontinue treatment if no recovery after a 2-week delay, or if there is a third occurrence of platelets < 75 x 10^9/L			
For grade 3 or 4 thrombocytopenia **during** treatment	1st	-	Reduce to 1 dose level	Reduce to 75% of original dose
	2nd	Reduce to 1 dose level	-	Reduce to 25% of original dose
	3rd	Discontinue treatment		
Diarrhea				
Do not retreat with mFOLFIRINOX until resolution of diarrhea for at least 24 hours without antidiarrheal medication				
Diarrhea ≥ grade 3 *OR* Diarrhea with fever and/or ≥ Grade 3 neutropenia	1st	Reduce to 1 dose level	-	-
	2nd	-	Reduce to 1 dose level	Reduce to 75% of original dose
	3rd	Discontinue treatment		
Mucositis				
Grade 3 or 4 mucositis or hand-foot syndrome		-	-	Reduce to 25% of original dose
Neurotoxicity				
persistent grade 3 paresthesias/dysesthesias, OR transient grade 2 symptoms lasting >7 days	-	-	-	No change

Table 7. Recommended Dose Modifications for mFOLFIRINOX Toxicities				
Toxicity	**Occurrence**	**Irinotecan**	**Oxaliplatin**	**Flurouracil**
Grade 4 or persistent grade 3 paresthesia/dysesthesia		-	Discontinue	-
Other Toxicities				
Any other toxicity ≥grade 2, except anemia and alopecia, can justify dose reduction if medically indicated.				
For other non-hematologic toxicities: if grade 2, hold treatment until ≤grade 1; if grade 3 or 4, hold treatment until ≤grade 2.				

In the event of hepatic or renal impairment, mFOLFIRINOX may be managed according to recommendations described in **Table 8** and **Table 9**, respectively.

Table 8. Recommended Dose Modifications for mFOLFIRINOX-related Hepatic Toxicities				
Transaminases	**Bilirubin†**	**Irinotecan**	**Oxaliplatin**	**5FU**
	1-1.5 X ULN or Gilbert's	Consider dose reduction	No change	No change
> 3 X ULN*	>1.5-4 X ULN	Omit	No change	No change
	> 4 X ULN	Omit	No change	Omit
* or 5 X ULN with liver metastases † If bilirubin values increases, consider investigating for reversible causes such as biliary obstruction and reevaluate after stent.				

Table 9. Recommended Dose Modifications for mFOLFIRINOX-related Renal Impairment			
Creatinine Clearance (mL/min)	**Oxaliplatin (% previous dose)**	**Fluorouracil (% previous dose)**	**Irinotecan (% previous dose)**
>60	No change	No change	No change
>30-60	Caution	No change	No change
10-30	Discontinue	Consider dose reduction	Caution
<10	Discontinue	Consider dose reduction	Caution

7.2.2 RECOMMENDED GA TOXICITY MANAGEMENT

All toxicities observed during the course of GA treatment regimens will managed according to institutional standards. Supportive care measures are described in Section 7.7. The dosing levels described in **Table 10** are provided as general recommendations, but any changes to the GA regimen is ultimately at the discretion of the treating physician. All GA dose interruptions or modification(s) should be recorded in the appropriate electronic case report form (eCRF).

Table 10. Recommended GA Dose Levels			
Drug agent	**Starting Dose**	**1st Dose reduction**	**2nd Dose reduction)**
nab-paclitaxel (mg/m²)	125	100	75
gemcitabine (mg/m²)	1000	800	600

Participants should be discontinued from study therapy if there is any need for further reductions of nab-paclitaxel or gemcitabine that is required beyond the 2 allowable dose reductions shown in **Table 10**. Refer to **Table 11** for recommended management of GA toxicities.

Table 11. Recommended Dose Modifications for GA Toxicities	
Toxicity	**Management**

Table 11. Recommended Dose Modifications for GA Toxicities		
	nab-Paclitaxel dose	**Gemcitabine dose**
Grade 3 or 4 febrile neutropenia	Hold until afebrile and ANC ≥ 1.5 x 10^9/L, then ↓1 dose level	
Grade 2 or 3 skin toxicity	Reduce 1 dose level and continue; discontinue if persists	Reduce 1 dose level and continue; discontinue if persists
Grade 3 or 4 sensory neuropathy	Hold until ≤ grade 1, then Reduce 1 dose level OR consider discontinuing for Grade 4.	No change
Grade 3 other toxicity, including mucositis, diarrhea (except nausea/vomiting/alopecia)	Hold until ≤ grade 1, then Reduce 1 dose level	Hold until ≤ grade 1, then Reduce 1 dose level
Grade 4 other toxicity or any cystoid macular edema	Discontinue	Discontinue
Pneumonitis	Hold and investigate; discontinue if confirmed.	

7.2.3 HEMATOLOGIC DOSE MODIFICATIONS DURING DAYS 8 AND 15 OF CYCLE

Omitted doses during the cycle will not be made up. Note day 15 dose modifications depend on day 8 dosing.

Table 12. Recommended Dose Modifications for GA-related Hematological Toxicities			
Day 8 counts x 10^9/L	**Day 8 nab-Paclitaxel and Gemcitabine doses**	**Day 15 counts x 10^9/L**	**Day 15 nab-Paclitaxel and Gemcitabine doses**
ANC ≥ 1 and platelets ≥ 75	Day 1 dose	**If Day 8 dose unchanged from Day 1:**	
		ANC ≥ 1 and platelets ≥ 75	DAY 1 DOSE
		ANC 0.5-0.99 or platelets 50-74	DAY 1 DOSE, add G-CSF[a]
		ANC < 0.5 or platelets < 50	OMIT
ANC 0.5- 0.99 or platelets 50-74	Reduce 1 dose level	**If Day 8 dose was REDUCED:**	
		ANC ≥ 1 and platelets ≥ 75	DAY 1 DOSE, add G-CSF[a]
		ANC 0.5-0.99 or platelets 50-74	DAY 8 DOSE, add G-CSF[a]
		ANC < 0.5 or platelets < 50	OMIT
Day 8 counts x 10^9/L	Day 8 nab-paclitaxel and gemcitabine doses	Day 15 counts x 109/L	Day 15 nab-paclitaxel and gemcitabine doses
ANC < 0.5 or platelets < 50	Omit for Day 8	**If Day 8 dose was OMITTED:**	
		ANC ≥ 1 and platelets ≥ 75	Day 1 dose, add G-CSF[a]
		ANC 0.5-0.99 or platelets 50-74	Reduce 1 DOSE LEVEL, add G-CSF[a]
		ANC < 0.5 or platelets < 50	OMIT
[a] If G-CSF is not available, suggest reducing an additional dose level. G-CSF is optional for isolated thrombocytopenia.			

7.2.4 HEPATIC IMPAIRMENT

Participants with hepatic impairment may be at increased risk of myelosuppression and should be closely monitored. Nab-paclitaxel is not recommended in patients with metastatic pancreatic cancer who have moderate to severe hepatic impairment.

Table 13. Recommended Dose Modifications for GA-related Hepatic Toxicities				
Bilirubin		**AST**	**Nab-paclitaxel* (% previous dose - suggested)**	**Gemcitabine* (% previous dose - suggested)**
>1 to ≤ 1.5 x ULN	and	≤ 10 x ULN	100%	100%
>1.5 to ≤ 5 x ULN	and	≤ 10 x ULN	Insufficient data; discontinue	Reduce to 75% of original dose
> 5 x ULN	or	> 10 x ULN	Discontinue	Discontinue
*Based on clinical judgment of treating physician – less conservative adjustments may be considered if hepatic changes are secondary to disease rather than hepatic cirrhosis or hepatitis.				

Table 14. Recommended Dose Modifications for GA-related Renal Toxicities		
Creatinine Clearance (mL/min)	**Nab-paclitaxel* (% previous dose - suggested)**	**Gemcitabine* (% previous dose –suggested)**
≥ 30 to < 90	100%	100%
< 30	Discontinue	Discontinue
*Based on clinical judgment of treating physician		

7.2.5 RECOMMENDED LOSARTAN TOXICITY MANAGEMENT

Table 15. Recommended Losartan Dose Levels	
Dose Level (DL)	**Losartan**
DL1$_{\text{Starting Dose}}$	25 mg PO QD
DL2 $_{\text{maintenance}}$	50 mg PO QD

7.2.5.1 *Cycle 1*

Participants will initiate losartan at a dose of 25 mg PO QD (**Table 14**). Participants experiencing symptoms of hypotension (e.g., lightheaded) and or have systolic BP <100 mm Hg during this first 2-weeks (based on any un/scheduled vitals assessment) will have losartan treatment interrupted for 7 (± 2) days. If systolic BP remains <100 mm Hg after 1 week (i.e., by Cycle 2 Day 1), losartan should be discontinued.

7.2.5.2 *Cycle 2+*

Participants experiencing symptoms of hypotension (e.g., lightheaded) and or have an average systolic BP <100 mm Hg while receiving losartan at 50 mg PO QD will have losartan treatment interrupted for 7 (± 4) days. Losartan dosing should be managed as follows:

1. If other causes for hypotension are identified (e.g., infection, dehydration), then losartan should be interrupted until other cause is resolved. After which, losartan may be re-initiated at 25 mg PO QD, and if after 1 week the systolic BP is sustained >100 mm Hg, then the dose may be increased to 50 mg PO QD.

2. Absent an alternative explanation for hypotension, if, after the 1 week interruption, the participant's average systolic BP is >100 mm Hg, then losartan may be re-initiated at 25 mg PO QD for 7 days, and if the systolic BP remains above 100 mm Hg after a period 7 (± 2) days, then the dose may be increased to 50 mg PO QD. At the discretion of treating physician, and in consultation with the investigator, continuous dosing of losartan may be maintained at 25 mg PO QD.

3. Absent an alternative explanation for hypotension, if, after the 1 week interruption, the participant experiences sustained lightheadedness or sustained systolic BP <100 mm Hg, then losartan should be permanently discontinued.

4. Absent an alternative explanation for hypotension, any participant that requires more than 2 consecutive dose interruptions for hypotension (average systolic BP is <100 mm Hg), then losartan will be permanently discontinued.

Note that any participant discontinuing losartan may still continue to remain on-study.

7.3 RADIATION THERAPY

After completing approximately 4 months (~8 cycles) of systemic chemotherapy (i.e., FOLFIRINOX or GA), participants will have their disease restaged (Re-stage II). The protocol defined algorithm for participants receiving RT is described in Section 3.1. For participants with tumor vessel involvement at baseline, if findings at Re-stage II shows resolution of tumor contact with pancreatic vasculature, then participants may receive short-course RT as described in Section 7.3.1.1. Participants with tumor vessel involvement that is persistent at Re-stage II evaluation may receive long-course RT with or without a radiosensitizer as described in Section 7.3.1.2.

Participants with any clinically-relevant condition that would contraindicate RT may, in opinion of the treating physician, proceed to undergo surgery (if eligible). Other deviations from the protocol defined algorithm for choice of RT is permitted at the discretion of the treating radiation oncologist or recommendation of the multi-disciplinary tumor board. The reason for not following the protocol defined RT algorithm should be recorded.

All RT treatment will be administered between Monday and Friday, and will not occur on Saturdays, Sundays or holidays. There should be no more than a 14 day interruption between the planned administration of each fraction; however, interruptions longer than this will not be considered deviations, and participants may continue to with planned RT if deemed appropriate based on the clinical judgement of the treating radiation oncologist. Interruptions to planned RT greater than 14 days should be recorded. A delayed start to RT beyond after chemotherapy beyond 4 weeks is permitted at the discretion of the principal investigator.

7.3.1 DOSE SPECIFICATIONS

All RT will be carried out in accordance with institutional standards. The choice of external radiation therapy (conformal 3-D, intensity modulated radiation therapy [IMRT], volumetric modulated arc therapy (VMAT)) is based on the discretion the treating radiation oncologist. 6MV or greater photons will be used. Beam arrangement should be consistent with institutional practice.

7.3.1.1 *Short-course RT dose specifications*

The prescribed dose is 30 Gy in 10 fractions of 3 Gy delivered 5 days a week. Treatment plans must be normalized such that 95% of the planned tumor volume (PTV) receives 30 Gy and the minimum dose (D_{min}) to the tumor is 85% of the prescribed dose (25.5 Gy). The maximum dose (D_{max}) to the PTV must not exceed 110% of this dose (33 Gy).

7.3.1.2 *Long-course RT dose specifications*

At the discretion of the treating radiation oncologist or recommendation of the multidisciplinary tumor board, RT will be administered in either 15 fractions (37.5-67.5 Gy) or 25 fractions (45-50 Gy) over 5 days a week as described in **Table 15**. In both regimens, RT may be given concurrently with capecitabine (825 mg/m^2 PO BID) or 5-FU (225 mgm^2/day given as a continuous infusion) as described in Section 7.3.4.

Table 16. Long-course RT Dose Prescriptions

	Total Prescribed Dose (Gy)	Dose/Fraction (Gy)	# of Fractions	Schedule
15 Fraction (15#) RT regimen	67.5	4.5	15	Daily
	45	3	15	Daily
	37.5	2.5	15	Daily
25 Fraction (25#) RT regimen	45	1.8	25	Daily
	50	2	25	Daily

For the 15# RT regimen, the target volumes planning goals along with minimum and maximum doses to the PTV are described in **Table 16**

Table 17. Dosimetric Objectives and constraints for 15# RT Regimen

Target Volumes	Optimal dose	Acceptable Variation
PTV_67.5*	95% of the PTV must receive 99% of prescribed dose	95% of PTV is covered to ≥ 95%
	D_{max} must be ≤ 120% of prescribed dose	D_{max} is located within internal target volume (ITV)
PTV_45*	95% of the PTV must receive 99% of prescribed dose	95% of PTV is covered to ≥ 95%
	D_{max} is located within internal target volume (ITV)	
PTV_37.5*	95% of the PTV must receive 99% of prescribed dose	95% of PTV is covered to ≥ 95%
	D_{max} is located within internal target volume (ITV)	
* D_{max} is located within internal target volume (ITV)		

For the 25# RT regimen, the target volumes planning goals along with minimum and maximum doses to the PTV are described in **Table 15**.

Table 18. Dosimetric Objectives and constraints for 25# RT Regimen

Target Volumes	Optimal dose	Acceptable Variation
PTV_45	95% of the PTV must receive 97% of prescribed dose	95% of PTV is covered to ≥ 95%
	D_{max} must be ≤ 110% of the prescribed dose (49.5 Gy)	D_{max} is located within PTV
	D_{min} must be ≥ 90% of prescribed dose (40.5 Gy)	
	D_{max} is located within internal target volume (ITV)	
PTV_50	95% of the PTV must receive 95% of	95% of PTV is covered to ≥ 80%

Table 18. Dosimetric Objectives and constraints for 25# RT Regimen		
Target Volumes	**Optimal dose**	**Acceptable Variation**
	prescribed dose	of ITV PRV bowel
	D_{max} must be ≤ 120% of the prescribed dose (60 Gy)	
	D_{max} is located within internal target volume (ITV)	

7.3.2 LOCALIZATION, SIMULATION AND PLANNING

All simulation, planning, and treatment is to be performed in accordance with institutional standards.

7.3.2.1 *Treatment Volumes*

The gross tumor volume (GTV) will be the primary tumor plus any involved regional lymph nodes identifiable on CT/MRI scan.

The clinical target volume (CTV) will be defined as the GTV plus 0.5 cm. The PTV will be the CTV plus 0.5 cm.

The normal structures to be contoured are: left and right kidneys, liver, stomach, duodenum, small intestine, spinal cord

7.3.2.2 *Treatment Planning Simulation*

Treatment planning will be based on a helical pancreatic CT per established institutional protocol and should include oral contrast to delineate the small bowel. IV contrast can be included, unless contraindicated due to allergy or renal insufficiency, in which case an MRI scan of the abdomen or CT without contrast should be performed.

Participants should be simulated (and treated) supine with arms up. Immobilization is strongly recommended and management of motion should follow institutional standards, including:

- Breath-hold (with the use of Active Breathing Control [ABC], SDX, or similar devices)
- Self-held breathing with respiratory monitoring (e.g. RPM) as a beam-hold mechanism.
- Fluoroscopic/electromagnetic gating or tracking using implanted fiducial markers

The normal structures to be contoured are: left and right kidneys, liver, stomach, duodenum, small intestine, spinal cord. If the duodenum is invaded by the tumor, the normal duodenum outside of this region should be contoured as the critical structure. Normal tissue dose-volume constraints for each of the 3 RT regimens are described in **Table 18**.

Table 19. Normal tissue dose-volume constraints		
Regimen	**Structure**	**Constraints**
Short-course 30 Gy (10 Fractions)	Kidney_L Kidney_R	90% of the volume equivalent to one kidney ≤ 15 Gy; V15 ≤ 30% for each kidney
	Liver	Mean dose ≤ 20 Gy
	Small Bowel	D_{max} to a small point of 0.03 cc must be ≤ 36 Gy.
	Stomach	D_{max} to a small point of 0.03 cc must be ≤ 36 Gy.
	Spinal cord	D_{max} to a small point of 0.03 cc must be ≤ 30 Gy.
	Duodenum	D_{max} to a small point of 0.03 cc must be ≤ 36 Gy

Table 19. Normal tissue dose-volume constraints		
Regimen	**Structure**	**Constraints**
15# RT regimen	Kidney_L Kidney_R	V18 ≤ 33% for each kidney
	Liver	Mean dose ≤ 24 Gy
	Large Bowel (+3-5 mm)	D_{max} to a small point of 0.03 cc must be ≤ 50 Gy
	Small Bowel (+3-5 mm)	D_{max} to a small point of 0.03 cc must be ≤ 40 Gy
	Stomach PRV (Stomach +3-5 mm)	V37.5 Gy ≤ 40 cc; D_{max} to a small point of 0.03 cc must be ≤ 45 Gy
	Spinal cord	D_{max} to a small point of 0.03 cc must be ≤ 30 Gy
	Duodenum PRV (Duodenal segments 1 and 2 and 3-5 mm expansion)	V37.5 Gy ≤ 40 cc; D_{max} to a small point of 0.03 cc must be ≤ 45 Gy.
	Spleen	Mean dose ≤ 6 Gy
25# RT regimen	Kidney_L Kidney_R	V20 ≤ 33% for each kidney
	Liver	Mean dose ≤ 28 Gy
	Small Bowel	D_{max} to a small point of 0.03 cc must be ≤ 58 Gy V50 Gy ≤ 10 cc V45 Gy ≤ 135 cc
	Stomach	D_{max} to a small point of 0.03 cc must be ≤ 60 Gy V50 Gy ≤ 5 cc V45 Gy ≤ 75 cc
	Spinal cord	D_{max} to a small point of 0.03 cc must be ≤ 30 Gy
	Duodenum PRV (Duodenal segments 1 and 2 and 3-5 mm expansion)	D_{max} to a small point of 0.03 cc must be ≤ 60 Gy V56 Gy ≤ 5 cc V45 Gy ≤ 30 cc

7.3.3 QUALITY ASSURANCE

Per institutional standard of care, the treating radiation oncologist will perform a RT Quality Assurance Review of the treatment plans prior to the participant starting their treatment.

7.3.4 CHEMOTHERAPY DURING RADIATION THERAPY

The 15# and 25# RT regimens are intended to be administered concurrently with 5FU or capecitabine consistent with institutional standards. The choice of 5FU or capecitabine is at the discretion of the treating oncologist.

7.3.4.1 *Capecitabine*

Oral capecitabine should be administered at a dose of 830mg/m^2 twice daily on the days that participants are receiving RT (i.e., Monday-Friday). Suggested dose modification instructions are provided in Section 7.3.4.3.

7.3.4.2 *Fluorouracil*

5FU continuous infusion (200 – 250 mg/m^2/day) is given on the first day of radiation and

continues until completion of the planned 15# or 25# RT regimen. The continuous infusion is 5 or 7 days each week, depending on institutional policy. Suggested dose modification instructions are provided in Section 7.3.4.3.

7.3.4.3 *Recommended dose modifications for fluorouracil (5FU) or capecitabine given concurrently with radiation*

Hematologic Toxicity should be managed according to institutional standards. Recommended dose modification are described in **Table 19**.

Table 20. Recommended Management of 5FU or Capecitabine Hematologic Toxicity	
Toxicity	**Recommended Dose Modification**
ANC > 1000 and platelets > 75,000	No dose modification
ANC 500-999 and/or platelets 50,000-75,000	Continue radiation. Hold 5FU or capecitabine until ANC > 1000 and platelets > 75,000, then resume at permanent 25% dose reduction.
ANC < 500 and/or platelets < 50,000	Hold 5FU or capecitabine and radiation until ANC > 1000 and platelets >75,000 then resume radiation and restart fluorouracil at permanent 25% dose reduction.
NOTE: Patients who have required two dose reductions and who experience a third episode of ANC < 1000 and platelets < 75,000 can complete radiation but should not receive additional 5FU	

Hematologic Toxicity should be managed according to institutional standards. Recommended dose modification are described in **Table 20**. Note that participants who experience an AE unrelated to study treatment (e.g., deep venous thrombosis, pulmonary embolus or non-neutropenic infection), do not require dose modifications; rather, 5FU or capecitabine treatment may be interrupted and resumed after recovery from these adverse events. Only toxicities related to treatment require dose modifications.

Table 21. Recommended Management of 5FU or Capecitabine Non-hematologic Toxicity	
Toxicity	**Recommended Dose Modification**
Grade 3 or 4 AE, 1st occurrence	Hold fluorouracil or capecitabine and radiation until toxicity has resolved to grade ≤ 2, then resume radiation and 5FU with a permanent 25% dose reduction.
Grade 3 or 4 AE, 2nd occurrence	Hold fluorouracil or capecitabine and radiation until toxicity has resolved to grade ≤ 2, then resume radiation and fluorouracil with a permanent 25% dose reduction.
Grade 3 or 4 AE, 3rd occurrence	Hold 5FU or capecitabine and radiation until toxicity has resolved to grade ≤ 2, then resume radiation and fluorouracil with a permanent 25% dose reduction.
Grade 3 or 4 AE, 4th occurrence or Grade 3 or 4 AE that persists for > 4 weeks	Discontinue 5FU or capecitabine and radiation permanently
Grade 2 Hand/Foot Syndrome	Hold capecitabine until resolves to grade ≤ 1, then resume at permanent 25% dose reduction

Table 21. Recommended Management of 5FU or Capecitabine Non-hematologic Toxicity	
Toxicity	**Recommended Dose Modification**
Grade 3 Hand/Foot Syndrome	Hold capecitabine until resolves to < grade 1, then resume at permanent 50% dose reduction
NOTE: Based on the clinical judgment of the treating physician, radiation may continue when 5FU/capecitabine is held due to toxicity associated with these drug agents	

7.4 SURGERY

Participants in this study are planned for complete resection based on the recommendation of the multidisciplinary tumor board; however, the final decision to for surgical eligibility falls to the judgment of the operating surgeon. Surgical resection of the participant's pancreatic tumor will be performed using standard surgical techniques (e.g., pancreaticoduodenectomy or pancreatectomy), and may include exploratory laparotomy to assess further assess resectability. In general:

(a) Pancreaticoduodenectomy (i.e., Whipple technique) is the recommended surgical technique for PDAC localized in the pancreas head and uncinate. This surgical technique may include skeletalization of the anterior, lateral, and posterior borders of the superior mesenteric artery (SMA) down to the level of the adventitia.
(b) Distal pancreatectomy with En-bloc splenectomy is recommended for participants with adenocarcinoma located in the left pancreas (body or tail),

In general, surgery should take place approximately 1-4 weeks following completion of RT, or last chemotherapy administration (if RT is omitted). Longer delays are permitted, however, if in the best interest of participant's safety. If surgery is delayed, repeat imaging within 28 days of the surgery date may be requested (per standard of care or as clinically indicated) to confirm no distant disease precluding surgery with curative intent.

Information regarding the surgery will be recorded including:

- Time to surgery (from completion of RT, or last chemotherapy administration [if RT is omitted]),
- Operation performed,
- Requirement for vascular resection and reconstruction,
- Completeness of the resection (R0, R1 or R2),
- Duration of the operation,
- Blood loss,
- Length of stay
- Need for re-admission within 30 days of surgery

7.5 DISCONTINUATION FROM STUDY INTERVENTION

Participants MUST discontinue investigational products (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact.
- Any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the

investigator, indicates that continued participation in the study is not in the best interest of the participant

- Termination of the study by Sponsor-Investigator
- Loss of ability to freely provide consent through imprisonment, or involuntarily incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness.
- Disease progression in the absence of clinical benefit as determined by the Investigator.
- Specific study drug discontinuation criteria described in Sections 7.2.1 and 7.2.2.
- Noncompliance of the participant with protocol-mandated procedures based on the judgment of the Sponsor-Investigator.
- Participant becomes pregnant.

If a participant has not progressed following discontinuation of study drug(s), every effort should be made to continue to obtain radiographic tumor assessments until documented progression or until the participant has started alternate cancer therapy.

All participants who discontinue study treatment should comply with protocol-specified follow-up procedures as outlined in Section 8.11. The only exception to this requirement is when a participant withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study treatment is discontinued prior to the participant's completion of the study, the reason for the discontinuation must be documented in the participant's medical records and entered on the appropriate CRF.

7.6 TREATMENT PERIOD AND MAINTENANCE

The trial intends to direct the standard of care treatment of participants to receive mFOLFIRINOX and/or GA (approximately 4 months), after which participants may continue directly to surgery, or proceed to receive short-course (approximately 1 to 3 weeks) or long-course (approximately 4 to 8 weeks) RT that is consistent with the neoadjuvant treatment of resectable/borderline-resectable pancreatic cancer. These treatment decisions may be guided by an institutionally established multi-disciplinary tumor board if warranted. The multi-disciplinary tumor board's discussion of each participant's medical case may be held in-person, or conducted electronically (e.g., teleconferencing, email). At the completion of standard of care RT, eligible participants will proceed to undergo surgical resection (if eligible). After surgical resection, all study participants will no longer be on protocol-directed therapy and will proceed to the end-of-treatment visit and follow-up (Section 8.7). Participants that discontinue study treatment and/or do not undergo surgical resection will similarly proceed to the end-of-treatment visit and follow-up (Section 8.7).

7.7 CONCOMITANT MEDICATION AND SUPPORTIVE CARE GUIDELINES

Supportive measures for optimal medical care are to be given throughout the study as indicated by the treating physician's assessment of the participant's medical need and institutional and general medical guidelines for the care of participants receiving treatment for their PDAC. Medications required to treat AEs, manage cancer symptoms or concurrent diseases, or provide

supportive care are allowed in general. These may include anti-emetics, analgesics, anti-pyretics, anti-diarrheals, pancreatic enzyme supplements, appetite stimulants, antacids, H2-blockers, proton pump inhibitors, anxiolytics, anti-depressants, sleep aids, and other common medicines as needed. The participant must be told to notify the investigational site about any new medications begun after the start of the study treatment. All medications (other than investigational products) and significant non-drug therapies (including vitamins, herbal medications, physical therapy and blood transfusions) administered during the study must be listed on the case report form (CRF). Expected supportive care apart of institutional pathways to address common reactions to treatment (e.g. atropine for acute cholinergic syndrome listed in the Beacon plan under PRN Medications"). Many of the agents associated with supportive care in this context are therefore part of the Beacon plan. These medications are reviewed before every chemotherapy administration. Source documentation is from the signed treatment Beacon plan; the conmed log is not updated again with the same information.

7.7.1 CLINICALLY SIGNIFICANT DEHYDRATION

Intravenous fluids to maintain hydration during chemotherapy should be managed per institutional standard of care.

7.7.2 GASTROINTESTINAL

Anti-emetics, anti-diarrheal agents, and acid suppressive therapies (e.g., antacids, H2 blockers, and proton pump inhibitors) may be prescribed per institutional guidelines.

Study participants may receive anti-emetic therapy as needed during their treatment which may include ondansetron, prochlorperazine, haloperidol and lorazepam. Participants may be premedicated for nausea and vomiting according to institutional standards. The use of anti-diarrheals will be administered per investigator's discretion according to institutional standards. First line agents such as loperamide and tincture of opium, and/or octreotide can be utilized.

7.7.3 ACUTE CHOLINERGIC SYNDROME

Irinotecan is associated with acute cholinergic syndrome (e.g., early diarrhea), and may be treated with atropine sulfate (e.g., 250 µg *s.c.*), unless clinically contraindicated. Atropine may be administered prior to irinotecan, if indicated.

7.7.4 INFECTION PROPHYLAXIS

The use, and choice, of prophylactic antibacterial, antifungal, and antiviral agents is recommended according to institutional guidelines. Use of anti-infective agents as prophylaxis and treatment must be documented on the CRFs.

7.7.5 TREATMENT OF FEVER AND NEUTROPENIA

Neutropenic fever (defined as ANC < 1000 cells/µL and known to be falling and temperature ≥38.0°C) will be treated per institution guidelines.

7.7.6 GROWTH FACTOR SUPPORT

Use of growth factor support to prevent neutropenia should be used as clinically indicated or at the treating physician's discretion, in accordance with institutional guidelines. The choice of

growth factor is at the investigator's discretion. Likewise, the use of an erythropoiesis-stimulating agent is at the discretion of the treating physician.

7.7.7 BLOOD PRODUCTS

All blood products are to be irradiated and leukocyte-reduced according to institution guidelines. Additionally, cytomegalovirus (CMV)-negative participants should receive CMV-negative blood products according to institution guidelines. Use of transfusion support must be documented on the case report forms.

7.7.8 DYSARTHRIA

Dysarthria (marble mouth) associated with irinotecan may be treated with diphenhydramine (50 mg IV) as needed, until symptoms resolve. Diphenhydramine premedication may be given before initiating subsequent cycles of irinotecan.

7.7.9 CONTRACEPTION

The study agents may cause embryo-fetal harm. Furthermore, it is not known if these agents have transient adverse effects on the composition of sperm. FOCBP and male participants must agree to use effective methods of contraception as described in **Appendix B**.

7.7.10 USE IN PREGNANCY

If a participant inadvertently becomes pregnant while on treatment with study agents, the participant will immediately discontinue study therapy. The site will contact the participant at least monthly and document the participant’s status until the pregnancy has been completed or terminated. The site will report the outcome of the pregnancy to Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The pregnancy will be recorded on the CRF and reported by the Investigator to the IRB. If a male participant impregnates his female partner, the pregnancy will be recorded on the CRF and reported by the Investigator to the IRB. Refer to Section 10.6.

7.7.11 USE IN NURSING WOMEN

It is unknown whether study agents or their metabolites are excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, participants who are breast-feeding are not eligible for enrollment. Participants must not breast-feed while receiving protocol therapy and for 30 days following the last dose of protocol therapy.

7.8 PRECAUTIONARY MEDICATIONS, TREATMENTS, AND PROCEDURES

No other concomitant therapies or investigational therapies are allowed during the study. Use of alternative medications (herbal or botanical for anticancer purposes) is not permitted during the study.

To prevent unwanted hepatic or gastro-intestinal toxicities while on study, participants are not permitted, unless at the discretion of the investigator, new over-the-counter drugs, as well as herbal and dietary supplements.

7.8.1 5-FU

- Initiation of 5-FU treatment regimen in patients stabilized on warfarin therapy is associated with marked elevations of prothrombin time and INR.
- Concurrent administration of 5-FU and phenytoin may result in increased serum levels of phenytoin.
- May increase the effects of warfarin and other anticoagulants.

5-FU should be administered in conjunction with medications that may affect dihydroprimidine dehydrogenase activity.

7.8.2 OXALIPLATIN

- May increase the effects of warfarin and other anticoagulants.
- Nephrotoxic agents may increase toxicity.
- Cold temperatures or cold objects can precipitate or exacerbate symptoms of acute peripheral neuropathy.
    - Concomitant use of ice for mucositis prophylaxis during infusion should be avoided as cold temperature can exacerbate acute neurological symptoms.

QT prolongation and ventricular arrhythmias (including fatal Torsade de Pointes) – avoid drugs known to prolong the QT interval (e.g., Class Ia and III anti-arrhythmics).

7.8.3 IRINOTECAN

- Irinotecan is a major substrate of cytochrome P450 CYP2B6 and CYP3A4. Risk of drug interactions causing decreased concentrations of irinotecan with CYP3A inducers. Risk of drug interactions causing increased concentrations of irinotecan with CYP3A inhibitors.
    - Avoid concomitant use of CYP3A4-inducing (e.g., rifampicin, carbamazepine, Phenobarbital, phenytoin) or inhibiting (e.g., ketoconazole, clarithromycin, indinavir, nefazodone, atazanavir, gemfibrozil) drugs.
    - Participants should also be counselled on the consumption of grapefruit, starfruit, Seville oranges juices or products.
    - Concomitant use of St John's Wort is contraindicated.

Prochlorperazine anti-emetic should be avoided on the same day as irinotecan treatment due to an increased risk of akathisia. Prochlorperazine may be taken as part of take-home regimen.

7.8.4 NAB-PACLITAXEL

No drug interaction studies have been conducted with nab-paclitaxel, but are likely to be similar to those reported for paclitaxel, which is metabolized by CYP2C8 and CYP3A4. Caution is recommended for concomitant use of nab-paclitaxel with CYP2C8 and CYP3A4 inhibitors, substrates, or inducers.

7.8.5 CAPECITABINE

Black-box warning: Participants receiving concomitant capecitabine and oral coumarin-derivative anticoagulant therapy should have their anticoagulant response (INR or prothrombin

time) monitored frequently in order to adjust the anticoagulant dose accordingly. A clinically important capecitabine-warfarin drug interaction was demonstrated in a clinical pharmacology trial. Altered coagulation parameters and/or bleeding, including death, have been reported in patients taking capecitabine concomitantly with coumarin-derivative anticoagulants such as warfarin or phenprocoumon.

7.8.6 LOSARTAN

- Co-administration of losartan with other drugs that raise serum potassium levels may result in hyperkalemia, and serum potassium in such participants should be monitored accordingly.
- Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists. Serum lithium in such participants should be monitored accordingly.
- Co-administration of NSAIDs (including selective COX-2 inhibitors) with angiotensin II receptor antagonists such as losartan may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible, and renal function should be monitored periodically in participants receiving losartan and NSAID therapy.

7.9 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

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

- No concomitant therapy or investigational anti-cancer therapy is allowed during the study. Use of alternative medications (herbal or botanical for anticancer purposes) is not permitted during the study. Concomitant participation in other trials investigating supportive care interventions (e.g., cancer-related cachexia) is permitted per PI discretion.
- Nab-paclitaxel is not recommended for use in patients with a history of interstitial lung disease, multiple allergies, progressive dyspnea or unproductive cough (cases of serious pneumonitis were reported in those treated with combination nab-paclitaxel and gemcitabine).
- Participant is pregnant or breastfeeding.
- Hypersensitivity to capecitabine or any of its components, or to 5FU
- Capecitabine is contraindicated in those with severe renal impairment (i.e., CrCl < 30 ml/min).
- Dual blockade of the Renin-Angiotensin System with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, syncope, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Do not co-administer aliskiren with losartan in participants with diabetes.

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management may be removed from the trial. Participants may receive other medications that the investigator deems to be medically necessary.

8. STUDY PROCEDURES/EVALUATIONS AND SCHEDULE

8.1 STUDY-SPECIFIC PROCEDURES

The timing and frequency for all study procedures is described in Schedule of Events (Section

8.11). A telehealth visit may be performed in lieu of an office visit, per PI discretion and institutional standards.

8.1.1 MEDICAL HISTORY

A medical history will be obtained by the investigator or qualified designee. In addition to collecting information on demographics, the medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the participant's PDAC will be recorded separately and not listed as medical history.

8.1.2 DISEASE ASSESSMENT

The investigator or qualified designee will obtain prior and current details regarding the participant's PDAC.

8.1.3 MEDICATION HISTORY

A complete medication history will be acquired concurrent with medical history.

8.1.4 PHYSICAL EXAMINATION

Physical exams must be performed by a medically qualified individual such as a licensed physician, Physician's Assistant or advanced Registered Nurse Practitioner as local law permits and per institutional standards. The physical examination to be conducted will include an evaluation of: general appearance; head, ears, eyes, nose, and throat; neck; skin; cardiovascular system; respiratory system; gastrointestinal system; lymphatic system, musculoskeletal system, and nervous system. All other physical exams after baseline will include an evaluation of any AEs, or any previously reported symptoms, or prior physical examination findings. All physical examinations will also include:

8.1.4.1 *Vital signs*

Vitals to be collected include BP, HR, temperature, and oxygen saturation by pulse oximetry. As part of screening, vitals should be obtained within 28 days prior to first dose of study agent. On day of planned treatment, vitals at baseline, should be collected prior to treatment start. Thereafter as indicated in schedule in Section 8.11.

Significant findings that were present prior to the signature of the informed consent must be included in the Medical History CRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event CRF.

8.1.4.2 *Height and weight*

Height and weight will be collected within 45 days of C1D1. Thereafter, only weight is required.

8.1.4.3 *Performance status*

Performance status will be determined as per assessment schedule in Section 8.11. Refer to Appendix A for performance criteria.

8.1.5 RADIOGRAPHIC OR OTHER IMAGING ASSESSMENTS

Radiographic imaging for disease assessment will follow standard of care and be performed according to institutional guidelines. Tumor imaging (e.g., computed tomography [CT], magnetic resonance imaging [MRI], or other imaging modalities such as fluorodeoxyglucose (^{18}F)-positron emission tomography [PET], ultrasound) should be performed as clinically indicated. Results of imaging performed while participants are enrolled in this study should be recorded in CRF.

Initial tumor imaging must be performed within a 28-day window during screening. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality, meet the requirements specified in the imaging manual, and performed within a 28-day window during screening. Initial tumor imaging may be performed up to 45 days prior to C1D1, at the discretion of the Principle Investigator. After completing on-study therapy, results of subsequent imaging assessments may be captured as part of study follow-up.

8.1.6 ELECTROCARDIOGRAM (ECG)

A standard 12-lead ECG should be performed only as clinically indicated.

8.1.7 ADVERSE EVENT EVALUATION

Toxicities and adverse experiences will be assessed at each visit using the NCI CTCAE 5.0. Safety will be monitored by assessing physical examination, vital signs, body height and weight, performance status, hematology, chemistry, coagulation, urinalysis, thyroid function, and pregnancy, as well as collecting of AEs at every visit.

Adverse events will be monitored from the time the participant signs the study Consent Form. Participants will be instructed to report all AEs during the study and will be assessed for the occurrence of AEs throughout the study, through to end of treatment visit. All AEs (serious and non-serious) must be recorded on the source documents and CRFs regardless of the assumption of a causal relationship with the study drug.

Abnormal laboratory values will only be recorded as an AE if determined to be clinically significant by the investigator.

For details on AE collection and reporting, refer to Section 10.

8.1.8 ASSESSMENT OF STUDY AGENT ADHERENCE

Participants that self-administer oral study agents (e.g., losartan) will check in with the investigator at each visit. Participants will receive instruction on how to administer study drug from a physician, clinical research nurse, or other designated, qualified healthcare provider.

8.2 LABORATORY PROCEDURES AND EVALUATIONS

Refer to Section 8.11 for a schedule of all laboratory test and procedures.

8.2.1 HEMATOLOGY

Hematologic profiling will be collected per institutional standards, and should include evaluation of hematocrit, hemoglobin, platelets, white blood cells with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils), and absolute lymphocyte count.

8.2.2 BIOCHEMISTRY

Blood chemistry will be collected per institutional standards and should include the following:

- Albumin
- Alkaline phosphatase[A]
- Alanine aminotransferase[A]
- Aspartate aminotransferase[A]
- Calcium
- Chloride
- Creatinine
- Glucose
- Total bilirubin[A]
- Total protein
- Total CO2
- Potassium
- Sodium
- Urea or blood urea nitrogen, depending on local practice

[A] Tests for ALT, AST, alkaline phosphatase, and total bilirubin must be conducted and assessed concurrently. If total bilirubin is ≥2 × upper limit of normal (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin.

8.2.3 URINALYSIS

Urinalysis to be performed only as clinically indicated. If performed results should be collected in CRF.

8.2.4 COAGULATION PANEL

Coagulation assays to be performed only as clinically indicated (e.g., INR, prothrombin time, and PTT). If performed results should be collected in CRF.

8.2.5 PREGNANCY TEST

A serum (β-HCG) or urine pregnancy test is required during screening for all persons of childbearing potential. The pregnancy test is required within 72 hours of initiating protocol therapy. If the urine pregnancy test is positive, a serum pregnancy test must be performed per institutional standards.

8.2.6 TUMOR MARKERS

CA 19-9 and/or CEA will be collected per institutional standards and/or per investigator discretion

8.3 EXPLORATORY STUDIES

8.3.1 BIOLOGICAL SAMPLE COLLECTION

Tissue is collected for this study will be used to support one or more of the exploratory studies described in Appendix C. In general, biopsy samples may (depending on tissue availability) be used for further profiling of cellular and molecular tumor characteristics based on emerging data.

8.3.1.1 *Pretreatment Biospecimen Collection*

Participants will be consented to have pretreatment tissue biopsy provided that the biopsy (e.g., EUS-guided FNA) is planned per standard of care, for cytologic or histologic proof pancreatic ductal carcinoma during screening. Similarly, if during screening a staging laparoscopy is planned per standard of care, then participants will be asked to consent to the collection of tumor tissue for research. Six core biopsies are recommended, but additional cores may be collected if deemed feasible by the provider. If during screening, no standard-of-care tissue biopsy is planned, then no additional research-only procedure will be mandated and participants will remain eligible for trial participation. In such cases, participants will be consented for the requisition of archival tissue blocks (if possible) or a recommended minimum of twenty (20) FFPE unstained slides, and one (1) Hematoxylin and Eosin (H&E) slide.

Cores preserved in 10% neutral-buffered formalin will be delivered to the Oregon Pancreatic Tumor Registry (OPTR). Additional cores for optional exploratory research analytics may be preserved in additional formats and distributed directly to research laboratories at OHSU (Appendix C). At a minimum, samples should be labeled with the following information:

- Participant Study ID
- Date of collection

Shipping of Specimens

Freshly isolated samples should be transported in a closed container from clinic to OHSU research laboratories for processing as described above.

Wong Laboratory
Knight Cancer Research Building, Room 3000
2720 S. Moody Avenue
Portland, OR 97201
Tel: 503 494-8953 | Email: wongme@ohsu.edu

Tumor tissue is to be shipped/couriered for processing to the following address:

OPTR Study Coordinator
OHSU, CLSB 4N079
2730 SW Moody Ave
Portland, OR 97201-5042
Phone: (503) 494-8988 | Fax: (503) 346-8281 | optr@ohsu.edu

8.3.1.2 *Excess tumor collection at time of planned surgery (only for participants with resectable or borderline resectable disease undergoing planned surgery)*

Participants with disease that is amenable to surgical intervention will undergo planned surgical resection of PDAC lesions. As part of consenting to study participation, either core surgical biopsies or tumor pieces will be collected from the pancreas. Core biopsies will be separated into two tubes, with half of the sample processed fresh for preservation of viable cells, and the other half fixed in FFPE. Tumor pieces will also be split, with a portion frozen or preserved in FFPE, and a portion used for generating primary cultures. Specific core preservation formats may change to support exploratory research analytics (Appendix C). Samples should be labeled and couriered as described above.

8.3.2 BLOOD COLLECTION FOR RESEARCH

Peripheral blood for research purposes will be drawn from participants scheduled to have venipuncture for routine clinical purposes. The timing for blood collections is described in Section 8.11, Schedule of Events; however, at the discretion of the investigator, the frequency blood collections may be reduced or omitted from each study participant. If after blood collection, the treatment is held, per institutional standards and as long as treatment is resumed within two weeks, a subsequent research blood draw will not be collected at the treatment's reattempt. Research blood will be processed for evaluation in the biological experiments described in Appendix C or may be stored as part of a bio-repository for future related studies.

i) Collection and Handling of Specimens

Up to 40 mL of blood will be collected into the appropriate blood collection tubes as directed by the PI or the study team.

ii) Shipping of Specimen

All whole blood collection tubes must be labeled with the minimum following information:
- Participant Study ID
- Date of collection

Specific handling and shipping instructions will be provided by the PI or study team based on method of sample collection. All samples must be shipped on day of collection to:

OPTR Study Coordinator
OHSU, CLSB 4N079
2730 SW Moody Ave
Portland, OR 97201-5042
Phone: (503) 494-8988 │Fax: (503) 346-8281│optr@ohsu.edu

8.4 SCREENING ASSESSMENTS

A screening (consultation) visit may occur as part of standard of care. If a participant is eligible for the study after review of key inclusion/exclusion criteria, additional screening visits will be scheduled while staff members are requesting insurance authorization to participate in a clinical trial. The following will be reviewed at screening visit:

i) Clinical history and physical exam (per standard of care), and
ii) informed consent obtained and documented

Toxicities which occur prior to the start of treatment will not be subject to analysis. Consent must be obtained before initiation of any clinical screening procedure that is performed solely for the purpose of determining eligibility for this research study. Evaluations performed as part of routine care before informed consent can be utilized as screening evaluations if done within the defined time period.

8.5 BASELINE ASSESSMENTS

Baseline assessments should occur prior to start of window treatment with study therapy on Day

1. Participants will be evaluated for medical history, physical examination, vital signs, performance status, concomitant medications, blood sampling for hematology and laboratory tests, and pretreatment biopsy, as well as any other specific assessments listed in Section 8.11, Schedule of Events (**Table 21**).

8.6 ASSESSMENTS DURING TREATMENT

Specific on-study assessments are listed in the Section 8.11, Schedule of Events (**Table 21**, **Table 22**). Under certain circumstances (e.g., clinic holiday, inclement weather) scheduled visits may be delayed by additional 7 days from the intended study visit.

8.7 EARLY TERMINATION VISIT

Participants that discontinue study treatment early, undergo surgery, and do not withdraw from the study, should be evaluated for surgical margin status (e.g., R0, R1). The EOT visit should coincide with any planned post-surgical visit per institutional standards. EOT assessments are listed in, Section 8.11, Schedule of Events (**Table 24**). If a participant does not reach EOT or terminates participation early due to transition to hospice or death, an EOT visit will not be conducted.

8.8 END OF TREATMENT VISIT

A single end of treatment visit should be conducted as clinically indicated and following institutional standards. Preferably, the end of treatment visit should occur prior to the initiation of any other off-protocol interventional therapy. This planned end of treatment visit should coincide with the standard of care post-surgical follow-up visit or any follow-up visit with a surgery, medical and/or radiation oncologist that is consistent with institutional standards. The assessments for this end of treatment visit are listed in Section 8.11, Schedule of Events (**Table 24**).

8.9 FOLLOW-UP

After the end of treatment visit, participants will be followed every 3 months (± 1 month) for the first 6 months, then every 6 months (± 1 month) for up to 2 years from the start of study treatment per institutional standards. Any variation in follow up visits will not be considered deviations, as long as institutional standards are maintained. This information may be updated periodically via electronic health records, or follow-up contact may be made with the participant (e.g., by phone) or their treating physician to that end. Participants removed from protocol therapy for unacceptable AE(s) will be followed until resolution or stabilization of the AE. The assessments for this follow-up visit are listed in Section 8.11, Schedule of Events (**Table 24**).

Follow up assessments, including physical exams, hematology, biochemistry, and research blood samples will be performed and/or collected only when convenient and feasible for the patient, per institutional standards. Any physical exam, lab work, and/or research blood not performed/collected, will not be considered a deviation, as long as institutional standards are maintained.

8.10 UNSCHEDULED VISITS

Unscheduled study visits may occur at any time if medically warranted. Any assessments performed (e.g., laboratory or clinical assessments) should be recorded in (e)CRF.

8.11 SCHEDULE OF EVENTS

Table 22. Study Assessments for mFOLFIRINOX Regimen

Visit Days (± 7 Days [D])*	Screening**	mFOLFIRINOX Treatment Cycles[Δ]									Re-stage II
		Cycle 1[§]	Cycle 2	Cycle 3	Cycle 4	Re-stage I	Cycle 5	Cycle 6	Cycle 7	Cycle 8	
	D -45 to D1	D1	D1	D1	D1		D1	D1	D1	D1	
mFOLFIRINOX		X	X	X	X		X	X	X	X	
Losartan		Continuous Daily Administration (refer to Section 7.1.3)									
Informed consent	X										
Inclusion/exclusion criteria	X										
Prior/concomitant medications[A]	X	X	X	X	X		X	X	X	X	
Physical Examination[B]	X	X	X	X	X		X	X	X	X	
Hematology[C]	X	X	X	X	X		X	X	X	X	
Biochemistry[D]	X	X	X	X	X		X	X	X	X	
CA19-9 [E]	X		X		X			X		X	
CEA [E]	X		X		X			X		X	
ECG	***only as clinically indicated***										
Urinalysis	***only as clinically indicated***										
Pregnancy test [F]	X										
AE assessment [G]	***continually assessed***										
Radiographic imaging [H]	X					X					X
Research Tumor tissues[I]	X										
Research blood samples [J]		X	X	X	X		X	X	X	X	

* Study visits may be performed ±7 days of the planned
** Screening may occur up to 45 days from initiating study treatment.
§ Baseline visit should be conduct on Cycle 1 Day 1 prior to initiating study therapy, but may occur up to 7 days earlier.
Δ FOLFIRINOX treatment cycles are 14 days. The FOLFIRINOX treatment cycle is the default schedule. If systemic chemotherapy is switched from FOLFIRINOX to GA, then the study schedule and subsequent visits are to be adjusted according to the GA treatment schedule in **Table 22**.
A For concomitant medications – enter new medications at baseline and those started during the trial through to the EOT visit.
B All physical exams will include assessing weight, vital signs (including blood pressure), and ECOG performance status. Height will be obtained at screening only.
C Hematology profiling per institutional standards, including: hematocrit, hemoglobin, platelets, white blood cells with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils), and absolute lymphocyte count. For Baseline/Screening, blood should be collected and profiled within 28 days of treatment start.

[D] Biochemistry tests should be collected per institutional standards, including: comprehensive metabolic panel (Na, K, Cl, CO2, BUN, Creatinine, Ca, Glucose, Albumin, Alkaline Phosphatase, total Bilirubin, AST, total Protein, ALT), amylase, and lactate dehydrogenase. Refer to Section 8.2.2. For Baseline/Screening, blood chemistry should be collected and profiled within 28 days of treatment start.

[E] If screening CA19-9 or CEA falls outside of screening window, it is allowed per investigator discretion as long as a C1D1 CA19-9 is drawn.

[F] For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated, if required, per institutional guidelines.

[G] AEs and laboratory safety measurements will be graded per NCI CTCAE version 5.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness. Record grade 3 and 4 AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs occurring up until 30 days after the last dose of trial treatment, or until resolution/stabilization of treatment-related toxicities.

[H] Radiographic imaging will be performed as clinically indicated and follow institutional standards. Initial tumor imaging at screening will be performed within the 28-day window during screening. Initial tumor imaging may be performed up to 45 days prior to C1D1, at the discretion of the Principle Investigator. If surgery is delayed, repeat imaging within 28 days of the surgery date may be requested (per standard of care or as clinically indicated) to confirm no distant disease precluding surgery with curative intent. Additional imaging may be performed if clinically indicated.

[I] Tissue biopsies are not mandatory, and should be optionally performed if a biopsy is performed per standard of care. Likewise, if staging laparoscopy is clinically indicated per standard of care, pre-treatment tissue may be collected at this time. Excess tumor tissue may be collected at the time of surgery.

[J] Research blood draws should be collected at same time as standard of care evaluations, including any pre- and/or post-surgical blood draws required per standard of care. Per discretion of the investigator, the frequency blood collections may be reduced or omitted from each study participant. If after blood collection, the treatment is held, per institutional standards and as long as treatment is resumed within two weeks, a subsequent research blood draw will not be collected at the treatment's reattempt

Table 23. Study Assessment for GA Regimen

Visit Days (± 7 Days [D])*	GA Treatment Cycles[Δ]						Re-stage II
	Cycle 1			Cycle 2			
	D1	D8	D15	D1	D8	D15	
Gemcitabine	X	X	X	X	X	X	
Nab-Paclitaxel	X	X	X	X	X	X	
Losartan	Continuous Daily Administration (refer to Section 7.1.3)						
Prior/concomitant medications[A]	X			X			
Physical Examination[B]	X			X			
Hematology[C]	X	X	X	X	X	X	
Biochemistry[D]	X	X	X	X	X	X	
CA19-9 [E]	X			X			
CEA [E]	X			X			
ECG	***only as clinically indicated***						
Urinalysis	***only as clinically indicated***						
AE assessment [F]	***continually assessed***						

Radiographic imaging [G]							X
Research blood samples[H]	X		X	X		X	

[Δ] GA treatment cycles are 28 days.
[A] For concomitant medications – enter new medications at baseline and those started during the trial through to the EOT visit.
[B] All physical exams will include assessing weight, vital signs (including blood pressure), and ECOG performance status. Height will be obtained within 45 days of C1D1 .
[C] Hematology profiling per institutional standards, including: hematocrit, hemoglobin, platelets, white blood cells with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils), and absolute lymphocyte count. Should be collected pre-dose on Day 1; however prior results within 14 days of initiating on-study therapy are acceptable. Pre- and/or post-surgical hematology after completing window treatment may occur as clinically indicated.
[D] Biochemistry tests should be collected per institutional standards, including: comprehensive metabolic panel (Na, K, Cl, CO2, BUN, Creatinine, Ca, Glucose, Albumin, Alkaline Phosphatase, total Bilirubin, AST, total Protein, ALT).. Refer to Section 8.2.2
[E] If screening CA19-9 or CEA falls outside of screening window, it is allowed per investigator discretion as long as a C1D1 CA19-9 is drawn.
[F] AEs and laboratory safety measurements will be graded per NCI CTCAE version 5.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness. Record grade 3 and 4 AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs occurring up until 30 days after the last dose of trial treatment, or until resolution/stabilization of treatment-related toxicities.
[G] Radiographic imaging will be performed as clinically indicated and follow institutional standards. Initial tumor imaging at screening will be performed within 45 days prior to the first dose of trial treatment. If surgery is delayed, repeat imaging within 28 days of the surgery date may be requested (per standard of care or as clinically indicated) to confirm no distant disease precluding surgery with curative intent. Additional imaging may be performed if clinically indicated.
[H] Research blood draws should be collected at same time as standard of care evaluations, including any pre- and/or post-surgical blood draws required per standard of care. Per discretion of the investigator, the frequency blood collections may be reduced or omitted from each study participant. If after blood collection, the treatment is held, per institutional standards and as long as treatment is resumed within two weeks, a subsequent research blood draw will not be collected at the treatment's reattempt

Table 24. Study Assessments for RT Regimens

	Week 1					**Week 2**					**Week 3**					**Week 4**					**Week 5**				
RT Daily Fractions[†]	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Short-course RT	X	X	X	X	X	X	X	X	X	X															
15 Fraction RT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X										
25 Fraction RT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Losartan	Continuous Daily Administration (refer to Section 7.1.3)																								
Prior/concomitant medications[A]	X weekly					X weekly					X weekly					X weekly					X weekly				
Physical Examination[B]	X weekly					X weekly					X weekly					X weekly					X weekly				
Hematology[C]	X weekly					X weekly					X weekly					X weekly					X weekly				
Biochemistry[D]	X weekly					X weekly					X weekly					X weekly					X weekly				
CA19-9 & CEA	***only as clinically indicated***																								
AE assessment[E]	X weekly					X weekly					X weekly					X weekly					X weekly				
Research blood samples[F]	Every 2 weeks																								

[†] The specific considerations for a participant to receive RT, either short-course or long-course (i.e., 15 of 25 fractions), is described in Section 3.1.
[A] For concomitant medications – enter new medications at baseline and those started during the trial through to the EOT visit.
[B] All physical exams will include assessing weight, vital signs, and ECOG performance status. Height should be obtained at screening only. Physical examination may be omitted during short-course RT, per institutional standards
[C] Hematology profiling per institutional standards, including: hematocrit, hemoglobin, platelets, white blood cells with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils), and absolute lymphocyte count. Should be collected pre-dose on Day 1; however prior results within 14 days of initiating on-study therapy are acceptable. Pre- and/or post-surgical hematology after completing window treatment may occur as clinically indicated. Hematology labs may be omitted during short-course RT, per institutional standards.
[D] Biochemistry tests should be collected per institutional standards, including: comprehensive metabolic panel (Na, K, Cl, CO2, BUN, Creatinine, Ca, Glucose, Albumin, Alkaline Phosphatase, total Bilirubin, AST, total Protein, ALT). Refer to Section 8.2.2. Biochemistry labs may be omitted during short-course RT, per institutional standards
[E] AEs and laboratory safety measurements will be graded per NCI CTCAE version 5.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness. Record grade 3 and 4 AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs occurring up until 30 days after the last dose of trial treatment, or until resolution/stabilization of treatment-related toxicities.
[F] Research blood draws should be collected at same time as standard of care evaluations, including any pre- and/or post-surgical blood draws required per standard of care. Per discretion of the investigator, the frequency blood collections may be reduced or omitted from each study participant.

Table 25. Surgery, End of treatment (EOT), and Follow-up Assessments

	Surgery[§]	End of treatment (EOT)[‡]	Follow-up[†]
Margin Status	X		
Physical Examination[A]		X	X
Hematology[B]		X	X
Biochemistry[C]		X	X
AE assessment[D]		X	
Clavien-Dindo Classification		X	
Research Tumor tissue[E]	X		
Research blood samples[F]	X	X	X
Radiographic imaging[G]	X	X	X[H]

[§] Surgery should be performed at least 1-4 weeks following the last dose of study treatment. In the unlikely event that a participant does not undergo surgery, these individuals may consent to an optional post-treatment biopsy (i.e., 1-4 weeks following the last dose of study treatment).
[‡] An EOT should be conducted as clinically indicated and following institutional standards. Assessments listed under EOT do not need to occur on the same date and can instead be performed as clinically indicated and following institutional standards.
[†] Participants will be followed according to planned standard of care visits every 3 months (± 1 month) for the first 6 months. Thereafter, participants will be followed once every 6 months (±1 month) for up to 2 years from start of treatment.
[A] All physical exams will include assessing weight, vital signs, and ECOG performance status. Height should be obtained at screening only. Physical exams, will be performed only when convenient and feasible for the patient, per institutional standards.
[B] Hematology profiling per institutional standards, including: hematocrit, hemoglobin, platelets, white blood cells with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils), and absolute lymphocyte count. Hematology collected only when convenient and feasible for the patient, per institutional standards.
[C] Serum chemistry tests should be collected per institutional standards, including: comprehensive metabolic panel (Na, K, Cl, CO2, BUN, Creatinine, Ca, Glucose, Albumin, Alkaline Phosphatase, total Bilirubin, AST, total Protein, ALT). Refer to Section 8.2.2. Biochemistry collected only when convenient and

Table 25. Surgery, End of treatment (EOT), and Follow-up Assessments

	Surgery[§]	End of treatment (EOT)[‡]	Follow-up[†]
Margin Status	X		

feasible for the patient, per institutional standards.

[D] AEs and laboratory safety measurements will be graded per NCI CTCAE version 5.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness. Record grade 3 and 4 AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs occurring up until 30 days after the last dose of trial treatment, or until resolution/stabilization of treatment-related toxicities.

[E] Tissue biopsies are not mandatory, and should be optionally performed if a biopsy is performed per standard of care. Likewise, if staging laparoscopy is clinically indicated per standard of care, pre-treatment tissue may be collected at this time. Excess tumor tissue may be collected at the time of surgery.

[F] Research blood draws should be collected at same time as standard of care evaluations, including any pre- and/or post-surgical blood draws required per standard of care. Per discretion of the investigator, the frequency blood collections may be reduced or omitted from each study participant. Research blood samples will be collected only when convenient and feasible for the patient, per institutional standards.

[G] Radiographic imaging will be performed only as clinically indicated and follow institutional standards. The results of imaging performed per standard of care, for the purpose of assessing disease response or status, should be recorded.

[H] Radiographic imaging will be performed at End of Study will coincide with standard of care imaging for participants without clinical evidence of progression to confirm participant is progression-free. If after blood collection, the treatment is held, per institutional standards and as long as treatment is resumed within two weeks, a subsequent research blood draw will not be collected at the treatment's reattempt.

9. EFFICACY MEASURES

9.1 MARGIN STATUS

All participants that undergo surgical resection (per standard surgical techniques [e.g., pancreaticoduodenectomy or distal pancreatectomy]) will have a comprehensive pathological review of the resected tumor specimen based on according to the American Joint Committee on Cancer [AJCC] staging system (8th edition).[49] Margin status will be classified as R0 or R1 as follows:

- R0 margin status is defined as the absence of any tumor cells within 1 mm from the resection margin.[50] Also referred to as pathological complete response (pCR).
- R1 margin status is defined as cases either:
  - R1<1 mm - cases with a tumor-free margin <1 mm from the resection margin
  - R1 direct - tumor cells directly at the margin

9.2 IMAGING RESPONSE

All assessments of imaging response to standard of care systemic chemotherapy (e.g., FOFIRINOX or GA) at Re-staging I and II, respectively, will be abstracted from the radiologist's clinical report. Disease progression (recurrence or relapse) will be based on radiologist's assessment in clinical records noting an increase lesion size or occurrence of new lesion(s).

9.3 PROGRESSION-FREE SURVIVAL (PFS)

PFS is defined as the time from start of systemic chemotherapy to the first of either recurrence or relapse (anywhere in the body) or death at time of last follow-up at 24-months from start of study treatment. Participants who are lost to follow up, or are still alive at last follow-up will be censored at the time of last assessment.

9.4 DISEASE-FREE SURVIVAL (DFS)

DFS is defined as the time from surgical resection to the date of recurrence or relapse (anywhere in the body) or death at time of last follow-up at 24-months from start of study treatment. Participants who are lost to follow up, or are still alive at last follow-up will be censored at the time of last assessment.

9.5 OVERALL SURVIVAL (OS)

OS is defined as the time from start of systemic chemotherapy to death (from any cause) at time of last follow-up at 24-months from start of study treatment. Participants who are lost to follow up, or are still alive at last follow-up will be censored at the date of last contact.

9.6 SURGICAL COMPLICATIONS

Surgical complications will be based on the Clavien-Dindo classification per PI and/or treating oncologist in the review of the surgical discharge summary and daily progress notes in the patient's medical records shown in Table 21. Complications will be captured up to 30 days from date of surgery.

Table 26. Classification of Surgical Complications

Grade	Definition

Grade I	Any deviation from the normal post-operative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs such as antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other that such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also needed.
Grade III	Requiring surgical, endoscopic, or radiological intervention.
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complications (including CNS complications)* requiring IC/ICU management.
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVa	Multi-organ dysfunction.
Grade V	Death of a patient
Suffix “d”	If the patient suffers from a complication at the time of discharge, the suffix “d” (for “disability”) is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

*Brain hemorrhage, ischemic stroke, subarachnoid bleeding, but excluding transient ischemic attacks.
CNS, central nervous system; IC, immediate care; ICU, intensive care unit.
Adapted from Dindo et al.[48]

10. SAFETY

10.1 SPECIFICATION OF SAFETY PARAMETERS

The Investigator is responsible for monitoring the safety of participants who have enrolled in the study. Safety assessments will be based on medical review of adverse events and the results of safety evaluations at specified time points as described in Section 8.11, Schedule of Events.

10.2 DEFINITIONS

10.2.1 ADVERSE EVENT (AE)

An adverse event is defined as any undesirable physical, psychological or behavioral effect experienced by a participant during their participation in an investigational study, in conjunction with the use of the investigational product, whether considered intervention-related (21 CFR 312.32 (a)). In general, this includes signs or symptoms experienced by the participant from the time of signing the informed consent to completion of the study.

AEs may include, but are not limited to:

- Subjective or objective symptoms spontaneously offered by the participant and/or observed by the Investigator or medical staff.
- Clinically significant laboratory abnormalities.
- A significant worsening of the participant’s condition from study entry.
- Disease signs and symptoms and/or laboratory abnormalities existing prior to the use of the study treatment that resolve but then recur after treatment.
- Disease signs and symptoms and/or laboratory abnormalities existing prior to the use of the study treatment which increase in frequency, intensity, or a change in quality after

treatment.

10.2.2 SERIOUS ADVERSE EVENT (SAE)

An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor-investigator, it results in any of the following outcomes:

- Death,
- A life-threatening adverse event,
- In-patient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and/or participant may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include:

- Allergic bronchospasm requiring intensive treatment in an emergency room or at home,
- Blood dyscrasias or convulsions that do not result in in-patient hospitalization, or
- The development of drug dependency or drug abuse.

10.2.3 UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers UPs involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

1. Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
2. Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

This study will use the OHRP definition of UP.

10.2.4 SEVERITY OF EVENT

The Investigator will grade the severity of each AE using, when applicable, the current version of the CTCAE v5.0. In the event of an AE for which no grading scale exists, the Investigator will classify the AE as defined below:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
Grade 4: Life-threatening consequences; urgent intervention indicated.
Grade 5: Death related to AE.

Note: a semi-colon indicates 'or' within the description of the grade.

10.2.5 ASSESSMENT OF CAUSALITY RELATIONSHIP TO STUDY INTERVENTION

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below:

Definitely Related: There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Potentially Related: There is some evidence to suggest a causal relationship
Unrelated: The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology.

10.3 EXPECTEDNESS

The Investigator will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

10.4 ADVERSE EVENT LISTS

Neoadjuvant administration of mFOLFIRINOX or GA, with or without RT, and surgery is the standard of care approach to treating patients with resectable/borderline resectable PDAC. Both FOLFIRINOX and GA treatment regimens are widely used and have well-established safety profiles.[9-17,19]

10.4.1 ADVERSE EVENT LIST FOR MFOLFIRINOX

Refer to the respective package inserts for 5-FU, irinotecan, and oxaliplatin. AEs associated with each drug agent are summarized in **Table 22**.

Table 27. Common and Severe AEs for drug agents comprising mFOLFIRINOX regimen

Irinotecan – Common AEs	
System	**AE (grade, frequency (%))**
Dermatologic	• Alopecia (43.1% to 60%)
Endocrine metabolic	• Weight decreased (30%)
Gastrointestinal	• Abdominal pain (all grade, 17.2% to 67.7%; grade 3 and 4, 2.1% to 14%), • Constipation (all grade, 30% to 43.9%; grade 3 and 4, 0.4% to 10%), • Diarrhea, All grade (early-onset, 43% to 51%; late-onset, 72.4% to 88%), • Loss of appetite (all grade, 34.2% to 55%; grade 3 and 4, 2.1% to 7.2%), • Nausea (all grade, 66.9% to 86%; grade 3 and 4, 2.1% to 17%), • Vomiting (all grade, 44.8% to 67%; grade 3 and 4, 3.5% to 14%)
Hematologic	• Anemia (all grade, 60% to 97.2%), • Drug-induced eosinophilia, leukopenia (all grade 63% to 96.9%),

	• Neutropenia (all grade 54% to 96.9%), • Thrombocytopenia (all grade, 32.6% to 96%)
Hepatic	• Increased bilirubin level (19.1% to 87.6%)
Neurologic	• Asthenia (all grade, 57.9% to 76%; grade 3 and 4, 9% to 19.5%), • Dizziness (15% to 23.1%), • Parasympathomimetic adverse reaction (28.3%)
Respiratory	• Cough (17% to 26.7%), • Dyspnea (9.7% to 27.6%)
Irinotecan – Serious AEs	
Cardiovascular	• Disorder of cardiovascular system
Gastrointestinal	• Diarrhea, Grade 3 and 4 (4.9% to 31%), • Gastrointestinal perforation
Hematologic	• Anemia (grade 3 and 4, 2.1% to 8.4%), • Febrile neutropenia (adults, 2% to 7.1%), • Hemorrhage (1% to 5%), • Infectious disease, Neutropenic (1% to 2.2%), • Leukopenia (grade 3 and 4, 17.4% to 37.8%), • Neutropenia (grade 3 or 4, adults, 26% to 53.8%), • Thrombocytopenia (grade 3 and 4, up to 4%), • Thromboembolic disorder (5.4% to 11.7%)
Immunologic	Hypersensitivity reaction
Respiratory	Interstitial lung disease
Oxaliplatin – Common AEs	
System	**AE (grade, frequency (%))**
Gastrointestinal	• Abdominal pain (Monotherapy, 31%; combination therapy, up to 39%), Constipation (Combination therapy, up to 32%), • Diarrhea (Monotherapy, 46%; combination therapy, up to 76%), • Loss of appetite (Monotherapy, 20%; combination therapy, up to 35%), • Nausea (Monotherapy, 64%; combination therapy, 64% to 83%), • Stomatitis (Monotherapy, 14%; combination therapy, up to 42%), • Vomiting (Monotherapy, 37%; combination therapy, 40% to 64%)
Hematologic	• Anemia (all grades, monotherapy, 64%; combination therapy, 25% to 81%), Granulocytopenic disorder (grade 3 and 4 (39% to 45%), • Leukopenia, (all grades, monotherapy, 13%; combination therapy, up to 85%), Neutropenia, (all grades, Monotherapy, 7%; combination therapy, 71% to 81%), • Thrombocytopenia (all grades Monotherapy, 30%; combination therapy, 44% to 77%)
Hepatic	• Abnormal alkaline phosphatase (Combination therapy, 14% to 16%), ALT/SGPT level abnormal (Monotherapy, 36%; combination therapy, 5% to 31%), • AST/SGOT level abnormal (Monotherapy, 54%; combination therapy, 11% to 47%)
Musculoskeletal	• Backache (Monotherapy, 11%; combination therapy, 19%)
Neurologic	• Paresthesia (62% to 77%)
Respiratory	• Cough (Monotherapy, 11%; combination therapy, up to 35%)
Other	• Fatigue (Monotherapy, 61%; combination therapy, up to 70%), • Fever (Monotherapy, 25%; combination therapy, 29%)
Oxaliplatin – Serious AEs	
Cardiovascular	• Edema (Monotherapy, 5%; combination therapy, up to 15%), • Prolonged QT interval, Torsades de pointes

Endocrine	• Metabolic acidosis
Gastrointestinal	• Bowel obstruction, • Colitis (including clostridium difficile) • diarrhea, • acute pancreatitis
Hematologic	• Anemia (grade 3 or 4, Monotherapy, 1%; combination therapy, 1% to 3%), • Febrile neutropenia (Combination therapy, up to 12%), • Hemolytic anemia, Immuno-allergic, Leukopenia, (grade 3 or 4, Combination therapy, 13% to 24%), • Neutropenia (grade 3 or 4, Combination therapy, 36% to 53%), • Thrombocytopenia (grade 3 or 4, Monotherapy, 3%; combination therapy, 2% to 5%), • Thrombocytopenia, Immuno-allergic
Hepatic	• Increased liver function test (Combination therapy, 57%), • Veno-occlusive disease of the liver
Immunologic	• Anaphylaxis, hypersensitivity reaction (Monotherapy, grade 3 or 4, 1% to 3%; combination therapy, all grades, 6% to 12%), • Infusion reaction
Musculoskeletal	• Rhabdomyolysis
Neurologic	• Dysesthesia, Pharyngolaryngeal (1% to 38%), • Neuropathy, Acute or persistent (Overall neuropathy, 69% to 92%; acute neuropathy, 56%; persistent neuropathy, 21% to 60%), • Posterior reversible encephalopathy syndrome (less than 0.1%)
Ophthalmic	• Transient visual loss
Otic	• Hearing loss
Renal	• Hemolytic uremic syndrome, • Interstitial nephritis, acute
Respiratory	• Dyspnea (Monotherapy, 13%; combination therapy, up to 20%), • Pneumonitis (Severe), • Pulmonary fibrosis (Less than 1%)
Other	• Angioedema, • Sepsis
5-FU – Common AEs	
Dermatologic	Allergic contact dermatitis, Crust on skin, Hand-foot syndrome due to cytotoxic therapy, Pruritus, Scar, Sensation of burning of skin, Sore skin, Ulcer of skin or mucosa
Gastrointestinal	Diarrhea, Inflammatory disease of mucous membrane
Hematologic	Leukocytosis
5-FU – Serious AEs	
Cardiovascular	Angina pectoris, Cardiotoxicity, Nonspecific ST-T abnormality on electrocardiogram
Gastrointestinal	Gastrointestinal ulcer
Hematologic	Myelosuppression, Anemia, leukopenia, thrombocytopenia
Neurologic	Hyperammonemic encephalopathy, Neurotoxicity

10.4.2 ADVERSE EVENT LIST FOR GA

Refer to the respective package inserts of nab-paclitaxel and gemcitabine. AEs associated with each drug agent are summarized in **Table 28**.

Table 28. Common and Severe AEs for drug agents comprising GA regimen

GEMCITABINE	
ORGAN SITE	**SIDE EFFECT* (%)**
Cardiovascular	Arrhythmia (rare)
	Arterial thromboembolism (rare)
	Heart failure (rare)
	Hypertension (<2%)
Dermatological	Alopecia (14%)
	Rash (25%) (may be severe)
Gastrointestinal	Constipation (8%)
	Diarrhea (12%)
	Mucositis (8%)
	Nausea, vomiting (64%) (severe 18%)
General	Edema (20%)
	Fatigue (40%) (in combination with paclitaxel)
	Flu-like symptoms (37%)
	Other (radiosensitizer)
Hematological	Hemolytic uremic syndrome (<1%)
	Myelosuppression ± infection, bleeding (25%) (severe)
Hepatobiliary	Elevated LFTs (68%) (10% severe)
Hypersensitivity	Hypersensitivity (rare)
Infection	Infection (9%) (severe 1%)
Injection site	Injection site reaction (4%)
Musculoskeletal	Musculoskeletal pain (16%)
Nervous System	Peripheral neuropathy (3%)
	PRES (rare)
	Somnolence (9%)
Renal	Creatinine increased (7%)
	Proteinuria (36%)
Respiratory	Adult respiratory distress syndrome (ARDS) (rare)
	Dyspnea (8%)
	Pneumonitis (rare)
Vascular	Capillary leak syndrome (rare)
	Gangrene (rare)
	Vasculitis (rare)
Nab-Paclitaxel	
ORGAN SITE	**SIDE EFFECT* (%)**
Cardiovascular	Arterial thromboembolism (<1%)
	Atrioventricular block (rare)
	Bradycardia (<1%)
	Cardiotoxicity (<10%) (prior cardiac history or cardiotoxins)
	ECG changes (35%)
	Hypotension (5%)
	Venous thromboembolism (rare)
Dermatological	Alopecia (90%)
	Nail disorder (1%)
	Other - Scleroderma-like skin changes (rare)
	Photosensitivity (rare)
	Rash, pruritus (9%) (may be severe)
Gastrointestinal	Anorexia (very common)
	Constipation (very common)

	Dehydration (<10%)
	Diarrhea (27%) (may be severe)
	Esophagitis (rare)
	GI obstruction (<1%)
	GI perforation (<1%)
	Mucositis (7%)
	Nausea, vomiting (30%)
General	Edema (10%)
	Fatigue (47%) (8% severe)
Hematological	Hemolytic uremic syndrome (rare)
	Myelosuppression ± infection, bleeding (80%) (9% severe)
	Thrombotic thrombocytopenic purpura (TTP; rare)
Hepatobiliary	Elevated LFTs (39%) (rarely severe)
	Pancreatitis (<1%)
Hypersensitivity	Hypersensitivity (4%) (rarely severe)
Injection site	Injection site reaction (1%) (including extravasation and radiation recall; rarely may be severe)
Metabolic / Endocrine	Tumor lysis syndrome (rare)
Musculoskeletal	Musculoskeletal pain (44%) (8% severe)
Nervous System	Autonomic neuropathy (rare)
	Cognitive disturbance (rare)
	Cranial neuropathy (rare)
	Dizziness (rare)
	Mood changes (rare)
	Sensory neuropathy (71%) (10% severe)
Ophthalmic	Conjunctivitis (rare)
	Eye disorders (13%) (1% severe including keratitis and blurred vision)
	Optic neuritis (rare)
	Other - Cystoid macular edema (rare)
	Watering eyes (rare)
Renal	Creatinine increased (11%)
	Renal failure (<10%) (acute)
Respiratory	Cough, dyspnea (12%)
	Other - Lung Fibrosis (rare)
	Pneumonitis (rare)
	Pneumothorax (rare)
Rare - refers to events with incidence < 1%	

10.4.3 ADVERSE EVENTS LIST FOR LOSARTAN

The safety profile of losartan is well-established. AEs associated with losartan are summarized below. Refer to package insert for additional information.

Treatment with losartan potassium was well-tolerated with an overall incidence of adverse events similar to that of placebo. In controlled clinical trials, discontinuation of therapy for adverse events occurred in 2.3% of patients treated with losartan potassium and 3.7% of patients given placebo. In 4 clinical trials involving over 1000 patients on various doses (10 to 150 mg) of losartan potassium and over 300 patients given placebo, the adverse events that occurred in 2% of patients treated with losartan potassium and more commonly than placebo were: dizziness (3% vs. 2%), upper respiratory infection (8% vs. 7%), nasal congestion (2% vs.

1%), and back pain (2% vs. 1%). Less common adverse reactions also reported are summarized in **Table 29**.

Table 29. Less Common AEs for losartan*	
Blood and lymphatic system disorders	Anemia
Psychiatric disorders	Depression
Nervous system disorders	Somnolence, headache, sleep disorders, paresthesia, migraine.
Ear and labyrinth disorders	Vertigo, tinnitus.
Cardiac disorders	Palpitations, syncope, atrial fibrillation, CVA.
Respiratory, thoracic and mediastinal disorders	Dyspnea.
Gastrointestinal disorders	Abdominal pain, constipation, nausea, vomiting.
Skin and subcutaneous tissue disorders	Urticaria, pruritus, rash, photosensitivity. Musculoskeletal and connective tissue disorders: Myalgia, arthralgia.
Reproductive system and breast disorders	Impotence.
General disorders and administration site conditions	Edema.
*The definition (i.e., frequency) of less common AEs for losartan is not defined in package insert	

10.5 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an UP, AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, upon review by a study monitor, or during an audit. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, seriousness, expectedness, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and date of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed through to the end of treatment visit.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE after the participant provides informed consent.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent need only be documented one time, or until there is a change in the grade, at which point the new grade will be documented one time.

At each study visit, the Investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization, as determined by the treating provider in accordance with institutional standards.

The Investigator will record all reportable events with start dates occurring any time after the participant provides informed consent through the end of treatment visit. AEs will be evaluated

using the current version of the CTCAE v5.0. Any SAE that occurs after treatment with alternative therapy will be reported only if the Investigator or current treating physician has assessed the SAE as related to the study treatment.

10.6 REPORTING PROCEDURES

10.6.1 OHSU IRB REPORTING OF UNANTICIPATED PROBLEMS AND ADVERSE EVENTS

Unanticipated Problems and AEs will be reported to OHSU IRB according to the policies, procedures and guidelines posted on the OHSU IRB web site.

Events that must be reported by the Investigator to the IRB are detailed in the OHSU IRB **Investigator Guidance: Prompt Reporting Requirements (HRP-801)**. Events that meet the criteria for OHSU RNI must be reported to the IRB within 5 days of learning of the event. At a minimum, events requiring reporting to the IRB include:

- Any new or increased risk related to the research, including AEs or IND safety reports that require a change to the protocol or consent,
- New FDA black box warning,
- Publications identifying new risks,
- Data Safety Monitoring Board/Committee letters recommending changes or discussing new risks
- Unanticipated adverse device effect
- Unauthorized disclosure of confidential participant information

10.6.2 MEDWATCH REPORTING

The Investigator is required to report some events to the FDA through the Mandatory MedWatch reporting program, even if the trial involves a commercially available agent. Events to be reported include any UPs (i.e., not listed in the package insert) and any SAEs with a suspected association to 5-FU, irinotecan, oxaloplatin, gemcitabine, nab-paclitaxel, or losartan.

Adverse events that occur during clinical studies are to be reported to FDA as specified per applicable investigational new drug/biologic regulations using FDA Form 3500 (MedWatch Voluntary Reporting form, available here). A copy of the MedWatch form and supporting materials will be kept on file in the study regulatory binder.

10.6.3 REPORTING OF PREGNANCY

To ensure participant safety, each pregnancy in a participant on study treatment must be reported within 24 hours of learning of its occurrence. The pregnancy should be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or any pregnancy- or childbirth-related and/or newborn complications.

The pregnancy should be recorded and reported by the Investigator to the IRB. Pregnancy follow-up should be reported using the same form. Any SAE experienced during pregnancy must also be reported.

If while on study treatment a participant's sexual partner becomes pregnant, the pregnancy and

pregnancy outcomes must also be reported as described above. Consent to report information regarding the pregnancy should be obtained from the pregnant individual.

10.7 STUDY STOPPING RULES

The overall study will be paused, and appropriate authorities (e.g., IRB, Knight Data and Safety Monitoring Committee) notified if the following events occur:

- Life-threatening grade 4 toxicity attributable to protocol therapy that is unmanageable, or unexpected.
- Death suspected to be related to study treatment.

11. STATISTICAL CONSIDERATIONS

11.1 STATISTICAL HYPOTHESIS

This is an open-label, non-randomized, phase II trial to assess the efficacy of an adaptive treatment strategy that allows for early switching of neoadjuvant systemic chemotherapy in patients with resectable and borderline resectable pancreatic cancer, or patients with locally-advanced, unresectable pancreatic cancer (LAPC).

11.2 SAMPLE SIZE DETERMINIATION

Murphy et al[20] reported on a single arm phase II trial in which 48 patients (27 male, 21 female) with newly diagnosed BRPC were given eight cycles of neoadjuvant FOLFIRINOX as well as short-course or long-course chemoradiation. In this study, the R0 resection was achieved in 31 of 48 patients (65%). However, reported R0 rates across other studies can vary widely (26% to 87%). [14,16,17,51] Moreover, the impact of providing an early switch to GA in the neoadjuvant setting after failing FOLFIRNOX has only been evaluated in a small retrospective cohort study of 25 patients, of which 11 proceeded to undergo surgical resection, of which 9 (81.8%) had an R0 resection.[43] Without an adequate historical benchmark, the study will estimate the precision of the proportion of R0 in order to assess the clinical utility of allowing for early switching of neoadjuvant therapies. Based on the literature, and assuming that the proportion of R0 is 60%, a sample size of 32 patients will allow us to estimate the proportion with an exact 95% CI (0.41, 0.76); that is, a width of 0.35 for the 95% CI. Given that the major purpose of this study is to provide a good estimate for the proportion of R0 to be used as a benchmark for future studies, we deemed the width of the 95% CI as adequate. Assuming that 80% of enrolled participants will finish systemic chemotherapy (FOLFIRINOX or GA) and undergo surgery (20% loss), a total of 40 participants with resectable or BRPC will be enrolled towards the primary endpoint.

An additional 20 participants with LAPC will be enrolled as part of an exploratory cohort to estimate the proportion of individuals that achieve an R0 resection. A prior clinical study has suggested that neoadjuvant FOLFIRINOX with losartan followed by individualized CRT in patients with LAPC is associated with an R0 resection rate of 61%. The impact of providing an early switch to GA in the neoadjuvant setting after failing FOLFIRNOX has not been sufficiently explored in patients with LAPC. This exploratory cohort will be used as a benchmark for future studies.

11.3 POPULATIONS FOR ANALYSES

11.3.1 COHORTS AND SUBGROUPS

Resectable and BRPC participants (n = 40) and LAPC participants (n = 20) will be analyzed as two separate disease cohorts.
Subgroup analysis will be performed for those receiving NeoOPTIMZE adaptive therapy followed by radiation therapy, where indicated (treatment subset).

11.3.2 SAFETY ANALYSIS SET

The safety analysis set includes all enrolled participants who received at least 1 dose of systemic chemotherapy (FOLFIRINOX or GA). All safety analyses will be conducted using the safety population. Analysis for demographics, baseline characteristics, disease history, on-study treatment summaries and participant disposition will also be conducted using this safety population.

The surgery safety analysis set is a sub-set of the safety analysis set that includes all participants who undergo surgical resection of their pancreatic cancer (per institutional standard).

11.3.3 EFFICACY ANALYSIS SET

The efficacy analysis set includes all participants enrolled in the study who received at least 1 dose of systemic chemotherapy (FOLFIRINOX or GA) and had at least 1 post-baseline disease assessment.

11.4 DESCRIPTION OF STATISTICAL METHODS

11.4.1 DESCRIPTIVE STATISTICS

Descriptive statistics will be used to summarize disposition, demographics, baseline characteristics, baseline disease characteristics, study drug administration, and safety outcomes. Descriptive summaries of discrete data will present the sample size and the incidence as frequency and percentage. Descriptive summaries of continuous data will present the sample size, group mean, standard deviation, median, and range. Confidence intervals (CI) may be included as appropriate. The analyses will be stratified by disease cohort (Resectable or BRPC patients vs. LAPC patients).

11.4.1.1 *Baseline Descriptive Statistics*

Summaries of demographics, baseline characteristics, and baseline disease characteristics will be presented for participants using the safety analysis set to include the following:

Demographics: • Sex (Male, Female) • Age (continuous) • Ethnicity • Race	**Baseline Disease characteristics:** • Disease stage at study entry • Mutational status (if reported)
Baseline Characteristics: • Height (cm) • Weight (kg) • ECOG performance status	

11.4.1.2 *On-study Treatment Summaries*

Overall exposure to study drugs (FOLFIRINOX and/or GA) and RT, the numbers of participants completing each cycle, and the dose intensity will be summarized using descriptive statistics.

11.4.2 ANALYSIS OF PRIMARY ENDPOINT

Using the surgery analysis set, the proportion of resectable or BRPC participants with R0 resection will be estimated with exact 95% CI.

11.4.3 ANALYSIS OF THE SECONDARY ENDPOINTS

Using the efficacy analysis set for resectable and BRPC participants, the estimated distribution of the PFS, and OS will be plotted using Kaplan Meier curves and reported with median survival and 95% confidence intervals (if available) for the full population and for the treatment subset (NeoOPTIMIZE plus RT). DFS will be analyzed similarly using the surgery analysis set and using surgical patients in the treatment subset (NeoOPTIMIZE plus RT).~~When feasible, sub-group analyses for the different treatment regimens (i.e., GA or mFOLFIRINOX ± RT [i.e., short- or long-course, or both RT modalities combined]) will be performed for PFS, DFS, and OS.~~

The incidence of grade ≥3 toxicities will be determined using the safety analysis set for all participants (both disease cohorts). The exact 95% confidence interval will be reported with the point estimate of toxicity rate.

Peri- and post-operative complications occurring within 30 days following surgery will be categorized per the Clavien-Dindo classification system. Using the surgery analysis set for resectable and BRPC participants, the proportion of participants with peri- and post-operative complications occurring within 30 days following surgery, and the proportion of 30-day post-operative mortality will be estimated and reported with two-sided exact 95% confidence intervals. ~~If necessary, the proportion of 30-day post-operative mortality may be estimated from the Kaplan Meier method.~~

11.4.4 ANALYSIS OF THE EXPLORATORY ENDPOINTS

Using the safety analysis set, the levels of CA19-9 will descriptively reported (across all participants).

Using the surgery analysis set, the proportion of LAPC participants with R0 resection will be estimated with exact 95% CI.

When adequate data are available, PFS, DFS and OS for LAPC patients will be analyzed as described above using the LAPC efficacy set, and the LAPC treatment subset (NeoOPTIMZE plus RT).Surgical complications and 30-day post-operative mortality will be estimated as above using the LAPC surgical set, when there are sufficient numbers of participants undergoing resection. Results will be qualitatively described when statistical measures are not feasible.

11.4.5 SAFETY ANALYSES

Adverse events will be tabulated by the Medical Dictionary for Regulatory Activities (MedDRA Version 21.1) preferred term and system organ class and a preferred term. The severity of the AE will be assessed by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 criteria. Descriptive statistics using the safety analysis set will be used to report on all on-study grade ≥ 3 AEs per CTCAE v5.0. Grade 3-4 laboratory abnormalities will be summarized using worst grade NCI CTCAE v 5.0 criteria.

11.5 HANDLING OF MISSING DATA

Missing data will not be imputed. Whenever possible, the analysis will be conducted using all available data. Missing data will be reported in the descriptive summary, and it will be noted if participants were excluded from the analysis due to missing data.

12. CLINICAL MONITORING

12.1 OHSU KNIGHT COMPREHENSIVE CANCER CENTER DATA & SAFETY MONITORING PLAN

All clinical trials at the Knight are required to have a Data and Safety Monitoring Plan (DSMP). This study is under the oversight of the Knight Comprehensive Cancer Center's DSMC as described in the Knight institutional DSMP. The Knight DSMP outlines the elements required to ensure the safety of clinical trial participants, the accuracy and integrity of the data, and the appropriate modification of cancer-related clinical trials for which significant benefits or risks have been discovered or when the clinical trial cannot be successfully concluded. The Knight DSMP also describes the methods and procedures for ensuring adequate, risk-based oversight of cancer-related research at OHSU.

As described in the Knight DSMP, regardless of a trial's risk level and any specific Knight oversight in place, the Investigator is singularly responsible for overseeing every aspect of the design, conduct, and final analysis of his/her investigation. The Knight DSMC reviews and monitors data for this study. The DSMC comprises clinical and research specialists who have experience in oncology and who have no direct relationship with the study. The DSMC will address any issue that raises questions about data integrity or trial participant safety with the Investigator and study team. Should any major concern arise, the Knight DSMC may also recommend corrective action, and determine whether to suspend or terminate the study.

The Knight DSMC initially reviews each protocol to determine the risk profile of the trial design. This assessment establishes trial reporting requirements commensurate with the risk, and also directs the scope and frequency of Quality Assurance audits. The DSMC may adapt report and audit requirements at any time, if indicated, (refer to Knight DSMP for additional details on reporting and audit frequency). The Investigator will submit trial-specific data reports for the

DSMC to assess toxicity and safety data; the report must provide the DSMC with such information as: up-to-date participant accrual; current dose level information; DLT information; unexpected AEs that have been reported; AEs and SAEs reported by category; AEs of special or clinical interest; summary of any death on study; summary of all deaths occurring within 30 days of intervention; deviations from the approved protocol that have been reported; eligibility exceptions; any inspection, audit, or monitor report; publications and/or developments that may affect scientific validity, participant safety or the ethics of the trial, and a summary of trial status. The study team will provide other information (e.g. scans, laboratory values) upon request.

12.2 CLINICAL DATA & SAFETY MONITORING

The OHSU Investigator is ultimately, singularly responsible for overseeing every aspect of the investigation, including design, governing conduct at all participating sites, and final analysis of study data.

If monitoring is required, per the Knight DSMP, then monitoring visits will be performed during the study to ensure that the rights and well-being of human participants are protected, that the reported trial data are accurate, and that the conduct of the trial is in compliance with the protocol, GCP, and applicable regulatory requirements. In this case, details of monitoring activities, including designation of assigned monitoring entities, scope of monitoring visits, timing, frequency, duration of visits, and visit reporting, will be included in a separate TSMP.

If monitoring is required, per the Knight DSMP, then the Investigator agrees that the monitor will be permitted to conduct monitoring visits at appropriate intervals. The Investigator agrees to provide all relevant information and documentation as requested by the monitor, including access to all original study documents and source data (electronic medical records and/or source documents, if necessary). The monitor will conduct source data review and verification as outlined in the TSMP and, following each visit, will generate a report summarizing the visit findings.

In the absence of a formal monitoring plan, the Investigator may work with their study team to conduct and document internal monitoring of the study to verify protection of human participants, quality of data, and/or ongoing compliance with the protocol and applicable regulatory requirements.

If at any time Investigator noncompliance is discovered at OHSU or any participating site (if applicable), the Sponsor-Investigator shall promptly either secure compliance or end the participation of the participating study site.

Independent audits will be conducted by the Knight DSMC to verify that the rights and well-being of human participants are protected, that the reported trial data are accurate, that the conduct of the trial is in compliance with the protocol and applicable regulatory requirements, and that evidence of ongoing investigator oversight is present.

12.3 QUALITY ASSURANCE & QUALITY CONTROL

The investigational site will provide direct access to all trial related source data/documents, and reports for the purpose of monitoring by the monitor and/or sponsor, and auditing by the Knight DSMC and/or regulatory authorities.

All clinical trials at the Knight Cancer Institute are required to have a Data and Safety Monitoring Plan. All clinical work conducted under this protocol is subject to ICH GCP guidelines. This includes inspection of study-related records by the lead site, sponsor, its designee, or health authority representatives at any time.

QA audit activities will occur as detailed in the Knight institutional DSMP. All discrepancies, queries, deviations, observations, and findings of non-compliance will be compiled into a final audit report. The PI must review and assess each finding, and generate a response to the audit report that incorporates a Corrective and Preventative Action (CAPA) plan. The CAPA must analyze root cause(s) of noncompliance to determine the appropriate changes to correct and resolve issues, and prevent recurrence.

Quality Control (QC) activities will occur to monitor and ensure the safety of study participants and the validity and integrity of data. Monitoring will be a continuous, ongoing and multifaceted process. This includes review by the Knight DSMC and IRBs, as well as internal data quality control, review and evaluation. Site monitoring visits are central to this process, and will include reporting to appropriate individuals with oversight responsibilities.

The Sponsor-investigator, or study monitor, will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

13. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

13.1 SOURCE DATA/DOCUMENTS

The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The Investigator will maintain adequate case histories of study participants, including accurate CRFs, electronic (e)CRFs and relevant electronic data capture (EDC) system (if applicable), and all relevant source documentation.

13.1.1 PARTICIPANT & DATA CONFIDENTIALITY

The information obtained during the conduct of this clinical study is confidential, and unless otherwise noted, disclosure to third parties is prohibited. Information contained within this study will be maintained in accordance with applicable laws protecting participant privacy, including the provisions of the Health Insurance Portability and Accountability Act (HIPAA).

Participant confidentiality is strictly held in trust by the participating Investigator(s) and study team. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or manufacturer supplying study product may inspect all documents and records required to be

maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and institutional regulations. Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored within the Knight Comprehensive Cancer Center per OHSU's Information Security Directives. Individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Knight Comprehensive Cancer Center research staff will be secured and password protected per OHSU's Information Security Directives. At the end of the study, or after the appropriate period of record retention stated in Section 13.1.4, all study databases will be de-identified and archived within the Knight Comprehensive Cancer Center.

13.1.2 DATA COLLECTION & STORAGE: PRIVACY, CONFIDENTIALITY & SECURITY

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Standard institutional practices will be followed as described in the OHSU's Information Security Directives to maintain the confidentiality and security of data collected in this study. Study staff will be trained with regard to these procedures.

Loss of participant confidentiality is a risk of participation. Efforts will be made to keep study participant identities confidential except as required by law. Participants' samples will be identified by code only. Specifically, each consenting participant will be assigned a unique coded identifier consisting of numbers. This identifier will be associated with the participant throughout the duration of their participation in the trial. The coded identifier will also be used to identify any participant specific samples.

Basic accrual tracking information (demographic, consent, visit information) will be captured in OHSU's electronic clinical information research system (eCRIS), hosted on OHSU secure servers and managed by OHSU's information technology group at their data center in downtown Portland, Oregon. Any additional printed documents containing participant identifiers, such as those from the medical record to confirm eligibility, will be filed in binders and kept in a locked, secure location.

Study outcome data will be captured in electronic case report forms (eCRFs) using an electronic data capture (EDC) system that is approved by OHSU's office of Information Privacy and Security. To preserve confidentiality, PHI in the EDC system will be limited to just birth date and visit dates. The web-accessible EDC system is password protected and encrypted with role-based security, and administered by designated informatics staff within OHSU or Knight Comprehensive Cancer Center. All users of the database are assigned a unique ID, username, and password and must complete training appropriate to their role before they are authorized to enter, access, and store data in the database.

Where applicable, data from correlative studies may be entered into the EDC system by study personnel. All other electronic data extracts will be stored only on local study site computers

and restricted drives, which are limited to only study investigators and staff with authorization to access the data. Quality assurance will be conducted as outlined in Section 12.3, Quality Assurance & Quality Control.

13.1.3 FUTURE USE OF STORED SPECIMENS AND DATA

Each participant who signs consent will be assigned a unique coded identifier consisting of numbers. This identifier will be associated with the participant throughout the duration of their participation in the trial. The coded identifier will be used to identify any participant specific samples. Blood and tissue samples that are collected for the purposes of this protocol will be stored until they can be analyzed and will then be destroyed unless the participant consents to participation in the Oregon Pancreas Tumor Registry (OPTR). If the participant agrees, any remaining samples (tumor) may be stored in the OPTR (IRB# 3609) indefinitely and further analyzed to address scientific questions and/or development of biological tests related to pancreatic cancer.

13.1.4 MAINTENANCE OF RECORDS

Records and documents pertaining to the conduct of this study, source documents, consent forms, laboratory test results and medication inventory records, must be retained by the Investigator for a period of 2 years until after the investigation is discontinued. It is the responsibility of the sponsor to inform the Investigator when these documents no longer need to be retained.

If the Investigator relocates or for any reason withdraws from the study, the study records must be transferred to an agreed upon designee, such as another institution or another investigator at OHSU. Records must be maintained according to institutional or FDA requirements.

13.2 PUBLICATION AND DATA SHARING POLICY

This study will adhere to the requirements set forth by the ICMJE and FDAAA that requires all clinical trials to be registered in a public trials registry (e.g., ClinicalTrials.gov) prior to participant enrollment. Authors included in the publication of findings from this trial must have participated in the work and take public responsibility for appropriate portions of the content.

13.2.1 DATA SHARING POLICY FOR GENOME-WIDE ASSOCIATION STUDIES (GWAS)

Dissemination of any genetic (genotypic and phenotypic) will be consistent with the permissions and limitations delineated on the study consent signed by study participants. Any genetic data shared publically will be completely de-identified. Documentation that describes how the institutions have considered the interests of the research participants, such as privacy and confidentiality is required.

13.2.2 DATA SHARING WITH EXPLORATORY OBSERVATIONAL STUDIES

Associated clinical data will be shared with investigators of the ongoing, OHSU, prospective observational study entitled *"The Use of Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE MRI) in the Management of Pancreatic Cancer"* (IRB#9694) study if they are consented to IRB#9694. Note that participation in IRB#9694 is not required for participation in this trial.

13.3 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. Conflicts of interest, for all study group members, should be disclosed and managed according to OHSU's established policies and procedures.
Refer to link: https://o2.ohsu.edu/integrity-department/conflict-of-interest/index.cfm

14. ETHICS/PROTECTION OF HUMAN PARTICIPANTS

14.1 ETHICAL STANDARD

The Investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Participants of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR 213 (if applicable), and/or the ICH E6.

14.2 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

14.3 INFORMED CONSENT

Written informed consent will be obtained from all participants in this trial, as stated in the Informed Consent section of 21 CFR Part 50. Documentation of the consent process and a copy of the signed consent shall be maintained in the participant's medical record.

14.3.1 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreement to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families as appropriate. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The Investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks/benefits of the study, alternatives to participation, and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the

participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

14.4 PROTOCOL REVIEW

The protocol and informed consent form for this study must be reviewed and approved in writing by the OHSU Knight Comprehensive Cancer Center's Clinical Research Review Committee (CRRC) and the appropriate IRB prior to any participant being consented on this study.

14.5 CHANGES TO PROTOCOL

Any modification of this protocol must be documented in the form of a protocol revision or amendment submitted by the Investigator and approved by the CRRC and IRB, before the revision or amendment may be implemented. The only circumstance in which the amendment may be initiated without regulatory approval is for a change necessary to eliminate an apparent and immediate hazard to the participant. In that event, the Investigator must notify the IRB (and sponsor/FDA if under an IND/IDE) within 5 business days after the implementation.

If Sponsor-investigator holds an IND application for this study, the FDA must also be notified of changes to the protocol per 21 CFR 312.

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APPENDIX A: PERFORMANCE STATUS

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	**Descriptions**	**Percent**	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B: CONTRACEPTION

Females of childbearing potential who are sexually active with a non-sterilized male partner or partners of male participant must use 2 highly effective method of contraception. These include: levonorgestrel-releasing intrauterine system (e.g., Mirena®), copper intrauterine device, and hormonal methods. Appropriate hormonal contraceptives include: Etonogestrel-releasing implants (e.g. Implanon® or Norplant®), ethinylestradiol/etonogestrel-releasing intravaginal devices (e.g. NuvaRing®), medroxyprogesterone injection (e.g., Depo-Provera®), normal and low dose combined oral contraceptive pill, norelgestromin/ethinylestradiol-releasing transdermal system (e.g. Ortho Evra®), progesterone based oral contraceptive pill using desogestrel (NB, Cerazette® is currently the only highly effective progesterone-based)

Non-sterilized male participants, or partners of female participant, must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Abstaining from sexual activity for the total duration of the drug treatment and the drug washout period is an acceptable practice for both female and male participants; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female participant should also refrain from breastfeeding throughout this period.

APPENDIX C: EXPLORATORY RESEARCH

The following describes exploratory research assays that may be conducted in an effort to better understand the tumor biology of pancreatic cancer. The ability to conduct any of the assays described herein is limited to sample availability. Any excess samples may be stored for future research.

A-1. EXOSOME PROFILING

Exosomes are vesicles secreted from living cells. In cancer, these exosomes are responsible for intercellular communication that can facilitate tumor promoting enterprises such as immune evasion, angiogenesis, and metastases. The extent to which PDAC-derived exosomes are involved in promoting tumor progression and treatment resistance remains unknown.

i) Methods of Assessment

Exosomes will be recovered from blood plasma samples using commercial kits (e.g., Total Exosome Isolation Reagent [ThermoFisher]) and established methods. Various molecular assays (e.g., ELISA, Mass Spectroscopy, RNA Seq) will be used to quantitative analyze the proteomics, transcriptomics and metabolomics of the exosomes.

ii) Outcome Measure

Quantitative analysis of proteomics, transcriptomics and metabolomics of the PDAC-derived exosomes as it relates to clinical outcomes.

A-2. MUTATIONAL GENE PROFILING

Mutations and aberrant gene expression within tumor biopsy samples may be identified using the GeneTrails® Comprehensive Solid Tumor Panel, a custom gene assay that is processed and analyzed within OHSU's KDL. A portion of tumor tissue collected from surgical resection will be used for these studies. The tumor tissue collected will be preserved in FFPE for subsequent DNA extraction. The custom assay provides information on clinically informative alterations on profiled genes. Alterations may include single nucleotide substitutions, insertions, deletions, and gains or losses in gene copy number. Up to 50 alterations may be reported for any sample, although most will have less than 10. The panel has a lower limit of detection of ~3-5% mutant allele.

i) Methods of Assessment

A portion of the tumor biopsy specimens (FFPE) will be processed and analyzed within OHSU's KDL according to established institutional standards.

ii) Outcome Measure

Characterization of genetic alterations based on custom gene panel.

A-3. MICROSATELLITE INSTABILITY

Possible microsatellite instability (MSI) may be assessed within OHSU's KDL using polymerase

chain reaction (PCR) per institutional standards. A portion of tumor tissue collected from surgical resection will be used for these studies. Peripheral blood will be collected and may also be used as a matched control. The tumor tissue collected may be preserved in FFPE for subsequent DNA extraction. Possible MSI will be evaluated using PCR to co-amplify 5 mononucleotide markers (BAT-25, BAT-26, NR-21, NR-24, MONO-27), and 2 pentanucleotide markers (Penta C and Penta D). The mononucleotide markers are used for MSI determination and the pentanucleotide markers are used to confirm identity match in the tumor tissue and matched control blood in each participant. Samples with instability in two or more of these mononucleotide markers are designated MSI-High (MSI-H), whereas those with one unstable marker are designated MSI-Low (MSI-L). Samples with no detectable alterations are MSI-stable (MSS).

i) Methods of Assessment

A portion of the tumor biopsy specimens (FFPE) will be processed and analyzed within OHSU's KDL according to established institutional standards.

ii) Outcome Measure

Characterization of MSI profile.

A-4. MULTIPLEX IMMUNOHISTOCHEMISTRY AND CYCLIC IMMUNOFLUORESCENCE

Multiplex Immunohistochemistry (mIHC) and cyclic Immunofluorescence (cycIF) will be used to facilitate an examination of the tumor intrinsic and extrinsic mechanisms that may change during treatment and reduce therapeutic response. In this study mIHC and cycIF, with a panel of >100 validated antibodies will allow analysis of the molecular characteristics and organization of tumor cells and the microenvironments in which they live. The rationale for use mIHC is that it is easily implemented on conventional autostainers and so can be widely propagated particularly in CLIA environments. Likewise, cycIF enables very high dimension analysis on single FFPE sections using conventional reagents and existing instruments to generate high quality image data from a wide range of sample types.

Both mIHC[52] and cycIF[53,54] technologies provide the ability to comprehensively assess the functional states of cells within tissues at several levels. These assays are intended to provide three levels of information[55]: *(a) expression levels of epitopes that report on cell types and biological processes, (b) identity and organization of specific cell types, and (c) functional state of each cell type in environmental context thereby allowing assessment of the biological and clinical consequences of cell-environment interaction.* The latter information is statistically powerful since it allows each tissue section to be analyzed as a set of millions of individual cell-microenvironment interactions. Further, these assays allow assessment of subcellular localization which plays a critical role in the functionality of multiple proteins. We have validated panels of antibodies (**Table 25**) that enable assessment of several aspects of biology that may alter therapeutic sensitivity including aspects of (a) angiogenesis and lymphangiogenesis[56-58], (b) immune composition and activity[52,59], (c) differentiation state[54], (d) cell proliferation[53,60], and (e) and extracellular matrix composition.[54,61] Additional antibodies may be selected as more information becomes available.

Table 30. Summary protein panel for evaluation by mIHC and cycIF

Lymphoid panel	*PD-1, CD3, RORgt, CD56, CD8, Tbet, GATA3, FoxP3, PD-L1, CD20, CD45*
Myeloid panel,	*Tryptase, CD68, CSF1R, DC-SIGN, CD66b, CD83, CD163, MHCII, PD-L1, CD3/20/56, CD45, Tim3*
T cell functional panel	*CD45, CD3, CD4, CD8, IDO, Tbet, CD68, PD-1, Eomes, Ki67, Granzyme B, IL-10*
Lymphatic vessels	LYVE1, podoplanin, VEGFR3, PROX1
Hematogenous vessels	CD34, CD31, MECA79
Pericytes	aSMA, PDGFRb, NG2, Desmin
Endothelial cell activation &adhesion	P/E Selectin, ICAM-1, VCAM-1, FasL, VEGFR1, VEGFR2, EDN1
Fibroblasts	aSMA, CD140a, vimentin, FAP
Epithelial differentiation	CK5, CK7, CK8, CK14, CK17, CK19; actin, GFAP, MAP2, vinculin, TUBB3, pAURK, E-cadherin, N-cadherin, EpCAM, chromogranin A, CD44, Insulin
Cell status	HER2, EGFR, pEGFR (Tyr1068), MET, NGFR, ER, PgR, AR, PgR, Ki67, PCNA, CDK4, CycD1, CycA2, MCM6, pHistone H3, cleaved PARP, S6RP, pS6RP), RB, pRB, POL2A, p21, p27, pSRC, Bax, cCasp3, pCHK2, Bcl2, Survivin, gH2ax, cJun, FOXOA1, NFATc1, FOXA2, NF B, pSTAT3, cMYC, E2F1, pTyr, S100A4, HSP90b, KAP1.TIF1b, LAMP2, TPCN2, AKT, pAKT, pmTOR, pERK, TP53, pATM, 14-3-3, pNDRG1, CoxIV, Tubulin, LaminA/C, LaminB1, Fibrillian, NUP98, -catenin
Extracellular matrix	Collagen IV, laminin (pan), collagen 1 (pan)

A.4.1. Multiplex Immunohistochemistry

i) Method of Assessment

A portion of both tumor biopsy and resection specimens (FFPE) will be used for multiplex immuno-histochemistry (IHC) profiling as previously reported.[62]

ii) Outcome Measure

Multiplex IHC will be used to quantitatively assess the immune cell complexity (i.e., variations in lymphoid and myeloid lineages) and functional status of T cells within tumors of participants receiving treatment. Biomarkers markers to be evaluated include (but not limited to) those listed in **Table 25**.

A.4.2. Cyclic Immunofluorescence imaging (cycIF)

i) Method of Assessment

CycIF analysis will be performed on a single 4-5 µm thick FFPE section cut from core that is in as-close proximity to the sections used for mIHC. The cycIF process is iterative, involving four sequential steps: (a) Staining with fluorophore-conjugated antibodies against different protein antigens. We currently use antibodies conjugated to Alexa 488, 555, and 647. (b) Staining with Hoechst 33342 to mark nuclei. (c) Four-channel imaging at low and high magnification (10X, 20X, and 40X objectives). (d) Fluorophore oxidation using hydrogen peroxide, high pH, and UV light, followed by a wash step. A core set of antibodies (**Table 25**) will be used to interrogate samples.

ii) Outcome Measures

Develop multi-color cycIF imaging to enable spatial mapping of proteins to define the immune, microenvironmental, differentiation and proliferation status in treatment responsive and treatment resistant FFPE pancreas.

A-5. WHOLE EXOME AND TRANSCRIPTOME SEQUENCING

CLIA Whole Exome Sequencing using a hybrid-capture library and run on Illumina sequencing instrumentation will be performed on matched tumor/normal pairs derived from tumor surgical resection specimens and peripheral blood, respectively. Non-CLIA Whole Transcriptome Sequencing using the Illumina TruSeq RNA Access kit (or other whole transcriptome library preparation) and run on Illumina sequencing instrumentation will be performed on RNA from both tumor biopsy and surgical resection specimens.

i) Methods of Assessments

This study will evaluate the longitudinal DNA and RNA sequencing data being generated from participant's tissue collected during this clinical trial. This will include assessment of clonal selection and acquisition of new mutations driving resistance; identification of deregulated transcriptional networks induced after acquisition of resistance; and an integration of the data from across the two modalities.

ii) Outcome measures

Genomic alterations and transcriptional pathways associated with therapeutic resistance in each participant.

A-6. HIGH RESOLUTION STRUCTURAL ANALYSIS

A portion of the tumors will be examined using high resolution electron microscopy. This research will support goals of understanding structural heterogeneity and responses to therapy.

i) Methods of Assessments

Tumor tissues will be placed in EM fixative (2.5% glutaraldehyde + 2% paraformaldehyde) prior to resin embedding and imaging with scanning beam EM

ii) Outcome measures

Assessment of subcellular structures and cellular contacts pre- and post-therapy.

A-7. LIVE CELL PROPAGATION AND GROWTH INHIBITION

Propagated patient-derived cell models will be screened against multiple therapeutic strategies to learn about sensitivity as well as innate and adaptive resistance to therapeutics.

i) Methods of Assessments

Primary cells will be isolated and grown as necessary under short term growth conditions to provide enough cells to support the assay, which involves exposure to a panel of 30-400

different small molecule therapeutics. Effects on growth will be measured after 48-96 hours of exposure. Where feasible, long-term propagation of tumor-derived cells may also be attempted.

ii) Outcome measures

Cellular resistance or sensitivity to standard of care or targeted therapies will be quantified through multiple metrics.

A-8. FUSION GENE PROFILING

i) Method of Assessment

The potential for fusion genes within tumor biopsy samples will be assessed using the GeneTrails® Solid Tumor Fusion Gene panel (or an equivalent CLIA validated gene fusion assay), a custom assay that is processed and analyzed within OHSU's KDL. A portion of tumor tissue derived from core needle biopsy collected will be used for these studies. The biopsied tumor tissue collected may be FFPE for subsequent RNA extraction.

ii) Outcome Measure

Fusion genes* to be screened include:

AKT3	ALK	BRAF	EGFR	EGFR vIII	ERBB4	ERG	FGFR1
FGFR2	FGFR3	MET	NOTCH1	NOTCH2	NRG1	NTRK1	NTRK2
NTRK3	NUTM1	PDGFRA	RAF1	RET	ROS1		
Additional genes may be added as more information becomes available.							

This test is designed to detect fusions involving the genes listed above, and is agnostic with respect to fusion partners. All of the driver genes are known to play a role in cancer growth, and most of them are actionable with one or more targeted therapies. Submitted samples are examined microscopically and genomic RNA is extracted and purified from dissected, tumor-rich areas. Sequencing libraries are prepared from cDNA using an amplicon-based methodology and are sequenced by massively parallel sequencing on an Illumina NextSeq500. The gene fusions can be detected to the range of approximately 1-5% of input cells.

A-9. CELL FREE TUMOR DNA (CFDNA)

Assessing cfDNA facilitate determining mechanisms of resistance to the on-study therapeutic regimen by identifying genetic changes in tumors as they evolve. The notion that resistant tumors are often distinct clones that separated lineages from those that are identified at the beginning of therapy.

i) Methods of Assessments

Whole exome sequencing of ctDNA collected after disease progression. These studies will compare mutations identified before treatment with those present after treatment to identify genetic selection. Additional measure may include the number of genetic lesions shared between primary and resistant tumors.

ii) Outcome measures

cfDNA levels from serial blood samples for each participant.

A-10. CIRCULATING TUMOR DNA

i) Method of Assessment

Circulating tumor DNA may be isolated from peripheral blood and used to assess genomic alterations and tumor heterogeneity. DNA from peripheral blood cells and cell free DNA may be isolated and subjected to whole exome sequencing using a hybrid-capture library and run on Illumina sequencing instrumentation.

ii) Outcome Measures

Genetic alterations present in circulating tumor DNA may be compared to results from CLIA whole exome sequencing to estimate the genetic heterogeneity of a patient's disease.

A-11. REVERSE PHASE PROTEIN ARRAYS (RPPA)

Serial proteomic characterization of basal protein expression and modification levels will enable enhanced insight into the genomic evolution and therapeutic response of metastatic lesions.

i) Methods of Assessments

Reverse Phase Protein Arrays (RPPA) will require at least 10 mg of frozen tumor tissue to be lysed and protein will be extracted. Diluted lysates will be printed on nitrocellulose-coated slides and probed with approximately 300 validated primary antibodies followed by detection with Biotinylated secondary antibodies. Signal amplification will be achieved using the Vectastain Elite ABC kit from Vector Lab. The slides will be scanned, analyzed, and quantified to generate spot intensity values and estimate relative protein levels.

ii) Outcome Measures

RPPA data will be used to integrate the consequence of genetic aberrations in tumor biopsy samples, to validate therapeutic targets, and to demonstrate on- and off-target activity of drugs.

A-12. CIRCULATING TUMOR CELL (CTC) PROFILING

Circulating tumor cells (i.e. CTCs and circulating hybrid cells, CHCs) may be isolated from peripheral blood and analyzed for proliferative and apoptotic index to monitor the extent of tumor cell death.

i) Method of Assessment

Peripheral blood for hematology and serum biochemistry should be collected per institutional guidelines. In most cases, blood samples for research purposes will be drawn from participants scheduled to have venipuncture for routine clinical purposes. In some cases, when this is not possible, a research only blood draw will be undertaken. Peripheral blood mononuclear cells

may be assessed for CHC and CTC numbers and phenotype.

ii) Outcome Measures

Apoptotic, proliferative and dormant cells may be quantified and correlated with tumor metrics to determine the extent to which tumor cells in the peripheral blood serve as a sensor for treatment response. Other markers of biological interest, including cell signaling status, may be assessed by immunofluorescence or DNA/RNA sequencing in these cells.

A-13. DIELECTROPHORESIS (DEP) CHIP

Dielectrophoretic lab-on-a-chip devices will be tested for its ability to effectively separate PDAC cells as a novel platform for liquid biopsies.

i) Method of Assessment

In these experiments, peripheral blood collected for research will be assayed using custom DEP-CHIPS to evaluate device performance and their ability to isolate CTCs, cfDNA, as well as cell free constituents such as tumor-associated RNA, exosomes, and enzyme.

ii) Outcome Measures

Depending on sample availability and type of DEP-CHIP assays, the concentration of ell free DNA, RNA, exosome and enzyme biomarkers will quantified. Additional studies will further evaluate the validity of this device as a biomarker platform by comparing the isolated genes and proteins with corresponding clinical outcomes data.

A-14. PATIENT-DERIVED XENOGRAFT (PDX) MODELS

Mouse models of patient tumors may be generated to study tumor biology and response to therapy.

i) Method of Assessment

Fresh tumor tissue obtained from patients in this this trial with pancreatic ductal carcinoma (PDAC) will be implanted into mice to propagate the tumors. All mouse work will be performed under IACUC-approved protocol(s). Tumor tissues will either be implanted fresh or may be processed and stored at -80^{o}C as viable tissue for implantation at a later time. Successfully growing tumors will be removed and analyzed by similar metrics as described above (gene profiling, multiplex immunohistochemistry, and cyclic immunofluorescence) to compare to the parent tumor. These models may be used to understand the basic biology of PDAC or to explore the efficacy of novel targeted therapies. Once established, the tumors will be expanded in mice to generate a collection of PDAC PDX models. We will use these established models as pre- clinical models of PDAC tumors to test the efficacy of various chemotherapeutic agents on human tumors. Models established from tumors that do not respond to therapy may be used to understand resistance mechanisms.

ii) Outcome measures

We will evaluate feasibility of generating patient-derived mouse models using either the pre- or

post-drug treatment tumor tissues. We will compare the tumor cell and microenvironment composition, structural features, genetic alterations, and protein expression of the PDX tumor to the original patient tumor.