Feasibility Study of Neoadjuvant Gemcitabine/nab-Paclitaxel and Hypofractionated Image-Guided Intensity Modulated Radiotherapy in Resectable and Borderline Resectable Pancreatic Cancer

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2. LIST OF ABBREVIATIONS

Use this list as a starting point for abbreviations used in your protocol.

3D	3 Dimensional
5-FU	5 fluoro-uracil
AE	Adverse events
ANC	Absolute Neutrophil Count
AP/PA	Anterior to Posterior, Posterior to Anterior
APC	Argon Plasma Coagulation
BED	Biologically Equivalent Dose
BID	Twice Daily
CBC	Complete Blood Count
CBCT	Cone Beam Computed Tomography
CDDP	Cisplatin
Chemo	Chemotherapy
CPC	Cancer Protocol Committee
CRT	Chemoradiotherapy
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTV	Clinical Tumor Volume
D10cc	Minimum dose to the 10 milliliters of any volume receiving the highest dose
D2cc	Minimum dose to the 2 milliliters of any volume receiving the highest dose
DCI	Duke Cancer Institute
DLT	Dose Limiting Toxicity
Dmax	Maximum dose to any voxel within a volume
DUHS	Duke University Health System
ECOG	Eastern Cooperative Oncology Group
EFRT	Extended Field Radiotherapy
EQD2	Equivalent dose at 2 Gray per fraction
FIGO	International Federation of Gynecology and Obstetrics
G3 or G4	Grade 3 or Grade 4 toxicity
GCP	Good Clinical Practice
GOG	Gynecologic Oncology Group
GTV	Gross Tumor Volume
GU	Genitourinary
GY	Gray
HDR	High Dose Rate
ICRU	International Commission on Radiation Units and Measurement
ID	Identification
IMRT	Intensity Modulated Radiation Therapy (including Volumetric Modulated Arc Therapy)
IRB	Institutional Review Board
KPS	Karnofsky Performance Scale
kVOBI	Kilovoltage on-board imaging
LDR	Low Dose Rate
LINAC	Linear Accelerator
LRC	Loco-regional control
MRI	Magnetic Resonance Imaging.

MTD	Maximum Tolerated Dose
MV	Megavoltage
NCI	National Cancer Institute
OS	Overall Survival
PA	Para-aortic
PET	Positron Emission Tomography
PI	Primary Investigator
PTV	Planning Target Volume
RTOG	Radiation Therapy Oncology Group
SOC	Safety Oversight Committee
TD5/5	Toxic dose of 5% at 5 years
V18	Partial volume receiving greater than or equal to 18 Gray
WAI	Whole abdominal irradiation
WPRT	Whole Pelvic Radiotherapy

3. PROTOCOL SYNOPSIS AND RESEARCH SUMMARY

3.1 **Purpose**

This research protocol will evaluate the feasibility and acute toxicity of administering neoadjuvant gemcitabine and nab-paclitaxel with hypofractionated, image guided, intensity modulated radiotherapy (HIGRT) in resectable and borderline resectable pancreatic cancer.

Primary Objective

To determine if neoadjuvant gemcitabine/nab-paclitaxel and HIGRT is feasible in patients with potentially resectable pancreatic cancer and associated with Grade 3+ acute non-hematologic toxicity rate of <50% (excluding fatigue and alopecia).

Secondary Objectives

1. To evaluate grade ≥2 acute toxicity
2. To assess number of patients who undergo surgical resection
3. To assess R0 resection rate

Exploratory Objectives

1. To assess perioperative surgical complications (i.e. wound complications/infections, delayed gastric emptying, pancreatic leak, estimated blood loss, operative times)
2. To assess for late toxicity (greater than 6 month post neoadjuvant therapy)
3. To evaluate locoregional control and rate of distant metastasis
4. To evaluate median progression free survival (PFS)
5. To evaluate median overall survival (OS)
6. To evaluate pathologic complete response (pCR) and percentage of viable tumor in surgical specimen with this neoadjuvant regimen
7. To evaluate radiographic response after receipt of neoadjuvant gemcitabine/nab-paclitaxel and HIGRT
8. To explore the effects of this neoadjuvant regimen on markers of tumor perfusion and hypoxia
9. To evaluate cross-sectional measurements of muscle, visceral fat and subcutaneous fat at a consistent L3 vertebral body level on pre-treatment and follow-up scans to assess for patterns that predict mortality.

Hypotheses

1. The administration of neoadjuvant gemcitabine/nab-paclitaxel and HIGRT will be feasible and associated with <50% rate of grade 3+ acute non-hematologic toxicity (excluding fatigue and alopecia). The secondary and exploratory objectives are hypothesis-generating and to power future prospective trials in this area of study.

3.2 **Background and Significance**

Pancreatic cancer is the fourth leading cause of cancer-related death in the United States and accounts for roughly 40,000 deaths each year. [1] Patients generally present with locally advanced or metastatic disease that precludes cure since symptoms frequently prompt the diagnosis in the absence of effective screening strategies. Even among patients who present with localized disease, the 5-year overall survival (OS) is approximately 20%, but potentially higher in patients with complete surgical resection (R0) and uninvolved lymph nodes. [2, 3] Local and/or distant recurrence is common following resection, highlighting the importance of adjuvant therapy. [4, 5] Despite the use of neoadjuvant and adjuvant therapies, little

progress has been made in the last three decades, and the search for more efficacious treatment continues.[6]

In 2011, published results of a randomized control trial compared a multi-drug regimen of 5-fluorouracil (5-FU), leucovorin, irinotecan and oxaliplatin (FOLFIRINOX) to gemcitabine. Three hundred forty two patients < 76 years old with ECOG performance status of 0 or 1 were randomized with primary endpoint of overall survival. Median survival in the FOLFIRNOX group was 11.1 months compared to 6.8 months in the gemcitabine group. Objective tumor response was observed in nearly 30% of patients receiving FOLFIRINOX. Quality of life was also improved in the FOLFIRINOX arm despite higher rates of Grade 3 or 4 adverse events. [7] These median survival results are comparable to survival amongst patients with locally advanced, non-metastatic pancreatic cancer. [8-10]

Given the encouraging results of FOLFIRINOX in the metastatic setting, a number of single institution retrospective series have demonstrated reasonable toxicity rates and R0 resections in patients with borderline and locally advanced pancreatic tumors typically treated with a modified FOLFIRINOX regimen. [11-14] In a series from Pittsburgh of 25 patients (13 unresectable and 12 borderline resectable), 33% of patients went to surgery after FOLFIRINOX and 5 patients had a significant pathologic response. [14] At Massachusetts General, 22 patients with locally advanced pancreatic cancer received FOLFIRINOX. The objective response rate was 30% (in line with the randomized data) and 5 patients were able to undergo R0 resection after combination FOLFIRINOX and chemoradiotherapy (CRT). [13]

Some major concerns regarding the neoadjuvant administration of FOLFIRINOX are the associated toxicities. These have prompted many clinicians to deliver a modified FOLFIRINOX regimen, however, no standardization of dose modifications exist. Also unclear is how these drug/dose modifications affect the chemotherapeutic efficacy. In addition, the generalizability of this regimen to pancreatic cancer patients who are typically older and of poorer performance status makes this regimen less ideal. Given liver function inclusion criteria, the breakdown of pancreatic tumor location does not represent the majority of patients who present with pancreatic head lesions.

In addition to FOLFIRINOX, a randomized control trial demonstrated the superiority of combination gemcitabine with nab-paclitaxel compared to gemcitabine alone in patients with metastatic pancreatic cancer. This study of 861 patients with Karnofsky performance status score of 70 or more randomized patients to nab-paclitaxel (125mg/m^2) followed by gemcitabine (1000mg/m^2) days 1,8,15 every 4 weeks or gemcitabine monotherapy. The median overall survival was 8.5 months in the nab-paclitaxel/gemcitabine group compared with 6.7 months in the gemcitabine group (HR 0.72). The combination of gemcitabine/nab-paclitaxel resulted in reasonable toxicity profile with the most common adverse side effects of neutropenia/leukopenia, alopecia, nausea/diarrhea, fatigue and neuropathy. [15]

This trial had no age exclusion and more borderline performance status patients were enrolled compared to studies utilizing FOLFIRINOX, potentially making a regimen of gemcitabine/nab-paclitaxel more generalizable to newly diagnosed pancreatic cancer patients. Given the modest toxicity, the backbone of gemcitabine and nab-paclitaxel is felt to be ideal for the incorporation of additional or novel systemic agents.

Coinciding with alternative chemotherapy regimens to improve outcomes in pancreatic cancer patients, radiotherapy techniques to treat this patient group have evolved. High dose, image guided radiotherapy (HIGRT also called stereotactic body radiotherapy [SBRT] when a coordinate system is implemented) utilizes rigid patient immobilization and image guidance in an effort to deliver high doses of radiotherapy in a small number of fractions. Prospective data of SBRT in the subgroup of locally advanced, unresectable patients generally indicates high rates of freedom from local progression with reasonable acute and late toxicity with a variety of dose fractionation regimens. [16-18] A large retrospective study included patients with locally advanced and borderline resectable cancers again demonstrating high rates of local control with reasonable acute and late toxicities.[18] One single

institution, prospective study of SBRT has been performed to date in patients with resectable disease. Fifteen patients with resectable pancreatic cancer were treated on a Phase I dose escalation study with hypofractionated proton beam therapy with concurrent capecitabine. The dose used was 5 Gy per fraction x5 fractions. Eleven patients went on to surgery (progression of disease in those who did not go to surgery) with no associated perioperative complications. Pathologic assessment demonstrated significant fibrosis- 75% fibrosis as opposed to viable tumor. [19]
Given the high rates of both local and distant failure in potentially resectable pancreatic cancer patients, a combination of effective systemic therapy and local therapy is needed. In patients with a good performance status the combination of effective systemic therapy with gemcitabine/nab-paclitaxel and high dose local radiotherapy may improve disease outcomes. The primary objective of this study is to evaluate the toxicity of a neoadjuvant approach incorporating gemcitabine/nab-paclitaxel and HIGRT prior to surgical resection.

3.3 Design and Procedure

Prospective, single arm study in patients in newly diagnosed, previously untreated pancreatic cancer who are planned to undergo surgical resection

3.4 Selection of Subjects

Patients potentially eligible for study enrollment will be identified in the Radiation Oncology and GI oncology clinics. The treating radiation oncologist, medical oncologist or surgical oncologist (or their extenders) will introduce the study to patients and if the patient is interested he/she will meet with one of our clinical trials nurses for further details and consent.

3.5 Duration of Study

Patients will be on study therapy for approximately 6 months. The end of study participation will be 60 days post surgery. Thereafter patients will continue to be followed by the treating medical oncologist and/or radiation oncologist as per standard of care for follow up care.

3.6 Data Analysis and Statistical Considerations

Please see section 14 below for this information

4. INTRODUCTION

4.1 Study Disease

See Background and Significance section

4.2 Radiation Therapy

Simulation: Patients will undergo CT and/or MRI simulation utilizing customized immobilization. If patient is able to tolerate, respiratory motion management will be implemented (i.e. breath-holding technique, abdominal compression). Administration of IV and oral contrast is preferred for target and normal tissue delineation but at the discretion of the treating physician. A pretreatment renal scan to assess kidney differential may be performed at the discretion of the treating physician prior to initiation of treatment.
Treatment planning:
Gross Tumor Volume (GTV): tumor volume will be defined on the basis of endoscopic procedures, CT, and/or MRI imaging.
Clinical Target Volume (CTV):
The CTV should include the primary tumor and involved nodal areas with margin for microscopic disease extension. Additionally the following nodal regions are suggested based on tumor location as follows:

Pancreatic head: peri-pancreatic, para-aortic (celiac/SMA)
Pancreatic body: peri-pancreatic, para-aortic (celiac/SMA)
Pancreatic tail: peri-pancreatic, para-aortic (celiac/SMA) and splenic hilum
Portal and pancreaticoduodenal lymph nodes will not routinely be included unless concern for gross disease in this region. For the para-aortic nodes the most proximal 1-1.5cm of the celiac axis and proximal 2.5-3cm of the SMA from the take-off of the aorta should be contoured. These contours should be expanded by 1-1.5cm for the CTV.
Planning Target Volume (PTV): per treating physician discretion but typically CTV +0.5-1cm.
The following normal tissues will be contoured: Liver, stomach, duodenum, small bowel (peritoneal space (bowel bag), rather than bowel loops), right kidney, left kidney, and spinal cord.
Treatment Planning and Delivery:
Normal Tissue Constraints: At the discretion of the treating physician, however, the following constraints/prioritizations are recommended:

PTV	95% PTV covered by 95% Rx dose
Kidney	70% one kidney less than 15Gy
Liver	70%<24Gy
Spinal Cord	20Gy max
Small bowel	25Gy max
Duodenum	25Gy max
Stomach	25Gy max

3D conformal, IMRT or volumetric arc therapy (VMAT) are all permissible techniques for treatment delivery.
Dose: A dose of 5Gy x 5 fractions= 25Gy in total will be administered to the PTV.
Ideally, treatment will be delivered over 5 consecutive days for 5 total treatments. Treatment must be completed within a 10 day time period (inclusive of weekends/holidays).
Prior to each fraction of treatment, image guidance will be utilized to confirm positioning. kVOBI and cone beam CT (CBCT) will be utilized. Patients will be assessed weekly during radiation therapy as per standard of care.

4.2.1 Clinical experience

HIGRT, also called stereotactic body radiotherapy [SBRT], when a coordinate system is implemented) utilizes rigid patient immobilization and image guidance in an effort to deliver high doses of radiotherapy in a small number of fractions. This was first implemented in the treatment of brain metastases and there are now data for treatment of a variety of extracranial sites. Prospective data of HIGRT in the subgroup of locally advanced, unresectable pancreatic patients generally indicates high rates of freedom from local progression with reasonable acute and late toxicity with a variety of high dose fractionation regimens. [16-18] A large retrospective study included patients with locally advanced and borderline resectable cancers again demonstrating high rates of local control with reasonable acute and late toxicities. [19] One single institution, prospective study of SBRT has been performed to date in patients with resectable disease. Fifteen patients with resectable pancreatic cancer were treated on a Phase I dose escalation study with hypofractionated proton beam therapy with concurrent capecitabine. Eleven patients went on to surgery (progression of disease in those who did not go to surgery) with no associated perioperative complications.[19]

4.2.2 Study Drug

There is no investigational study drug. All chemotherapy administered to study subjects is standard of care.

4.2.3 Pre-clinical and clinical experience of study drug alone

Not applicable (please see above).

4.2.4 Clinical experience with combination of study drug and radiation therapy

Not applicable (please see above).

4.3 Study Purpose/Rationale

Given the high rates of both local and distant failure in potentially resectable pancreatic cancer patients a combination of effective systemic therapy and local therapy is needed. In patients with a good performance status the combination of effective systemic therapy with gemcitabine/nab-paclitaxel and high dose local radiotherapy may improve disease outcomes.

Chemotherapy

Standard neoadjuvant gemcitabine and nab-paclitaxel dosing is as follows:
Nab-Paclitaxel (125mg/m^2) days 1,8,15 every 28 days for 2 cycles
Gemcitabine (1000mg/m^2) days 1,8,15 every 28 days for 2 cycles
Starting dose of gemcitabine/nab-paclitaxel may be modified per treating physician discretion. Cycles are repeated every 4 weeks and therapy will be administered for a maximum of 2 cycles. Adjustments to dosing schedules and/ or dose modifications may be determined by the treating physician's clinical assessment. Gemcitabine/nab-paclitaxel will be commercially supplied.

Chemotherapy Agents

In this study, there is no investigational medicinal product. The chemotherapy combination, gemcitabine/nab-paclitaxel, is considered to be a standard-of-care, non-investigational combination medicinal product. The components of gemcitabine/nab-paclitaxel will be obtained from standard commercial sources and stored, formulated, and administered according to institutional standards and the respective product package inserts, when applicable.
Pre-medications (anti-emetics, hydration, antihistamines, corticosteroids, etc.), dosage, and administration for chemotherapy should be according to institutional standards and the respective product package insert(s), when applicable.

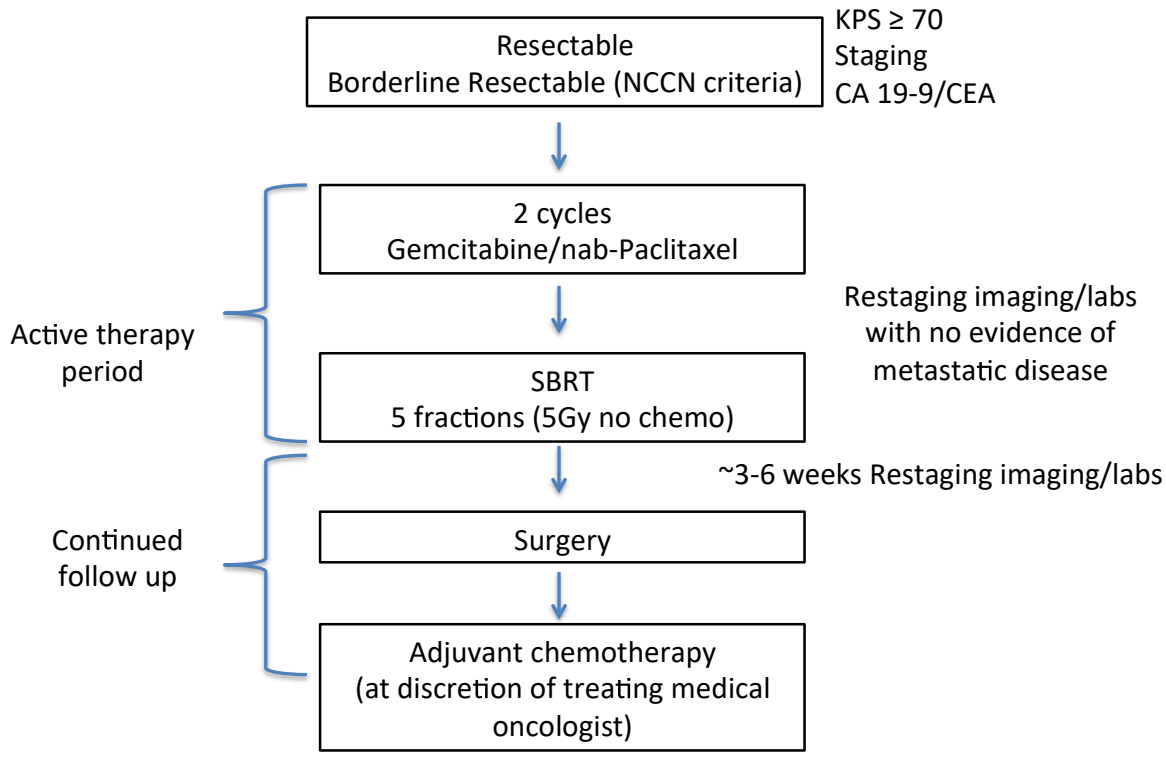
5. OBJECTIVES AND ENDPOINTS

	Objective	Endpoint	Analysis
Primary	To determine if neoadjuvant gemcitabine/nab-paclitaxel and hypofractionated image guided intensity-modulated radiotherapy (HIGRT) is feasible in patients with potentially resectable pancreatic cancer.	The neoadjuvant regimen will be considered feasible if (a) the trial can accrue 25 patients in no more than 3 years, (b) if at least 17 of the 25 patients adhere to the neoadjuvant regimen, and (c) the acute grade 3+ non-hematologic acute toxicity is less than 50% (excluding fatigue and alopecia)	See Section 3.6
Key Secondary	1. To evaluate grade ≥2 acute toxicity	1. CTCAE version 4 will be used for all toxicity assessments. The	See Section 3.6

		acute toxicity rate, defined as any non-hematologic grade 2+ toxicity occurring during HIGRT treatment through 60 days post-treatment, will be estimated with its exact 80% confidence interval. Likewise, we will determine the rate of grade 2+ hematologic toxicity occurring during treatment through 60 days post treatment and the proportion of patients requiring treatment breaks longer than 5 days.	
	2. To assess resection rate	2. Patients who undergo surgical resection will be documented	
	3. To assess R0 resection rate	3. Pathologic review will determine if an R0 resection has been performed.	
Exploratory	1. To assess perioperative surgical complication rates (i.e. wound complications/infections, delayed gastric emptying, pancreatic leak, estimate blood loss, operative time)	1. Perioperative surgical complications (within 60 days post surgery) will be recorded.	See Section 3.6
	2. To assess late toxicity with this neoadjuvant regimen	2. CTCAE version 4 will be used to assess late grade 3+ non-hematologic toxicity or Grade 4+ hematologic toxicity occurring 6 months or more after the completion of neoadjuvant therapy.	
	3. To evaluate local control and rate of distant metastasis with this neoadjuvant regimen	3. Local control and distant metastasis rate will be assessed at standard of care follow up appointments	
	4. To evaluate median progression free survival (PFS)	4. Disease progression will be assessed at standard of care follow up appointments	

	5. To evaluate median overall survival with this neoadjuvant regimen	5. Death (due to any cause will be recorded).	
	6. To evaluate pathologic complete response (pCR), percentage of viable tumor, percent fibrosis and histologic grading of treatment response in surgical specimen with this neoadjuvant regimen compared to historical control rates with chemoradiation (CRT) alone and neoadjuvant SBRT.	6. Response will be assessed at the time of pathologic review and appropriate data collected.	
	7. To evaluate radiographic response after receipt of neoadjuvant gemcitabine/nab-paclitaxel and HIGRT in the neoadjuvant setting	7. Radiographic response will be assessed by tumor measurements	
	8. To explore the effects of this neoadjuvant regimen on markers of tumor perfusion and hypoxia	8. Blood and urine will be obtained at baseline, prior to HIGRT, after HIGRT, and postoperatively. Urine will be collected in order to measure isoprostanes.	
	9. To evaluate cross-sectional area measurements of muscle, visceral fat and subcutaneous fat at a consistent L3 vertebral body level on pre-treatment and follow-up scans to attempt to assess for patterns that predict mortality.	9. Cross sectional measurements will be obtained using existing staging CT scans.	

6 STUDY SCHEMA



7 SUBJECT ELIGIBILITY

7.1 Inclusion Criteria

1. Patient has signed informed consent and is willing to comply with the protocol
2. Histologically or cytologically proven adenocarcinoma of the pancreas (within the last 90 days)
3. Either resectable or borderline resectable as determined on staging imaging (as defined by National Comprehensive Cancer Network [NCCN])
4. Patient is 18 years or older
5. Karnofsky performance status 70 or greater
6. The ANC count ≥ 1500, the platelet count ≥ 100,000 and hemoglobin ≥ 9g/dL
7. Laboratory values meet the following constraints: Bilirubin less than or equal to 2 mg/dL; AST and ALT less than or equal to 3 x ULN (stenting to improve biliary obstruction is permitted)
8. No evidence of metastatic disease based on imaging of the chest, abdomen and pelvis.

7.2 Exclusion Criteria

1. Metastatic disease on pretreatment imaging
2. Prior systemic therapy
3. Prior abdominal radiation. Any prior radiation must be approved by the Radiation Oncology PI
4. Previous treatment for pancreatic cancer

5. Patients with any serious/poorly controlled medical or psychological conditions that would be exacerbated by treatment, would complicate protocol compliance
6. Pregnant or lactating. Adequate birth control must be used if of child bearing potential per institutional policy. Negative pregnancy test in female patients of child-bearing potential per institutional policy. Post-menopausal women must have had amenorrhea for at least 18 months to be considered non-child bearing
7. Clinically significant peripheral vascular disease
8. Presence of active or chronic infection
9. Clinically significant atherosclerotic cardiovascular disease including patients with New York Heart Class II/III/IV CHF, ventricular arrhythmias requiring medication, myocardial infarction, cerebrovascular accident, transient ischemic attack, coronary artery bypass grafting, angioplasty, cardiac or other vascular stenting within the past 6 months
10. History of abdominal fistula, gastrointestinal perforation, intra-abdominal abscess within six months prior to treatment start
11. History of collagen vascular disease or inflammatory bowel disease (Crohn's or ulcerative colitis)
12. Current grade 2 or higher peripheral neuropathy
13. Anticoagulation with warfarin
14. History of arterial thromboembolic events or symptomatic pulmonary embolism within the past 6 months
15. Active bleeding diathesis or history of major bleeding, CNS bleeding, or significant hemoptysis within the past 6 months

9. INVESTIGATIONAL PLAN

8.1 Study Design

Please refer to study schema in section 6. Eligible subject population is outlined in section 3.4. Forty patients will be accrued to this prospective, single arm study in 5 years . Treatment duration is as outlined in scheme in section 6. Serum, plasma and urine will be collected as indicated in exploratory analysis (section 3.6).

8.1.1 Dose Escalation

Not applicable

8.1.2 Definition of Dose-Limiting Toxicity (DLT)

Not applicable

8.1.3 Dose Modification.

Dose Modifications and Toxicity Management of Chemotherapy

Treatment Parameters for Day 1 of Each Cycle

Treatment on **day one** of each cycle should be delayed until:

- Absolute neutrophil count (ANC) is $\geq$ 1,500/mm^3 **and** hemoglobin is $\geq$ 9g/dL
- Recovery to grade $\leq$ 1 from any clinically significant treatment-related non-hematologic toxicity. Subjects may continue drug with grade 2 toxicity if not considered clinically significant by treating physician (i.e. alopecia).
- Laboratory only abnormalities are permitted but must meet the following criteria:
    1. Not considered clinically significant in the treating physician's judgment (with the exception of ANC and hemoglobin)
    2. No clinical symptoms
    3. Do not require treatment modifications or delays or result in a medical intervention.

However, caution is needed to ensure re-treatment is considered safe and in the interest of the subject.

Investigators should be vigilant and alert to early and overt signs of myelosuppression, infection, febrile neutropenia and related events, so that these complications can be promptly and appropriately managed. Appropriate dose modifications should be made by treating physician. Suggested dose modification levels for each agent are noted below. Patients should be made aware of these signs and encouraged to seek medical attention at the earliest opportunity.

No dose reductions for gemcitabine/nab-paclitaxel are required for Grade 1 and 2 toxicities, except for those considered clinically significant, intolerable to the patient due to prolonged duration or adverse effects on quality of life.

For Grade 2-3 or persistent intolerable Grade 2 non-hematologic toxicity (e.g., fatigue, diarrhea, nausea, vomiting, neuropathy, respiratory symptoms, etc), refer to gemcitabine/nab-paclitaxel prescribing information for dose modification guidance which is at the treating physician's discretion. If the initiation of a cycle is delayed for ≥ 4 weeks, continuation of treatment must be discussed with the principal investigator.

Potential Dose Level Modifications for Each Agent

Agent	Initial Dose	Level –1	Level –2	Level –3
Nab-Paclitaxel	125mg/m2	100mg/m2	75mg/m2	Discontinue
Gemcitabine	1000 mg/m2	800mg/m2	600mg/m2	Discontinue

Chemotherapy toxicity assessment will be performed at the standard of care visits (typically days 1,8,15 during systemic therapy). During the course of radiotherapy, acute toxicity will be assessed at the standard treatment visit. Given the short duration of radiation treatment it is unlikely that dose modifications will be made. Radiotherapy treatments may be discontinued at the discretion of the treating physician for any reason.

8.1.4 Safety Considerations

To further evaluate the safety and toxicity profile of the therapy combination, an interim safety analysis will be performed after the first five patients in have completed study therapy. Accrual will not be halted during this analysis. All grade 4-5 AEs will be tabulated and reviewed. If > 20% of patients experience treatment-related grade 4-5 AEs, a decision will be made to either 1) halt the trial and all further accrual, 2) amend the protocol for more aggressive dose modification and/or 3) institute additional clinical monitoring.

8.1.5 Treatment Interruptions during RT

Although we do not anticipate side effects resulting in a break in treatment there is the low possibility of duodenal/bowel perforation or bleeding secondary to radiation treatment. Prior prospective studies in resectable and unresectable pancreatic patients have not reported acute duodenal/bowel perforation. At the discretion of the treating physician radiotherapy will be discontinued.

8.1.6 Concomitant Medications/Therapies

No concomitant therapy. Gemcitabine/nab-Paclitaxel will be administered first followed by HIGRT alone. Supplemental medications during chemotherapy and radiation will be

administered per institutional polices. Growth factor support is allowed on this protocol at the treating physicians' discretion and per institutional policy.

8.2 Rationale for Selection of Dose, Regimen, and Treatment Duration

See section 4.1

8.3 Rationale for Correlative Studies

Blood and urine will be collected for future correlative studies. Specimens will be banked in a -80° freezer in locked facilities in the Radiation Oncology Department. Please see section 11.8.3 for further information.

Definition of Evaluable Subjects, On Study, and End of Study

Patient enrolled on the study who initiates planned therapy will be evaluable. Patient are "on study" during neoadjuvant gemcitabine/nab-Paclitaxel and HIGRT. End of study is defined as 60 days post surgery. We will continue to collect patient data for 2 years after diagnosis or until death. For the purposes of the primary endpoint of feasibility a patient who has received 2 cycles of gemcitabine/nab-paclitaxel (regardless of dose reductions) and HIGRT will be considered to have completed the neoadjuvant regimen.

8.4 Early Study Termination

This study can be terminated at any time for any reason by the PI. If this occurs, all subjects on study should be notified as soon as possible. Additional procedures and/or follow up should occur in accordance with Section 11.7, which describes procedures and process for prematurely withdrawn patients.

9 RADIATION THERAPY

9.1 Type, Classification, Location, and Short Description

Therapy is high dose image guided radiotherapy (HIGRT) delivered in 5 fractions.

9.2 Equipment

A linear accelerator with on board imaging is used for treatment delivery.

9.3 Dose Specifications

5Gy will be delivered in 5 fractions to a total dose of 25Gy (ideally in consecutive days but 5 fraction treatment must be completed in a 10 day time period).

9.4 Localization, Simulation, and Immobilization

Simulation: Patients will undergo CT and/or MRI simulation utilizing customized immobilization. If patient is able to tolerate, respiratory motion management will be implemented (breath-hold, abdominal compression, etc.). Administration of IV and oral contrast is preferred for target and normal tissue delineation but at the discretion of the treating physician. A pretreatment renal scan to assess kidney differential may be performed at the treating physician's discretion prior to initiation of radiation treatment.

9.5 Imaging

Prior to each fraction of treatment, image guidance will be utilized to confirm positioning. kVOBI and cone beam CT (CBCT) will be utilized.

9.6 Treatment Planning/Target Volumes

Gross Tumor Volume (GTV): tumor volume will be defined on the basis of CT, EUS, and MRI imaging.

Clinical Target Volume (CTV):

The CTV should include the primary tumor and involved nodal areas with margin for microscopic disease extension. Additionally the following nodal regions are suggested based on tumor location as follows:
Pancreatic head: peri-pancreatic, para-aortic (celiac/SMA)
Pancreatic body: peri-pancreatic, para-aortic (celiac/SMA)
Pancreatic tail: peri-pancreatic, para-aortic (celiac/SMA) and splenic hilum
Portal and pancreaticoduodenal lymph nodes will not routinely be included unless concern for gross disease in this region. For the para-aortic nodes the most proximal 1-1.5cm of the celiac axis and proximal 2.5-3cm of the SMA from the take-off of the aorta should be contoured. These contours should be expanded by 1-1.5cm for the CTV.
Planning Target Volume (PTV): per treating physician discretion but typically CTV +0.5-1cm.

9.7 Dose Limitations for Normal Tissue

The following normal tissues will be contoured:
Liver
Stomach
Duodenum
Small bowel (peritoneal space, rather than bowel loops)
Right kidney
Left Kidney
Spinal cord

Normal Tissue Constraints: At the discretion of the treating physician, however, the following constraints/prioritizations are recommended:

PTV	95% PTV covered by 95% Rx dose
Kidney	70% one kidney less than 15Gy
Liver	70%<24Gy
Spinal Cord	20Gy max
Small bowel	25Gy max
Duodenum	25Gy max
Stomach	25Gy max

9.8 Treatment Verification

Imaging and treatment verification will be confirmed by a physicist and treating physician (or physician designee) prior to the delivery of each fraction.

9.9 Quality Assurance of Dose Distribution

Quality assurance will be performed of each treatment plan prior to delivery by a physicist.

10.STUDY DRUG

There is no study drug involved. The chemotherapy Gemcitabine/nab-Paclitaxel is FDA-approved for patients with metastatic pancreatic cancer, but they will used off-label in this study as Standard of care.

11.PATIENT ASSESSMENTS

As per standard of care all patients will have staging chest, abdomen and pelvis imaging. Standard labs will include the following: CMP, CBC with differential, CEA, and CA 19-9. If applicable, pregnancy test will be obtained prior to chemotherapy and HIGRT initiation. Blood and urine biomarker specimens will be

obtained at baseline, prior to HIGRT, after HIGRT, and postoperatively. Prior to surgery, patients will be asked to consent to tumor banking in the Duke Biospecimen Repository and Processing Core (BRPC) for future studies

Required studies	Screen visit	gemcitabine/nab-paclitaxel	HIGRT	Prior to surgery	Post op	Initial F/U	At 6-mos. and 12-mos. following therapy	Years 2 through 5	
								Every 6 mos.	Every 12 mos.
History and Physical exam	X			X (focused H&P)	X (focused H&P)	X (focused H&P)	x	x	x
Treatment visit		X (typically days 1,8,15 during chemo)	X (weekly)						
Weight	X	X	X	X	X	X	X	X	X
CBC	X			X		X [4]	X [4]	X [4]	X [4]
Chemistries	X			X		X [4]	X [4]	X [4]	X [4]
Liver Function	X			X		X [4]	X [4]	X [4]	X [4]
Pregnancy test (per institutional policy)	X		X						
CEA/CA 19-9	X [1]	X		X		X [4]	X [4]	X [4]	X [4]
Chest imaging	X[2]	X		X		at MD discretion)	(at MD discretion)	(at MD discretion)	(at MD discretion)
Abdominal/pelvic imaging	X[3]	X		X		at MD discretion)	(at MD discretion)	(at MD discretion)	(at MD discretion)
Toxicity assessment	Continuous Toxicity Assessment								
Serum collection	X		X	X	X				
Urine collection	X		X	X	X				

11.1 Pretreatment Evaluations/Management

Not applicable

[1] Completed within 30 days of initiating chemotherapy
[2] Completed within 30 days of initiating chemotherapy
[3] Completed within 30 days of initiating chemotherapy
[4] Completed at the discretion of the treating MD

11.2 Screening Examination

The screening examination will take place within 2 weeks of initiating chemotherapy. An informed consent must be signed by the patient before any study screening procedure takes place. If however, standard of care evaluation procedures have been obtained and are within the screening evaluation time points, the SOC procedures do not need to be repeated and may be included in the screening examination. Imaging and tumor markers (CEA/CA19-9), if completed within 30 days of initiating chemotherapy do not need to be repeated, unless at the discretion of the treating physician.

11.3 Treatment Period

Treatment period will be from initiation of gemcitabine/nab-paclitaxel to 60 days post-surgery. Assessment will be performed by the respective medical oncologist during systemic therapy (typically day 1, 8, and 15 of each cycle) and weekly during by radiation oncologist during radiotherapy. Restaging imaging and labs will be performed after systemic therapy. If patient is found to have evidence of distant metastatic disease they will not proceed with HIGRT and will be treated at the discretion of the treating medical oncologist and/or radiation oncologist off study. Per standard of care patients will return for follow up (prior to surgery) 3-6 weeks post HIGRT with labs and restaging imaging. The decision to proceed with surgical resection after neoadjuvant therapy (chemotherapy and HIGRT) will be at the discretion of the treating physicians.

11.4 End of Treatment

End of study treatment is defined as 60 days post-surgery (+/- 7 days). Toxicity will also be assessed at this visit and appropriate follow up arranged.

11.5 Follow-up Period

Patients will remain on study for 2 years from diagnosis or until death. Approximately 10-15% may survive greater than 2 years and we will continue to collect outcomes data from the electronic records at clinic visits q 6 months through year 2, then annually years 2 through 5.

11.6 End of Study

Patients lost to follow up will be documented and censored at time of last follow up for statistical consideration purposes.

11.7 Early Withdrawal of Subject(s)

11.7.1 Criteria for Early Withdrawal

Subjects may voluntarily withdraw from the study at any time. The PI may also withdraw a subject from the study at any time based on his/her discretion. Reasons for PI-initiated withdrawal may include, but is not limited to the following:

- Adverse events
- Abnormal laboratory values
- Abnormal test procedure results
- Protocol deviation
- Administrative issues
- Disease progression
- Pregnancy

11.7.2 Follow-up Requirements for Early Withdrawal

11.7.3 Replacement of Early Withdrawal(s)

Subjects who prematurely withdraw will not be replaced unless neoadjuvant therapy has not been initiated.

11.8 Study Assessments

11.8.1 Medical History

History will include a 10-point ROS by medical oncology and radiation oncology.
Weekly treatment checks during radiation therapy will be focused histories.

11.8.2 Physical Exam

Physical examination of a least 7 systems (including Abdomen) will be included.
Weekly treatment checks during radiation therapy and follow up will be a focused examination.

11.8.3 Correlative Assessment

Blood and urine will be collected at aforementioned time points. Specimens will be stored in a -80° freezer in locked facilities in the Department of Radiation Oncology for future study and analysis. The specimens may be used specifically for this study and potentially for unspecified research. The reason, biomarkers and assays are changing rapidly. This study is expected to enroll over 3 years, during that time it is possible a new biomarker or assay could be developed that is relevant to the study of pancreatic cancer. A study amendment would be submitted in the event of this occurring.

12 SAFETY MONITORING AND REPORTING

The PI is responsible for the identification and documentation of adverse events and serious adverse events, as defined below. At each study visit, the PI or designee must assess, through non-suggestive inquiries of the subject or evaluation of study assessments, whether an AE or SAE has occurred.

12.1 Adverse Events

The original protocol was written to include neoadjuvant chemotherapy toxicity data capture for 25 enrolled patients. The trial has now been amended to increase sample enrollment to 40 patients. It is not felt to be clinically meaningful to continue to capture toxicity data for the neoadjuvant chemotherapy regimen of gemcitabine/nab-paclitaxel given the published data on this regimen in over 800 patients with metastatic disease.[20, 21] CTCAE v 4 non-hematologic acute toxicity Grade 2 or higher will be collected during the study period from time of HIGRT through postoperative period for the additional 15 enrolled patients.

An adverse event (AE) is any untoward medical occurrence in a subject receiving study therapy and which does not necessarily have a causal relationship with this treatment. For this protocol, the definition of AE also includes worsening of any pre-existing medical condition

An AE can therefore be any unfavorable and unintended or worsening sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of HIGRT, whether or not related to HIGRT. Abnormal laboratory findings without clinical significance (based on the PI's

judgment) should not be recorded as AEs. But laboratory value changes that require therapy or adjustment in prior therapy are considered adverse events.

From the time the subject signs the informed consent form through the End of Study visit (as defined in Section 11.4), all AEs must be recorded in the subject medical record and adverse events case report form.

AEs will be assessed according to the CTCAE version 4.0. If CTCAE grading does not exist for an AE, the severity of the AE will be graded as mild (1), moderate (2), severe (3), life-threatening (4), or fatal (5).

Attribution of AEs will be indicated as follows:

- Definite: The AE is clearly related to the study therapy
- Probably: The AE is likely related to the study therapy
- Possible: The AE may be related to the study therapy
- Unlikely: The AE is doubtfully related to the study therapy
- Unrelated: The AE is clearly NOT related to the study therapy

See section 8.1.4 for additional safety considerations.

12.1.1 AEs of Special Interest

No special AEs of particular concern or emphasis.

12.1.2 Reporting of AEs

No specific reporting requirements for AEs.

12.2 Serious Adverse Events

An AE is considered "serious" if in the opinion of the investigator it is one of the following outcomes:

- Fatal
- Life-threatening
- Constitutes a congenital anomaly or birth defect
- A medically significant condition (defined as an event that compromises subject safety or may require medical or surgical intervention to prevent one of the three outcomes above).
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption to conduct normal life functions.

12.2.1 Reporting of SAEs

SAEs will be reported to the IRB as per institutional policy.

12.3 Other Reportable Information

The study team will adhere to the institutional policy on subjects and pregnancy stringently.

12.4 Special Warnings and Precautions

Not applicable.

12.5 Safety Oversight Committee (SOC)

The Duke Cancer Institute SOC is responsible for annual data and safety monitoring of DUHS sponsor-investigator phase I and II, therapeutic interventional studies that do not have an independent Data Safety Monitoring Board (DSMB). The primary focus of the SOC is review of safety data, toxicities and new information that may affect subject safety or efficacy. Annual safety reviews includes but may not be limited to review of safety data, enrollment status, stopping rules if applicable, accrual, toxicities, reference literature, and interim analyses as provided by the sponsor-investigator. The SOC in concert with the DCI Monitoring Team (see Section 13.1 for Monitoring Team description) oversees the conduct of DUHS cancer-related, sponsor-investigator greater-than-minimal-risk intervention studies that do not have an external monitoring plan, ensuring subject safety and that the protocol is conducted, recorded and reported in accordance with the protocol, standing operating procedures (SOPs), Good Clinical Practice (GCP), and applicable regulatory requirements. The DCI Safety Oversight Committee (SOC) will perform annual reviews on findings from the DCI Monitoring Team visit and additional safety and toxicity data submitted by the Principal Investigator.

12.6 External Data and Safety Monitoring Board (DSMB)

Not applicable.

13. QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Monitoring

The Duke Cancer Institute (DCI) Monitoring Team will conduct monitoring visits to ensure subject safety and to ensure that the protocol is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, good clinical practice, and applicable regulatory requirements. As specified in the DCI Data and Safety Monitoring Plan, the DCI Monitoring Team will conduct routine monitoring after the third subject is enrolled, followed by annual monitoring of 1 – 3 subjects until the study is closed to enrollment and subjects are no longer receiving study interventions that are more than minimal risk.

Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns and may be initiated upon request of DUHS and DCI leadership, the DCI Cancer Protocol Committee, the Safety Oversight Committee (SOC), the sponsor, the Principal Investigator, or the IRB. All study documents must be made available upon request to the DCI Monitoring Team and other authorized regulatory authorities, including but not limited to the National Institute of Health, National Cancer Institute, and the FDA. Every reasonable effort will be made to maintain confidentiality during study monitoring.

13.2 Audits

The Duke School of Medicine Office of Audit, Risk and Compliance (OARC) office may conduct confidential audits to evaluate compliance with the protocol and the principles of GCP. The PI agrees to allow the OARC auditor(s) direct access to all relevant documents and to allocate his/her time and the time of the study team to the OARC auditor(s) in order to discuss findings and any relevant issues.

OARC audits are designed to protect the rights and well-being of human research subjects. OARC audits may be routine or directed (for cause). Routine audits are selected based upon risk metrics generally geared towards high subject enrollment, studies with limited oversight or monitoring, Investigator initiated Investigational Drugs or Devices, federally-funded studies, high degree of risk

(based upon adverse events, type of study, or vulnerable populations), Phase I studies, or studies that involve Medicare populations. Directed audits occur at the directive of the IRB or an authorized Institutional Official.

OARC audits examine research studies/clinical trials methodology, processes and systems to assess whether the research is conducted according to the protocol approved by the DUHS IRB. The primary purpose of the audit/review is to verify that the standards for safety of human subjects in clinical trials and the quality of data produced by the clinical trial research are met. The audit/review will serve as a quality assurance measure, internal to the institution. Additional goals of such audits are to detect both random and systemic errors occurring during the conduct of clinical research and to emphasize "best practices" in the research/clinical trials environment.

13.3 Data Management and Processing

13.3.1 Study Documentation

Study documentation includes but is not limited to source documents, case report forms, monitoring logs, appointment schedules, study team correspondence with sponsors or regulatory bodies/committees, and regulatory documents that can be found in the DCI-mandated "Regulatory Binder", which includes but is not limited to signed protocol and amendments, approved and signed informed consent forms, FDA Form 1572, CAP and CLIA laboratory certifications, and clinical supplies receipts and distribution records.

Source documents are original records that contain source data, which is all information in original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents include but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial. When possible, the original record should be retained as the source document. However, a photocopy is acceptable provided that it is a clear, legible, and an exact duplication of the original document.

13.3.2 Case Report Forms (CRFs)

REDCAP database will be the primary data collection document for the study. The CRFs will be updated in a timely manner following acquisition of new source data. Only the PI and persons listed as key personnel are permitted to make entries, changes, or corrections in the CRF.

An audit trail will be maintained automatically by the electronic CRF management system, REDCAP. All users of this system will complete user training, as required or appropriate per regulations.

13.3.3 Data Management Procedures and Data Verification

Clinical research nurses will have access to REDCAP based on their specific roles in the protocol. . The designated data manager will be managing the REDCAP database.

Completeness of entered data will be checked automatically by the eCRF system, and users will be alerted to the presence of data inconsistencies. Additionally, the data manager, and clinical

research nurses will cross-reference the data to verify accuracy. Missing or implausible data will be highlighted for the PI requiring appropriate responses (i.e. confirmation of data, correction of data, completion or confirmation that data is not available, etc.).

The database will be reviewed and discussed prior to database closure, and will be closed only after resolution of all remaining queries. An audit trail will be kept of all subsequent changes to the data.

13.3.4 Coding

All medical terms will be coded with MedDRA (Medical Dictionary for Regulatory Activities).

13.3.5 Study Closure

Following completion of the studies, the PI will be responsible for ensuring the following activities:

- Data clarification and/or resolution
- Accounting, reconciliation, and destruction/return of used and unused study drugs
- Review of site study records for completeness
- Shipment of all remaining laboratory samples to the designated laboratories

14 .STATISTICAL METHODS AND DATA ANALYSIS

Primary Objective: To determine if neoadjuvant gemcitabine/nab-paclitaxel and HIGRT is feasible in patients with potentially resectable pancreatic cancer.
The neoadjuvant regimen will be considered feasible if (a) the trial can accrue 25 patients in no more than 3 years, (b) if at least 17 of the 25 patients adhere to the neoadjuvant regimen, and the acute grade 3+ non-hematologic acute toxicity is less than 50% (excluding fatigue and alopecia).
Secondary Objectives:

1. To evaluate grade ≥2 acute toxicity

CTCAE version 4 will be used for all toxicity assessments. The acute toxicity rate, defined as any non-hematologic grade 2+ toxicity occurring during treatment through 60 days post-surgery, will be estimated with its exact 80% confidence interval (CI). Likewise, we will determine the rate of grade 2+ hematologic toxicity occurring during HIGRT treatment through 60 days post treatment and the proportion of patients requiring treatment breaks longer than 7 days.

The 15 additional patients will allow us to estimate the various toxicity rates of interest with more accuracy. For example, the table below shows the decrease in the width of the 80% CI when using a sample of 40 patients as compared to 25 patients. These calculations are given for two different estimated rates.

Sample size	Estimated rate	80% CI	Width of CI
25	0.50	0.37 – 0.63	0.26
40	0.50	0.40 – 0.60	0.20
25	0.20	0.10 – 0.30	0.20
40	0.20	0.12 – 0.28	0.16

2. To assess number of patients who undergo surgical resection.
3. To assess the R0 resection rate

The rates for secondary objectives 2-3 will be calculated with their exact 80% confidence intervals.

Exploratory Objectives:

1. To assess perioperative surgical complication (i.e wound complications/infections, delayed gastric emptying, pancreatic leak, estimated blood loss, operative time) within 60 days post-surgery

The rates for will be calculated with their exact 80% confidence intervals.

2. To assess late toxicity with this neoadjuvant regimen

Late toxicity will be defined as any Grade 3+ non-hematologic toxicity or Grade 3+ hematologic toxicity occurring after the completion of the neoadjuvant regimen up to 6 months post HIGRT. The proportion of patients experiencing any type of late toxicity will be estimated with it 80% CI.

3. To evaluate local control and rate of distant metastasis with this neoadjuvant regimen

Time-to-local-failure will be defined as the length of time from date of diagnosis to local failure; distant failures will be ignored and deaths will be censored. The distribution of time-to-failure will be estimated with the Kaplan-Meier method. Distant metastases will be defined as the length of time from enrollment to distant failure. The distribution of distant metastasis will be estimated with the Kaplan-Meier method.

4. To evaluate median progression free survival (PFS)

PFS will be defined as the length of time from date of diagnosis to local or distant failure or death, whichever comes first. The distribution of PFS will be estimated with the Kaplan-Meier method.

5. To evaluate median overall survival with this neoadjuvant regimen

Overall survival (OS) will be defined as the length of time from date of diagnosis to death due to any cause. The distribution of OS will be estimated with the Kaplan-Meier method.

6. To evaluate pathologic complete response (pCR), percentage of viable tumor, percent fibrosis and histological grading of treatment response in surgical specimen with this neoadjuvant regimen compared to historical control rates with chemoradiation (CRT) alone and neoadjuvant SBRT.

Pathologic complete response is defined as absence of viable cells in the surgical specimen (i.e., ypT0N0M0) as determined at the time of pathological review. The pCR rate will be estimated with its exact 80% confidence interval in all patients who go on to surgical resection and in only those patients who completed the neoadjuvant regimen. Histological grading of treatment response will be determined. The distribution of the percentage of viable tumor and percentage of fibrosis in the surgical specimen will be estimated with a boxplot.

7. To evaluate radiographic response after receipt of neoadjuvant gemcitabine/nab-paclitaxel and hypofractionated radiotherapy (RT) in the neoadjuvant setting

The distribution of tumor response on radiologic imaging after neoadjuvant gemcitabine/nab-paclitaxel and after HIGRT on restaging will be tabulated based on tumor measurements.

8. To explore the effects of this neoadjuvant regimen on markers of tumor perfusion and hypoxia

Blood and urine will be obtained at baseline, prior to HIGRT, after HIGRT, and postoperatively. Urine will be collected in order to measure isoprostanes. Each of the markers will be statistically analyzed as

follows. Side-by-side boxplots will be used to describe the distribution of the biomarker across time. The mean of the biomarker (with 80% CI) will be plotted against time. We hypothesize that this neoadjuvant regimen will modulate plasma, serum and urine markers of angiogenesis and oxidative stress in patients

ADMINISTRATIVE AND ETHICAL CONSIDERATIONS

15.1 Regulatory and Ethical Compliance

This protocol was designed and will be conducted and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, the Declaration of Helsinki, and applicable federal, state, and local regulations.

15.2 DUHS Institutional Review Board and DCI Cancer Protocol Committee

The protocol, informed consent form, advertising material, and additional protocol-related documents must be submitted to the DUHS Institutional Review Board (IRB) and DCI Cancer Protocol Committee (CPC) for review. The study may be initiated only after the Principal Investigator has received written and dated approval from the CPC and IRB.

The Principal Investigator must submit and obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent form. The CPC should be informed about any protocol amendments that potentially affect research design or data analysis (i.e. amendments affecting subject population, inclusion/exclusion criteria, agent administration, statistical analysis, etc.).

The Principal Investigator must obtain protocol re-approval from the IRB within 1 year of the most recent IRB approval. The Principal Investigator must also obtain protocol re-approval from the CPC within 1 year of the most recent IRB approval, for as long as the protocol remains open to subject enrollment.

15.3 Informed Consent

The informed consent form must be written in a manner that is understandable to the subject population. Prior to its use, the informed consent form must be approved by the IRB.

The Principal Investigator or authorized key personnel will discuss with the potential subject the purpose of the research, methods, potential risks and benefits, subject concerns, and other study-related matters. This discussion will occur in a location that ensures subject privacy and in a manner that minimizes the possibility of coercion. Potential subjects will have the opportunity to contact the Principal investigator or authorized key personnel with questions, and will be given as much time as needed to make an informed decision about participation in the study.

Before conducting any study-specific procedures, the Principal Investigator or designee must obtain written informed consent from the subject or a legally acceptable representative. The original informed consent form will be stored with the subject's study records, and a copy of the informed consent form will be provided to the subject.

15.4 Study Documentation

Study documentation includes but is not limited to source documents, case report forms (CRFs), monitoring logs, appointment schedules, study team correspondence with sponsors or regulatory bodies/committees, and regulatory documents that can be found in the DCI-mandated "Regulatory Binder", which includes but is not limited to signed protocol and amendments, approved and signed

informed consent forms, FDA Form 1572, CAP and CLIA laboratory certifications, and clinical supplies receipts and distribution records.

Source documents are original records that contain source data, which is all information in original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents include but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial. When possible, the original record should be retained as the source document. However, a photocopy is acceptable provided that it is a clear, legible, and an exact duplication of the original document.

A case report form (CRF) (RECAP database) will be the primary data collection document for the study. Only the Principal Investigator and clinical research nurses are permitted to make entries, changes, or corrections in the CRF. For paper CRFs, errors will be crossed out with a single line, and this line will not obscure the original entry. Changes or corrections will be dated, initialed, and explained (if necessary). The Principal Investigator or authorized key personnel will maintain a record of the changes and corrections. For electronic CRFs, an audit trail will be maintained by the electronic CRF management system.

15.5 Privacy, Confidentiality, and Data Storage

The Principal Investigator will ensure that subject privacy and confidentiality of the subject's data will be maintained. Research Data Security Plans (RDSPs) will be approved by the appropriate institutional Site Based Research group.

To protect privacy, every reasonable effort will be made to prevent undue access to subjects during the course of the study. Prospective participants will be consented in an exam room where it is just the research staff, the patient and his family, if desired. For all future visits, interactions with research staff (study doctor and study coordinators) regarding research activities will take place in a private exam room. All research related interactions with the participant will be conducted by qualified research staff who are directly involved in the conduct of the research study.

To protect confidentiality, subject files in paper format will be stored in secure cabinets under lock and key accessible only by the research staff. Subjects will be identified only by a unique study number and subject initials. Electronic records of subject data will be maintained using a dedicated database (Redcap), which is housed in an encrypted and password-protected DCI file server. Access to electronic databases will be limited to the research study team in the department of radiation oncology. The security and viability of the IT infrastructure will be managed by the DCI and/or Duke Medicine.

Upon completion of the study, research records will be archived and handled per DUHS HRPP policy.

Subject names or identifiers will not be used in reports, presentations at scientific meetings, or publications in scientific journals.

15.6 Data and Safety Monitoring

Data and Safety Monitoring will be performed in accordance with the DCI Data and Safety Monitoring Plan. For a more detailed description of the DSMP for this protocol, refer to Section 12 (Sections 12.5 and 12.6 in particular) along with section 13.

15.7 Protocol Amendments

All protocol amendments must be initiated by the Principal Investigator and approved by the IRB prior to implementation. IRB approval is not required for protocol changes that occur to protect the safety of a subject from an immediate hazard. However, the Principal Investigator must inform the IRB and all other applicable regulatory agencies of such action immediately.

15.8 Records Retention

The Principal Investigator will maintain study-related records for the longer of a period of:

- at least two years after the date on which a New Drug Application is approved by the FDA
- at least two years after formal withdrawal of the IND associated with this protocol
- at least six years after study completion
-

15.9 Conflict of Interest

The Principal Investigator and Sub-Investigators must comply with applicable federal, state, and local regulations regarding reporting and disclosure of conflict of interest. Conflicts of interest may arise from situations in which financial or other personal considerations have the potential to compromise or bias professional judgment and objectivity. Conflicts of interest include but are not limited to royalty or consulting fees, speaking honoraria, advisory board appointments, publicly-traded or privately-held equities, stock options, intellectual property, and gifts.

The Duke University School of Medicine's Research Integrity Office (RIO) reviews and manages research-related conflicts of interest. The Principal Investigator and Sub-Investigators must report conflicts of interest annually and within 10 days of a change in status, and when applicable, must have a documented management plan that is developed in conjunction with the Duke RIO and approved by the IRB/IEC.

15.10 Registration Procedure

Not applicable for this study

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