Protocol Title: A Prospective, Phase II Trial of Molecular Profiling to Guide Neoadjuvant Therapy for Resectable and Borderline Resectable Adenocarcinoma of the Pancreas

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CLINICAL STUDY PROTOCOL

Protocol Number = MCW PRO 15565;

A Prospective, Phase II Trial of Molecular Profiling to Guide Neoadjuvant Therapy for Resectable and Borderline Resectable Adenocarcinoma of the Pancreas

Indication:	Resectable and Borderline Resectable Pancreatic Cancer
Phase:	Phase II

This is an investigator-initiated study. The principal investigator Kathleen Christians, MD (who may also be referred to as the sponsor-investigator), is conducting the study and acting as the sponsor. Therefore, the legal/ethical obligations of the principal investigator include both those of a sponsor and those of an investigator.

PROTOCOL SUMMARY

Study Title: A Prospective, Phase II Trial of Molecular Profiling to Guide Neoadjuvant Therapy for Resectable and Borderline Resectable Adenocarcinoma of the Pancreas

Phase: Phase II

Number of Patients: 130 patients

Study Objectives

Primary Objectives:

1. To compare the resectability rate (percent of all patients completing therapy to include surgical resection) using a neoadjuvant treatment regimen selected by molecular profiling to historical results with standard neoadjuvant therapy and surgical resection.

Secondary Objectives:

1. To compare overall survival (OS) rates of resectable and borderline resectable pancreatic cancer patients treated with molecularly targeted neoadjuvant therapy followed by surgical resection to historical controls treated with standard neoadjuvant therapy and surgical resection.
2. To compare progression-free survival (PFS) rates of patients with resectable and borderline resectable pancreatic cancer treated with molecularly targeted neoadjuvant therapy followed by surgical resection to historical controls treated with standard neoadjuvant therapy and surgical resection.
3. To determine the frequency with which molecular profiling of a patient's tumor by IHC identifies a target for an approved, commercially-available chemotherapeutic regimen.
4. To compare the molecular profile of pretreatment biopsies and resected tumors. We will compare the molecular profile obtained at time of diagnosis (FNA) with the molecular profile obtained from the resected specimen.
5. To determine the extent of histologic treatment response to targeted chemotherapeutic regimens in resected tumors.*
6. To determine the prognostic relevance of radiological response among patients undergoing neoadjuvant therapy.
7. To determine the ability to generate primary xenografts of pancreatic cancer from resected tumors.*
8. To compare quality and outcomes of both patterns of recurrence and ultimately survival in patients who receive radiation therapy at FH/MCW versus other institutions.

Overview of Study Design:

This is a phase II study for resectable and borderline resectable pancreatic cancer which utilizes molecular profiling of tissue samples from the pancreatic cancer (obtained either through EUS/FNA biopsy at the time of diagnosis or from the surgical specimen) to guide chemotherapy selection.

Study Population:

Resectable Pancreatic Cancer (defined by):

1. No evidence of extra pancreatic disease
2. No evidence of tumor-arterial abutment (celiac, SMA or HA)
3. If tumor induced narrowing of the SMV, PV, or SMV-PV confluence is present, it must be ≤50% of the diameter of the vessel
4. Ca 19-9 <5000, when bilirubin is ≤2

Borderline Resectable Pancreatic Cancer (to include at least one of the following):

1. Tumor abutment ≤180° of the SMA or celiac axis
2. Tumor abutment or encasement of a short segment of the HA
3. Tumor induced narrowing of SMV, PV or SMV-PV of >50% of the diameter of the vessel.
4. Short segment occlusion of the SMV, PV or SMV-PV with a suitable PV above and SMV below, for reconstruction
5. CT or MRI findings suspicious for, but not diagnostic of, metastatic disease (based on review at each site's weekly multidisciplinary pancreatic cancer conference)
6. Biopsy proven N1 disease (regional lymph nodes involved) from pre-referral biopsy or EUS-guided FNA
7. Resectable tumor and CA 19-9 ≥5000

Inclusion criteria:

Eligibility for Screening consent:

1. Have adenocarcinoma of the pancreas or highly suspicious for pancreas adenocarcinoma per CT or MRI
2. 18 years of age or older
3. Able to understand and provide written informed consent or have LAR Legally Authorized Representative

Eligibility for Treatment consent,:

1. Histologic diagnosis of pancreatic adenocarcinoma
2. Have an ECOG performance status ≤ 2
3. Resectable or borderline resectable adenocarcinoma of the pancreas based on CT or MRI findings
4. Total leukocytes ≥3 $x10^3/\mu L$

5. Absolute neutrophil count (ANC) ≥1.5x 10^3/μL
6. Hemoglobin ≥9 g/dL
7. Platelets ≥100 x 10e3/μL
8. Creatinine clearance ≥60 mL/min or creatinine ≤1.5 mg/dL
9. Total bilirubin ≤ 2 mg/dL: At two weeks from biliary decompression, if the subject's serum bilirubin remains greater than two, but has demonstrated a progressive decline, the subject may be enrolled into the trial and appropriate modification and dose adjustments will be made to the predicted regimen.

Exclusion Criteria:

1. Have received chemotherapy or chemoradiation within 5 years prior to study enrollment
2. Have any previous history of another malignancy (other than cured basal or squamous cell carcinoma of the skin or cured in-situ carcinoma of the cervix) within 5 years of study enrollment
3. Uncontrolled co morbidities including, but not limited to, ongoing or active serious infection, symptomatic congestive heart failure, unstable angina, unstable cardiac arrhythmias, psychiatric illness, excessive obesity, or situations that would limit compliance with the study requirements or the ability to willingly give written informed consent
4. Known HIV, HBV, or HCV infection
5. Pregnant or breast-feeding patients or any patient with child-bearing potential not using contraception 4 weeks prior to treatment

Duration of Study: Accrual period: Approximately 48 months.

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ABBREVIATIONS

ADC	apparent diffusion coefficient
ALKP	alkaline phosphatase
ALT/SGPT	alanine transaminases
ANC	absolute neutrophil count
APTT	activated partial thromboplastin time
AST/SGOT	aspartate transaminases
CR	complete response
CRF	case report form
CT	computed tomography
CTCAE	common toxicity criteria for adverse events
ECOG	Eastern Cooperative Oncology Group
ERCC1	Excision Repair Cross-Complementation 1
EUS	endoscopic ultrasound
FNA	fine needle aspiration
FOLFOXIRI	irinotecan, oxaliplatin, leucovorin, 5-fluorouracil
Gem-XRT	gemcitabine and radiation
GGT	gamma glutamyl transferase
IRB	institutional review board
HA	hepatic artery
hENT1	human equilibrative nucleoside transporter 1
HIV	human immunodeficiency virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HPB	hepato-pancreatico-biliary
IHC/FISH	immunohistochemistry/fluorescence in situ hybridization (IHC/FISH)
LDH	lactate dehydrogenase
MPI	molecular profiling institute
N1	regional lymph nodes positive for tumor
NCI	national cancer institute

OS	overall survival
PBD	pancreatico-biliary disposition conference
PD	pancreaticoduodenectomy
PET	positron emission tomography
PFS	progression free survival
PR	partial response
PGD	progressive disease
PT	prothrombin time
PV	portal vein
PV-SMV	portal vein-superior mesenteric vein
RECIST	response evaluation criteria in solid tumors
RPMI	Roswell Park Memorial Institute (media)
RRM1	ribonucleotide reductase M1
SD	stable disease
SMA	superior mesenteric artery
SMV	superior mesenteric vein
SPARC	Secreted Protein And Rich in Cysteine
SUV	Standardized Uptake Value
TOP1	Topoisomerase 1 inhibitor
TYMS	Thymidylate synthase
ULN	upper limits of normal
XRT	radiation

1. INTRODUCTION

1.1. Background

Pancreatic cancer is the fourth leading cause of cancer death in the United States. There were 43,140 estimated new cases of pancreatic cancer in 2010 and 36,800 will succumb to this disease. Despite two decades of advances in imaging, diagnostics, and perioperative and intraoperative care, the actual 5-year survival rate of patients with small tumors, no lymphadenopathy and who are completely resected remains <30%.[1] These sobering statistics have led clinicians to search for new modalities and/or sequencing of therapy as part of a multidisciplinary approach to pancreatic cancer treatment.

Neoadjuvant, as opposed to adjuvant, therapy allows delivery of therapy to a well-vascularized tumor, ensuring that the drug can reach the tumor. It allows for the completion of therapy prior to surgery to prevent patient drop-out due to perioperative complication. Neoadjuvant therapy also acts as a selection tool for optimal surgical candidates by identifying aggressive tumor biology prior to surgery and therefore selecting out those who will not benefit from resection. Indeed, the recent report of gemcitabine-based preoperative (neoadjuvant) therapy has demonstrated the most favorable patient survival reported in a prospective trial.[2] More recently, there has been an increase in interest in developing anti-cancer agents which are targeted, such as Herceptin against HER2/neu in breast cancer, and bevacizumab against VEGF and tyrosine kinase inhibitors against GIST tumors. In contrast to indiscriminate applications of chemotherapy, targeted therapies developed based on tumor molecular profiles have been effective in several solid organ tumors. Similarly, in pancreatic cancer, the identification of key molecular targets may increase the efficacy of existing systemic agents by delivering the appropriate chemotherapy to the most vulnerable tumors.

The most common chemotherapeutic agents used in pancreatic cancer include gemcitabine, platinum agents, irinotecan, and 5-fluorouracil (5-FU) derivatives. In review of the literature, six specific molecular targets have been identified which are predictive of chemo sensitivity to these agents in *in vitro* and *in vivo* models. Specifically, low thymidylate synthase (TYMS) levels predict efficacy of 5-FU-based therapies and Capecitabine. Excision repair cross-complementing (ERCC1) protein repairs DNA damage caused by platinum agents. As a result, low ERCC1 protein levels have been demonstrated to predict efficacy of platinum agents. Similarly, low ribonucleotide reductase M1 (RRM1) predicts efficacy of gemcitabine, and elevated SPARC predicts sensitivity to nab-paclitaxel. Polymorphisms of topoisomerase I (TOP1) have been implicated in irinotecan resistance in lung and colorectal cancer.[3,4,5,6] hENT1 is a major transporter of gemcitabine and low levels are associated with gemcitabine resistance. In addition SMAD4 expression has been identified as a predictor of local versus distant disease progression in pancreatic cancers.[7,8]

1.2. Proposed Therapeutic Intervention

This protocol uses state-of-the-art immunohistochemistry (IHC) to determine if molecular targets are present in a patient's tumor. Then, chemotherapeutic regimens will be individualized and optimized for each patient's tumor, based on the molecular characterization of these targets. Success of the approach will be measured by comparing resectability rates, overall survival and progression-free survival for the study patients to historical data (i.e. gemcitabine or capecitabine-based chemo radiation for resectable patients and combined modality therapy for borderline resectable patients).[2,9] Prior to chemotherapy, radiation or surgery, the patient will consent to providing a specimen by (Endoscopic Ultrasound Fine Needle Aspiration) EUS/FNA or traditional biopsy for molecular profiling to determine the neoadjuvant therapy agent(s) of choice. Postoperatively the surgical specimen will also be profiled to guide any potential adjuvant regimen. We have previously shown proof of concept in our feasibility study entitled *Molecular Profiling of Endoscopic Ultrasound Fine Need Aspiration Specimens in Pancreas Cancer: A Feasibility Study.*[10]

2. OBJECTIVES AND STUDY DESIGN

2.1. Objectives

2.1.1. Primary Objective

The primary objective is to compare the resectability rate (percent of all patients completing therapy to include surgical resection) using a neoadjuvant treatment regimen selected by molecular profiling to historical results with standard neoadjuvant therapy and surgical resection.

2.1.2. Secondary Objectives (objectives noted by an asterisk (*) will be pursued only at the coordinating site)

1. To compare overall survival (OS) rates of resectable and borderline resectable pancreatic cancer patients treated with molecularly targeted neoadjuvant therapy followed by surgical resection to historical controls treated with standard neoadjuvant therapy and surgical resection.
2. To compare progression-free survival (PFS) rates of patients with resectable and borderline resectable pancreatic cancer treated with molecularly targeted neoadjuvant therapy followed by surgical resection to historical controls treated with standard neoadjuvant therapy and surgical resection.
3. To determine the frequency with which molecular profiling of a patient's tumor by IHC identifies a target for an approved, commercially-available chemotherapeutic regimen.

4. To compare the molecular profile of pretreatment biopsies and resected tumors. We will compare the molecular profile obtained at time of diagnosis (FNA) with the molecular profile obtained from the resected specimen.
5. To determine the extent of histologic treatment response to targeted chemotherapeutic regimens in resected tumors.*
6. To determine the prognostic relevance of radiological response among patients undergoing neoadjuvant therapy.
7. To determine the ability to generate primary xenografts of pancreatic cancer from resected tumors.*
8. To compare quality and outcomes of both patterns of recurrence and ultimately survival in patients who receive radiation therapy at FH/MCW versus other institutions.

2.2. Study Design

This is an open-label, multi-institution, phase II study in patients with resectable and borderline resectable pancreas cancer. MCW will be the coordinating site and University of Cincinnati will be a participating site. Patients will be staged with laboratory tests, contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) of the abdomen, a chest radiograph or contrast enhanced chest CT, and PET scan. MRI's and PET scans are at the physician's discretion. At initial staging, each patient will be classified resectable or borderline resectable based on review of all CT or MRI images (see sections 3.1.1 and 3.1.2 for definitions).

A patient is eligible for screening for this study when his/her disease is designated highly suspicious for cancer of the pancreas. After signing the screening consent form, patients will undergo EUS/FNA or have a tumor biopsy from a prior FNA or laparotomy/laparoscopy available for molecular profiling. When FNA (or previous biopsy) histology confirms pancreatic adenocarcinoma, the patient is eligible to participate in the study and will sign the enrollment consent form. Molecular profiling will be performed on tumor biopsies from approximately 288 eligible patients. Of these 288, 168 patients will sign enrollment consent but for clinical reasons only 130will begin treatment. Most patients will be enrolled at the coordinating site. IHC will be performed to assess specific molecular targets on tumor biopsies. It is expected that molecular targets will be identified in approximately 70% of tumor biopsies (i.e. 120 patients). Study patients will be treated neoadjuvantly with commercially available systemic therapy assigned on the basis of disease stage (resectable or borderline resectable) and identified molecular targets. No investigational treatments will be administered. Study patients who have no molecular targets identified on pre-treatment FNA/biopsy will be treated with neoadjuvant therapy according to current best standard of care.[2,9]

Patients whose disease is stable or responding by biochemical, clinical, and radiographic measures will be offered resection. Patients whose disease demonstrates progression but are still considered technically operable may receive additional therapy prior to resection *(see figures A page 48 and B page 49).* Patients whose disease demonstrates progression beyond operability will be taken off study. Treatment response will be evaluated in a multi-disciplinary setting and assessment of operability will be made at the discretion of the treating surgeon and include the following components: (1) feasibility of surgical resection, (2) decline in Ca19-9 levels (in patients for whom Ca19-9 is evaluable), and (3) acceptable performance status.

All study patients who proceed to surgery will undergo laparoscopy at the time of surgery to assess for occult metastases. Surgical resection will be performed using a standard technique[11] and patients will be followed for major surgical complications. Resectability rate, which measures the study's primary objective, is the proportion of patients who undergo a successful PD as compared to all patients who initiate neoadjuvant therapy.

Standardized histologic evaluation of the resected specimen will be performed. Histologic response to preoperative therapy will be graded (see Appendix B).[12]Molecular profiling will also be performed on the surgical specimen. Study patients will be restaged and will be given up to 4 months adjuvant therapy on study with restaging after each 2 months of therapy. If, at any point during restaging, the patient's disease has recurred, he/she will come off treatment and remain in follow-up for survival.

Study patients whose cancer does not recur after adjuvant therapy will be followed with serial CT scan and laboratory tests at 3 month intervals (plus or minus a 1 month window) to assess for disease recurrence and survival for the first 18 months following end of treatment and then at 6 month intervals thereafter until 5 years from date on study. Patients whose disease recurs during follow-up will remain in follow-up for survival only. If patients develop metastatic disease that is amenable to minimally invasive biopsy or resection, surgery may be considered to obtain tissue for further molecular characterization.

Sample size for screening is estimated at 288. Sample size for treatment will be 168 patients accrued over 4 years of which only 130patients will actually begin treatment. Details on sample size and power are included in Statistical Methods, Section 11.

Essential data will be collected while the patient is on study in order to evaluate the study objectives. This data will be collected directly from the patient's medical record and/or from the HPB Clinical Database. Relevant safety data concerning adverse events will also be collected. Whenever possible, initial staging and all restaging will be completed at the study site. Surgery must be performed by the

site's pancreatic cancer team. All nonsurgical therapies may be performed under the direction of the individual patient's local oncologists.

Several translational correlates are incorporated into the study design to further characterize the primary tumor genotype as well as to evaluate the accumulation of genetic alterations associated with the development of metastatic disease. After pathologic evaluation is complete, resected specimens of both primary and metastatic lesions will undergo repeat molecular profiling to evaluate for changes in molecular phenotype. To prepare the resected tumor for further molecular characterization, resected tumors will be expanded using a direct xenograft model.

2.2.1. Treatment Strategy

The treatment delivered to each patient will be first determined by clinical stage of disease (resectable vs. borderline resectable - see 3.1.1 and 3.1.2 for definitions) as summarized by *Figure A: page 48 (resectable) and Figure B: page 49 (borderline resectable).* All patients will undergo EUS/FNA biopsy and, based on the outcome of the molecular profiling analysis of the biopsy, treatment will be assigned as summarized in Figure C. In particular, tumor specimens will be evaluated for expression of RRM1, ENT1, TYMS, TOP1, ERCC1, SPARC and SMAD4. The staining pattern of the STREET panel will be reviewed in a multi-disciplinary conference at the coordinating site and a final treatment plan determined. The treatment plan will be communicated to the Principal Investigator or his/her designee at the participating site and to treating physicians. (see Letter Formats, Appendix M)

Research may take place in an inpatient or outpatient setting. The research-only procedures include the extra FNA passes, molecular profiling, and collection of blood at several time points throughout the study. Molecular profiling will be conducted only at the coordinating site, FH/MCW. Extra FNA passes and collection of blood at several time points throughout the study will be conducted at the enrolling site (FH/MCW or University of Cincinnati). Specimen collection will be conducted by the Surgical Oncology Tissue Bank staff or the Clinical Cancer Center Clinical Trials Office lab.

Procedures that this research encompasses but are standard of care (imaging including MRI, PET scan, Chest X-ray and CT Scans; Endosopic Ultrasound-guided Fine Needle Aspiration (EUS FNA; blood tests, medical team consultations, pregnancy test prior to chemotherapy and prior to surgery, chemotherapy, chemo-radiation therapy) may take place at FH/MCW or at another cancer treatment location. Surgery (pancreatico-duodenectomy) will be standard cancer care treatment and take place at the patient's enrolling site (FH/MCW or University of Cincinnati).

Those administering treatment will be deemed qualified to administer per Froedtert policy and/or MCW policy.

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TABLE 1:

THRESHOLD VALUES USED FOR IMMUNOCHEMISTRY INTERPRETATION					
Biomarker	**Intensity**		**Percent Stain**	**Interpretation**	**ACTION**
RRM1	**>=2+**	**AND**	**>=50%**	**HIGH**	**No Gem**
RRM1	**>=2+**	**AND**	**<50%**	***MODERATE***	**Gem**
RRM1	**<2**		**?**	**LOW**	**Gem**
RRM1	**0**			**NEGATIVE**	**Gem**
ENT1	**>=2**	**AND**	**>=25%**	**POSITIVE**	**Gem**
ENT1	**<2**	**OR**	**<25%**	**LOW**	**Gem**
ENT1	**0**			**NEGATIVE**	**No Gem**
TYMS	**>=2**	**AND**	**>=30%**	**HIGH**	**No 5-FU**
TYMS	**>=2**	**AND**	**<30%**	**MODERATE**	**5-FU**
TYMS	**1+**	**AND**	**>=25%**	**MODERATE**	**5-FU**
TYMS	**1+**	**AND**	**<=25%**	**LOW**	**5-FU**
TYMS	**0**			**NEGATIVE**	**5-FU**
TOP1	**>=2**	**AND**	**>=30%**	**HIGH**	**Irinotecan**
TOP1	**<2**	**OR**	**<30%**	**LOW**	**No Irinotecan**
TOP1	**0**			**NEGATIVE**	**No Irinotecan**
ERCC1	**3**			**HIGH**	**No Plat**
ERCC1	**2**	**AND**	**≥50%**	**HIGH**	**No Plat**
ERCC1	**2**	**AND**	**<50%**	**LOW**	**Platinum**
ERCC1	**0-1**			**LOW**	**Platinum**

SPARC	**>=2+**	**OR**	**>=30%**	**HIGH**	**nab**
SPARC	**<2+**	**AND**	**<30%**	**LOW**	**nab**
SPARC	**0**			**NEGATIVE**	**no nab**
SMAD4	**Intact**			**POSITIVE**	**No further therapy**
SMAD4	**Loss**			**NEGATIVE**	**Gem**

All patients who undergo neoadjuvant therapy and have disease stabilization or response, or do not progress to an inoperable state will undergo surgery. Neoadjuvant therapy must be initiated within 0-4 weeks after the enrollment consent is signed.

Adjuvant therapy will be administered as summarized in either *Figure D (page 51)* or *Figure E (page 52)*. Adjuvant therapy must be initiated within 4-12 weeks from date of surgery. Reference regimens will be used and no investigational treatments will be administered. If a molecular target cannot be identified by molecular profiling analysis, the patient will be treated with the best available therapies. The recommended treatment will take into account input from the medical oncology investigators, patient performance status, co-morbidities, and contraindications. When necessary, other relevant factors concerning the patient's clinical history and current medical literature will also be taken into consideration. The schema of biomarker and corresponding agents in *Figures C (page* ***Error! Bookmark not defined.****), D (page 51) and E (page 52)* will be periodically updated as methodologies and therapies are approved by the FDA. Each site will notify its respective IRB of changes made to the treatment strategies.

Throughout treatment on this protocol, dose modifications, supportive care, and treatment of chemotherapy-related toxicity will be made at the physician's discretion following manufacturer's guidelines (see Appendix F) and standard supportive care (Appendix L). If insurance denies coverage for the standard treatment that has been identified per the protocol, then another standard treatment will be identified by the investigator within the same schema pathway as the denied treatment (see Figure C, D or E).

2.2.2. [Neoadjuvant] Pre-operative Pathway for <u>Resectable</u> Patients

Patients with resectable pancreatic cancer will receive the following preoperative therapy: *(refer to Fig. A, p. 46)*

1. For resectable patients where molecular profiling is predictive:

- 6-8 weeks of best profile-directed therapy
- Restaging
- In the absence of disease progression - surgery

2. For resectable patients whose specimen is adequate but molecular profiling is not predictive (profile not predictive) or for inadequate specimens (target not identified):

- Gemcitabine or Capecitabine-based chemo radiation
- Restaging
- In the absence of disease progression – surgery – which should occur 3-6 weeks after Chemotherapy completion

2.2.3. [Neoadjuvant] Pre-operative Pathway for <u>Borderline</u> <u>Resectable</u> Patients

Patients with borderline resectable pancreatic cancer will receive the following preoperative therapy: *(refer to Fig. B, page 47)* * If at any restaging, unequivocal distant disease progression is identified on imaging patients will be considered to have progressive disease and proceed to off study follow-up.

1. For borderline resectable patients where molecular profiling is predictive:

- 6-8 weeks of best profile-directed systemic therapy
- Restaging*
- Chemo radiation
- Restaging*
- Surgery

2. For borderline resectable patients whose molecular profiling is successful, but a target is not predicted. (profile not predictive):

- Gemcitabine or Capecitabine-based chemo radiation
- Restaging*
- Surgery

3. For borderline resectable patients with inadequate specimens (target not identified):

- FOLFIRINOX (4 cycles)
- Restaging*
- Chemo radiation
- Restaging*

- Surgery which should occur 3-6 weeks after chemotherapy completion

2.2.4. [Neoadjuvant] Preoperative Treatment

2.2.4.1 [Neoadjuvant] Preoperative FNA Profiling Schema (Figure C page **Error! Bookmark not defined.**)

2.2.4.2. [Neoadjuvant] Preoperative Treatment Regimens

NOTE: all pre-operative regimens (a-j) are identical to post-operative regimens (a-j); and post-operative regimens (k-n) are not pre-operative options.

When dose reductions are necessary, the treating physician will refer to current package inserts. Dose reductions will be at the discretion of the treating physician who is expected to be in contact with the study team.

a. Gemcitabine-based XRT Treatment Regimen:

Chemotherapy: Gemcitabine 400mg/m$^{2\ IV}$ at fixed dose rate, infused over 40 minutes on Day 1 (day -2 to +1), and then weekly x 6 during radiation therapy.

Radiation: External-beam radiation therapy will be delivered 5 days/week over 5.5 weeks with 6-18-MeV photons. Using 3D conformal or IMRT techniques, patients will receive a total dose of 50.4 Gy prescribed to the 95% isodose at 1.8 Gy/fraction (28 fractions).2

b. Capecitabine-based XRT Treatment Regimen:

Chemotherapy: Capecitabine 825 mg/m^2 orally twice daily on Day 1 and continuing Monday through Friday during radiation.

Radiation: External-beam radiation therapy will be delivered 5 days/week over 5.5 weeks with 6-18-MeV photons. Using 3D conformal or IMRT techniques, patients will receive a total dose of 50.4 Gy prescribed to the 95% isodose at 1.8 Gy/fraction (28 fractions).[13]

c. FOLFIRINOX Treatment Regimen:

FOLFIRINOX: On Day 1, oxaliplatin 85 mg/m^2 IV infused over 120 minutes, irinotecan 180 mg/m^2 IV infused over 90 minutes, leucovorin 400 mg/m^2 IV infused over 120 minutes, followed by bolus fluorouracil (5-FU) 400 mg/m^2 IV; followed by 5-FU 2,400 mg/m^2 IV as a 46-hour continuous infusion, cycled every 2 weeks for a total of 2 months of therapy.[14]

d. FOLFIRI Treatment Regimen:

FOLFIRI: On Day 1, Irinotecan 180 mg/m^2 IV infused over 90 minutes, leucovorin 400 mg/m^2 IV infused over 120 minutes, followed by bolus fluorouracil (5-FU) 400 mg/m^2 IV; then 5-FU 2,400 mg/m^2 IV as a 46-hour continuous infusion, cycled every 2 weeks for a total of 2 months of therapy.

e. Gemcitabine w/irinotecan Treatment Regimen:

Gemcitabine 1,000 mg/m^2 IV infused over 30-40 minutes followed immediately by irinotecan 100 mg/m^2 IV infused over 90 minutes, both administered on Days 1 and 8 and cycled every 3 weeks for a total of 2 cycles. [16]

f. Gemcitabine w/ oxaliplatin Treatment Regimen:
Gemcitabine 1,000 mg/m^2 IV infused over 30-40 minutes on Day 1 and a 2-hour infusion of oxaliplatin 100mg/m^2 IV on day 2, cycled every two weeks for a total of 3 cycles.[17]

g. Gemcitabine w/ cisplatin Treatment Regimen:
Gemcitabine 750 mg/m^2 IV infused over 30-40 minutes and cisplatin 30 mg/m^2 IV infused over 30 minutes, cycled every 2 weeks for 3 cycles.[18]

h. Gemcitabine/capecitabine Treatment Regimen:
Gemcitabine 1000 mg/m^2 IV infused over 30-40 minutes Days 1, 8 and 15 and capecitabine 825mg/m^2 orally twice daily on days 1- 21 cycled every 4 weeks for a total of 2 cycles.[19]

i. Gemcitabine/nab-paclitaxel Treatment Regimen:
Nab-paclitaxel 125 mg/m^2 IV infused over 30-40 minutes (maximum infusion time not to exceed 40 minutes) followed by gemcitabine 1000mg/m^2 IV infused over 30-40 minutes on Days 1, 8, and 15, cycled every 28 days for a total of 2 cycles.[21]

j. Capecitabine/nab-paclitaxel Treatment Regimen:
Nab-paclitaxel 125 mg/m2 IV on day 1, 8) and capecitabine 825 mg/m2 PO BID days 1-14 on a Q3 week cycle. Repeat for 3 cycles.[22]

2.2.4.3. Disease Progression on Therapy

If the patient has <u>resectable</u> disease that progressed locally, but remains <u>resectable</u> and had:

1. Induction chemotherapy, then the patient may be given chemoXRT based on multidisciplinary review. Restaging will be performed upon completion of therapy to assess resectability.
2. ChemoXRT, then proceed to surgery.
3. ChemoXRT with development of indeterminate liver or lung lesions and/or rising

   CA19-9: Add an additional 2 months of chemotherapy per PI discretion.

   Restaging will be performed upon completion of therapy to assess resectability.

If the patient had <u>borderline resectable disease</u> that <u>progressed to locally advanced</u>:

1. Remove from treatment and place patient on survival follow up.

If the patient has unequivocal metastatic disease on imaging studies:

1. The patient will be considered inoperable, removed from treatment , and followed for survival.

2.2.5. [Adjuvant] Pathways for all patients after Postoperative Restaging

1. No evidence of disease, target is identified in surgical specimen, and molecular profiling is predictive:

If neoadjuvant ChemoXRT has not been given: 2-4 months of best profile-directed therapy (*See Figure D page 51).*

If neoadjuvant ChemoXRT has been given: 4 months of best profile-directed therapy. *(See Figure E page 52).*

2. No evidence of disease: target is not identified in the surgical specimen or target is identified in the surgical specimen and molecular profiling is not predictive:

If neoadjuvant ChemoXRT has not been given:

2 months of Chemo/XRT or

2 months ChemoXRT and standard chemotherapy (*See Figure D page 51).*

If neoadjuvant ChemoXRT has been given:

4 months of systemic therapy – target not identified or SMAD4 loss or

No further therapy – SMAD4 intact *(See Figure E page 52).*

3. Evidence of disease recurrence or metastasis:

Off-treatment, and moved to follow-up (see Section 6.5 for Follow-up).

2.2.6. [Adjuvant] Postoperative Treatment

2.2.6.1 [Adjuvant] Postoperative Profiling Schema no prior XRT (Figure D page 51)

2.2.6.2 [Adjuvant] Postoperative Profiling Schema when patient DID receive pre-operative XRT (Figure E page 52)

2.2.6.3. [Adjuvant] Postoperative Treatment Regimens

NOTE: all post-operative regimens (a-j) are identical to pre-operative regimens (a-j); and post-operative regimens (k-n) are not pre-operative options:

a. Gemcitabine-based XRT Treatment Regimen:

Chemotherapy: Gemcitabine 400mg/m^2 IV at fixed dose rate, infused over 40 minutes on Day 1 (day -2 to +1), and then weekly x 6 during radiation therapy.

Radiation: External-beam radiation therapy will be delivered 5 days/week over 5.5 weeks with 6-18-MeV photons. Using 3D conformal or IMRT techniques, patients will receive a total dose of 50.4 Gy prescribed to the 95% isodose at 1.8 Gy/fraction (28 fractions).2

b. Capecitabine-based XRT Treatment Regimen:

Chemotherapy: Capecitabine 825 mg/m^2 orally twice daily on Day 1 and continuing Monday through Friday during radiation.

Radiation: External-beam radiation therapy will be delivered 5 days/week over 5.5 weeks with 6-18-MeV photons. Using 3D conformal or IMRT techniques, patients will receive a total dose of 50.4 Gy prescribed to the 95% isodose at 1.8 Gy/fraction (28 fractions). [13]

c. FOLFIRINOX Treatment Regimen:

FOLFIRINOX: On Day 1, oxaliplatin 85 mg/m^2 IV infused over 120 minutes, irinotecan 180 mg/m^2 IV infused over 90 minutes, leucovorin 400 mg/m^2 IV infused over 120 minutes, followed by bolus fluorouracil (5-FU) 400 mg/m^2 IV; followed by 5-FU 2,400 mg/m^2 IV as a 46-hour continuous infusion, cycled every 2 weeks for a total of 2 months of therapy.[14]

d. FOLFIRI Treatment Regimen:

FOLFIRI: On Day 1, Irinotecan 180 mg/m^2 IV infused over 90 minutes, leucovorin 400 mg/m^2 IV infused over 120 minutes, followed by bolus fluorouracil (5-FU) 400 mg/m^2 IV; then 5-FU 2,400 mg/m^2 IV as a 46-hour continuous infusion, cycled every 2 weeks for a total of 2 months of therapy.[20]

e. Gemcitabine w/ irinotecan Treatment Regimen:

Gemcitabine 1,000 mg/m^2 IV infused over 30-40 minutes followed immediately by irinotecan 100 mg/m^2 IV infused over 90 minutes, both administered on Days 1 and 8 and cycled every 3 weeks for a total of 2 cycles. [16]

f.. Gemcitabine w/ oxaliplatin Treatment Regimen:

Gemcitabine 1,000 mg/m^2 IV infused over 30-40 minutes on Day 1 and a 2-hour infusion of oxaliplatin 100mg/m^2 IV on day 2, cycled every two weeks for a total of 3 cycles. [17]

g. Gemcitabine w/ cisplatin Treatment Regimen:

Gemcitabine 750 mg/m^2 IV infused over 30-40 minutes and cisplatin 30 mg/m^2 IV infused over 30 minutes, cycled every 2 weeks for 3 cycles. [18]

h. Gemcitabine/capecitabine Treatment Regimen:

Gemcitabine 1000 mg/m^2 IV infused over 30-40 minutes Days 1, 8 and 15 and capecitabine 825mg/m^2 orally twice daily on days 1- 21, cycled every 4 weeks for a total of 2 cycles. [19]

i. Gemcitabine/nab-paclitaxel Treatment Regimen:

Nab-paclitaxel 125 mg/m^2 IV infused over 30-40 minutes (maximum infusion time not to exceed 40 minutes) followed by gemcitabine 1000mg/m^2 IV infused over 30-40 minutes on Days 1, 8, and 15, cycled every 28 days for a total of 2 cycles. [21]

j. Capecitabine/nab-paclitaxel Treatment Regimen:

Nab-paclitaxel 125 mg/m2 IV on day 1, 8 and

capecitabine 825 mg/m2 PO BID days 1-14 on a Q3 week cycle. Repeat for 3 cycles.[22]

k. Gemcitabine alone Treatment Regimen:

Gemcitabine 1000 mg/m^2 IV infused over 30-40 minutes, cycled every week times 3 weeks; 1 week off and then 3 more weeks for a total of 6 cycles. [23]

l. Capecitabine alone Treatment Regimen:

Oral capecitabine 1,250 mg/m(2) administered twice daily (2,500 mg/m(2)/d) in 3-week cycles consisting of 2 weeks of treatment followed by 1 week without treatment. [24]

m. 5FU alone Regimen:

Give per physician discretion standard of care. [15,24]

n. No further treatment recommended:

Molecular profiling suggests that no further targets are identified.

2.2.7. Outcome Measures

Disease status will be assessed at each restaging evaluation (clinical parameters, CT and/or MRI imaging, tumor markers). If progression is not observed at the end of study therapy, patients will be assessed every 3 months (plus or minus a 1 month window) for the first 18 months after study therapy has ended and then every 6 months until 5 years after enrollment/registration. PFS and OS will be reported. Adverse events will be monitored and collected in a summary format summary format as delineated in the study calendar (sections 6.6 and 6.7). See Sections 8.1 and 8.2 for adverse event reporting details.

3. PATIENT SELECTION

3.1. Screening and Eligibility Criteria

To be eligible to sign a screening consent (see Appendix I: Eligibility Checklist) patients must:

- Have adenocarcinoma of the pancreas or highly suspicious for pancreas adenocarcinoma per CT or MRI
- 18 years of age or older
- Able to understand and provide written informed consent or have Legally Authorized Representative (LAR)

To be eligible to sign enrollment consent, the patient must have a confirmed diagnosis of pancreatic adenocarcinoma. After enrollment consent is signed, treatment eligibility is confirmed. If treatment eligibility is not met, the patient will be treated off study and will not be followed on study.

3.1.1. Treatment Eligibility Criteria:

- Enrollment consent must have been signed.
- Have an ECOG performance status ≤ 2
- Have biopsy-proven, resectable (defined in Section 3.1.2) or borderline resectable (defined in Section 3.1.3) adenocarcinoma of the pancreas based on CT or MRI findings as detailed in Sections 3.1.2 and 3.1.3. Biopsy must be / have been completed within 2 months prior to molecular profiling.
- Have adequate organ and bone marrow function as defined by:
    - total leukocytes ≥ 3 x$10^3/\mu L$
    - absolute neutrophil count (ANC) ≥ 1.5x $10^3/\mu L$
    - hemoglobin ≥ 9 g/dL
    - platelets ≥ 100 x 10e3/μL
    - creatinine clearance ≥ 60 mL/min or creatinine ≤ 1.5 mg/dL
    - bilirubin ≤ 2 mg/dL: At two weeks from biliary decompression, if the subject's serum bilirubin remains greater than two, but has demonstrated a progressive decline, the subject may be enrolled into the trial and appropriate modification and dose adjustments will be made to the predicted regimen. Eligibility of subjects whose bilirubin levels remain elevated above 2, without demonstrating a downward trend, will be determined at the discretion of the trial PIs and their treatment assignment.
    - aspartate transaminases (AST/SGOT) ≤ 3 x ULN
    - alanine transaminases (ALT/SGPT) ≤ 3 x ULN

- Female patients must be post-menopausal for > 1 year, surgically sterile, or have a negative pregnancy test and used at least one form of contraception for 4 weeks prior to Day 1 of the study, during study treatment and during the first 4 months after study treatment is discontinued. Male patients must be surgically sterile or use barrier contraception during the study and for 4 months after the last dose of any study drug.

3.1.2.Definition of Resectable Pancreatic Cancer includes all of the following:

- No evidence of extra pancreatic disease
- No evidence of tumor-arterial abutment (celiac, SMA [superior mesenteric artery] or HA [hepatic artery])
- If tumor induced narrowing of the SMV [superior mesenteric vein], PV [portal vein] or SMV-PV [superior mesenteric-portal vein] confluence is present, it must be ≤50% of the diameter of the vessel
- Ca 19-9 <5000, when bilirubin is ≤2

3.1.3. Definition of Borderline Resectable Pancreatic Cancer

To include at least one of the following:

- Tumor abutment ≤180° of the SMA or celiac axis
- Tumor abutment or encasement of a short segment of the HA
- Tumor induced narrowing of SMV, PV or SMV-PV of >50% of the diameter of the vessel.
- Short segment occlusion of the SMV, PV or SMV-PV with a suitable PV above and SMV below, for reconstruction
- CT or MRI findings suspicious for, but not diagnostic of, metastatic disease (based on review at each site's weekly multidisciplinary pancreatic cancer conference)
- Biopsy proven N1 disease (regional lymph nodes involved) from pre-referral biopsy or EUS-guided FNA
- Resectable tumor and CA 19-9 ≥5000

3.1.4. Definition of Locally Advanced

- Artery: Tumor encasement (> 180°) of SMA or celiac artery
- Vein Occlusion of SMV, PV or SMV-PV without suitable vessels above and below the tumor to allow for reconstruction (no distal or proximal target for vascular reconstruction)

- Extra pancreatic disease: No evidence of peritoneal, hepatic, or extra-abdominal metastases

3.1.5. Definition of Metastatic Disease

- Evidence of peritoneal or distant metastases

3.2. Exclusion Criteria

Any patient with one or more of the following will be excluded:

- Have received chemotherapy or chemoradiation within 5 years prior to study enrollment
- Have any previous history of another malignancy (other than cured basal or squamous cell carcinoma of the skin or cured in-situ carcinoma of the cervix) within 5 years of study enrollment
- Uncontrolled co morbidities including, but not limited to, ongoing or active serious infection, symptomatic congestive heart failure, unstable angina, unstable cardiac arrhythmias, psychiatric illness, excessive obesity, or situations that would limit compliance with the study requirements or the ability to willingly give written informed consent
- Known HIV, HBV, or HCV infection
- Pregnant or breast-feeding patients or any patient with child-bearing potential not using contraception 4 weeks prior to treatment

4. INFORMED CONSENT

The principles of informed consent will be strictly adhered to as dictated by the policies and procedures of the local approving IRB. Screening consent for tumor biopsy and enrollment consent for participation in the study will be obtained and documented. Patients who develop metastatic disease may choose to participate in additional translational correlative studies and will be asked to sign a separate consent for tissue procurement and molecular analysis.

5. SCREENING AND ENROLLMENT

Investigators or their appropriate designees will identify potentially eligible patients from their clinics, patient self-referrals, or referrals from other clinicians. Inclusion/exclusion criteria will be reviewed and patient eligibility will be confirmed after both screening and enrollment consents are signed and screening is complete. Globally, it is expected that approximate 288 patients will sign screening consents; 168 will sign enrollment consents. Of those 168, we expect 38patients to exclude before treatment starts and 130 will start study treatment globally. Of these global patients, up to 10 patients will sign screening consents and up to 6 will sign enrollment consents at our participating site, the University of Cincinnati. Of those it is expected that up to 4-6 will start treatment at the University of Cincinnati.

If the patient (or LAR, legally authorized representative) agrees to study participation, first, he/she must provide signed informed consent for study screening. After signing a screening consent form, each patient will be assigned a unique subject number. The investigator will then request a biopsy (EUS/FNA preferred) to obtain a tumor sample for the study if not already available. The tumor biopsy must be performed within 2 months prior to analysis, and the patient must not have any intervening anticancer treatment between the time of the biopsy and the IHC and microarray analysis.

When histology from the tumor biopsy confirms pancreatic adenocarcinoma, the patient will sign the enrollment consent and be evaluated for all inclusion/exclusion criteria. If all criteria are met, the subject will undergo study treatment. Neoadjuvant treatment must be initiated 0-4 weeks after signing the enrollment consent form.

6. CLINICAL MEASUREMENTS AND PROCEDURES

6.1. Methodology for Obtaining FNA Specimen

Patients, who do not have biopsy-confirmed diagnosis of pancreatic cancer and a cell block available for molecular analysis, or, who have specimens that are inadequate for molecular characterization, mayundergo an EUS/FNA biopsy. During EUS/FNA, extra passes will be obtained for processing into cell blocks that will be utilized for molecular profiling.

The study laboratory manual describes the methodology to be followed by the endoscopist for obtaining FNA specimens. See *Laboratory Manual: Section 2: Fine Needle Aspirate Sample Collection* (Appendix J). The endoscopist may alter the procedure as required for clinical purposes as technology evolves.

6.2. Methodology for Processing FNA Specimen and Shipping to Coordinating Site

The cell blocks will be made at the site where the subject is enrolled. Slides will also be made at either the participating site or the coordinating site. The participating site will ship cell blocks and, if available, slides to the coordinating site. The study laboratory manual describes the methodology to be followed for processing FNA specimens and shipping. See *Laboratory Manual* (Appendix J). Laboratory procedures may be revised as required to maximize processing quality.

6.3. Characterization of Specimen

6.3.1. Overview

After a diagnosis of pancreatic adenocarcinoma has been histologically confirmed, the remaining cell block will be used to perform further characterization of the tumor using IHC for the targets of interest.

6.3.2. Immunohistochemistry

Immunohistochemical staining for MASPIN, S100P, RRM1, ENT1, TYMS, TOP1, ERCC1, SPARC, and SMAD4 will be performed using the available cell block. The antibodies will be purchased from commercially available sources and the staining procedure has been optimized on retrospective cell blocks. IHC evaluation will be made using appropriate positive and negative controls. (See Table 1 (page 20) for interpretation of staining intensity and percent stain).[26]

6.3.3. Molecular Analysis

If adequate specimen is available, RNA and/or DNA will be extracted from the available cell blocks. Gene expression will be done on the following genes: RRM1, ENT1, TYMS, TOP1,ERCC1, and SPARC. Expression levels will be normalized to GUSB which is a housekeeping control gene. Mutational analysis is done using a single pool of primers to perform multiplex PCR for preparation of amplicon libraries from genomic "hot spot" regions and/or all-exon coverage of genes that are frequently mutated in human cancer genes. (See the study Lab Manual for a representative list of these genes).

6.3.4 Communication with treating physicians regarding STREET profiled therapy

The staining pattern of the STREET panel will be reviewed in a multi-disciplinary conference at the coordinating site and a final treatment plan determined. The treatment plan will be communicated to the Principal Investigator or his/her designee at the participating site and to treating physicians.

6.3.5 Radiation Therapy Data Review

Unique to this study is that patients have been able to receive the nonsurgical components of their treatment either here at Froedtert and the FMLH/MCW affiliates or at outside institutions. There is interest in reviewing all of the radiation therapy data for quality, including adherence to the protocol radiation dose/volume guidelines as well as reviewing contouring of targets and organs at risk, dose volume histograms, and dose distributions, and correlating this with outcome. There is data from national cooperative postoperative radiation trials, used for the treatment of pancreatic cancer, which reveal the difference in local control and survival that adherence to protocol parameters and radiation quality can make. We would like the opportunity to extend this review to this protocol and specifically focus on the quality of the radiation delivered both here at FMLH/MCW and outside of our institution. This will entail obtaining all of the radiation treatment planning records from the participants in the study with review of the contours, dose distribution, dose volume histograms, and patterns of recurrence to support the impact on local control and survival that the quality of the radiation delivered in the neoadjuvant and adjuvant setting can make.

6.4. Study Assessments

Patients will be evaluated as outlined in the study schema (see Sections 6.6 and 6.7).

1. Prior to neoadjuvant therapy

2. After 2 months of neoadjuvant therapy if 4 months of neoadjuvant therapy are planned (responding or stable disease)
3. Prior to surgery with assessment of disease status (responding or stable disease) or progressing but still operable.
4. 1-3 months after surgery / prior to adjuvant treatment with assessment of disease status.
5. After 2 months of adjuvant therapy if 4 months of adjuvant therapy are planned.
6. After final study therapy is complete with assessment of disease status.
7. Hematology will include CBC with differential including platelet count and hemoglobin. Biochemistry will include ALT/SGPT, AST/SGOT, total bilirubin, and GFR or creatinine. Tumor markers will include Ca 19-9 (for patients who express Ca 19-9), and CEA.

6.5. Follow-up

If a subject discontinues for any reason, molecular profile results will be given to the subject's physician to consider alternative therapies.

- Patients with inoperable disease progression will come off treatment and be followed for survival every 6 months.
- For patients without inoperable disease progression at the end of therapy, tumor assessments are to be undertaken every 3 months (plus or minus a 1 month window) for the first 18 months, then every 6 months for years until 5 years from enrollment on study.

6.6 Schedule of Visits, Procedures and Laboratory Tests

Resectable Arm Schedule of Events

	Visit Number:	1	2	3	4	5	6	~7	~8	~9	~10	11-17+	NA
	Visit Name:	**Screen** 0 3 weeks	**Enroll / Stage** 0-4 wks	**Chemo or ChemoXRT** 5-12 weeks	**#1 Restage** 0-6 weeks	**Surgery** one day	**#2 Restage** 4-12 weeks	**Chemo** 5-12 weeks	**#3 Restage** 0-6 weeks	**Chemo or ChemoXRT** 5-12 weeks	**#4 Restage** 0-6 weeks	**On Study FU** q 12 weeks x 6, then q 6 mos	**Survivial FU** q 6 mos
SCREENING CONSENT		X											
Obtain tissue and ship to central site	biopsy must not be older than 2 months at time of molecular profiling	X					X						
Adverse event assessment		X	X		X		X		X		X		
AT Coordinating SITE ONLY Blood for research	collect prior to start of therapy (x) = may collect at OR and/or at any restage	X			(X)	(X)	(X)		(X)		(X)	(X)	
ENROLLMENT CONSENT sign **after** bx confims diagnosis; pt may still exclude la			X										
Imaging: CT abd & pelvis with Chest CT or Chest Xray (standard care acti		X			X		X		X		X	X	
◘Imaging: PET & MRI (per MD discretion) (standard care activity)		X			X								
STREET Profiling of tissue			X				X						
Multidisciplinary Review 🕮	Staging determined; when applicable, protocol-directed standard care tx recommendations provided to treating MD		X		X		X		X		X	X	
*Standard Care Activities	Demographics	X											
	Medical History	X											
	☼Phys Exam	X			X		X		X		X		
	Tumor markers Ca 19-9♦, CEA	X			X		X		X		X		
Most Recent	Hematology: CBC with differential including platelet count and hemoglobin	X			X		X		X		X		
Most Recent	Biochemistry: dALT/SGPT, AST/SGOT, AlkP, total bilirubin, GFR or creatinine	X			X		X		X		X		
	Pregnancy test - as per standard †	X†			X†		X†		X†				
	ECOG Performance Status !!		!! X		X		X		X		X		
Inclusion Checklist	confirm inclusion just prior to onset of tx		X										
Confirm weekly that scheduled treatment is on track (patients being treated outside MCW system only				X	X	X	X	X	X	X	X		
Survival assessment												X	X

~ RESECTABLE patients On Study will participate in Visits 1, 2, 3, 4, 5, 6 & 11-17+. Visits 7, 8, 9 & 10 may or may not occur depending on the molecular profile.

◘ MRI abd/pelvis using a 3.0 Tesla see Section 7.2.3. PET & MRI at Baseline & for RESECTABLE at restage 1; for BORDERLINE at restage 1 and/or restage 2.

🕮 When it is determined a patient's disease has progressed, the patient will move to off-study follow-up.

* Prior study labs and examinations are required within 6 weeks prior to treatment onset unless otherwise specified.

!! ECOG must be ≤ 2 at onset of initial treatment; ECOG above 2 after onset of initial treatment is captured in AE assessment.

☼ Physical Exam to include: vital signs, weight, review of systems, symptom assessment, and should be completed at least once from one staging to the next.

♦ Bilirubin must be ≤ 2 when measuring Ca19-9. Only necessary for patient who express the CA19-9.

6.7 Schedule of Visits, Procedures and Laboratory Tests	Visit Number:	1	2	3 ~	4 ~	5	6	7	8	9~	10~	11~	12~	13-19+	NA
Borderline Resectable Arm	Visit Name:	**Screen** 0 3 weeks	**Enroll / Stage** 0-4 weeks	**Chemotherapy** 8-12 weeks	**#1 Restage** 0-2 weeks	**Chemo XRT** 5-7 weeks	**#2 Restage** 3-6 weeks	**Surgery** one day	**#3 Restage** 4-12 weeks	**Chemotherapy** 8-12 weeks	**#4 Restage** 0-2 weeks	**Chemotherapy** 8-12 weeks	**#5 Restage** 0-2 weeks	**On Study FU** q 12 weeks x 6, then q 6 mos	**Survival FU** q 6 mos
SCREENING CONSENT		X													
Obtain tissue and ship to central site	biopsy must not be older than 2 months at time of molecular profiling	X							X						
Adverse event assessment		X	X		X		X		X		X		X		
AT Coordinating SITE ONLY Blood for research	collect prior to start of therapy (x) = may collect at OR and/or at any restage	X			(X)		(X)	(X)	(X)		(X)		(X)	(X)	
ENROLLMENT CONSENT	sign **after** bx confirmed diagnosis; pt may still exclude l		X												
Imaging: CT abd & pelvis with Chest CT or Chest Xray	(standard care acti	X			X		X		X		X		X	X	
◘Imaging: PET & MRI (per MD discretion)	(standard care activity)	X			X		X								
STREET Profiling of tissue			X						X						
Multidisciplinary Review 🕮	Staging determined; when applicable, protocol-directed standard care tx recommendations provided to treating MD		X		X		X		X		X		X	X	
*Standard Care Activites	Demographics	X													
	Medical History	X													
	☼Phys Exam	X			X		X		X		X		X		
Most Recent	Tumor markers Ca 19-9♦, CEA	X			X		X		X		X		X		
Most Recent	Hematology: CBC with differential including platelet count and hemoglobin	X			X		X		X		X		X		
Most Recent	Biochemistry: dALT/SGPT, AST/SGOT, AlkP, total bilirubin, GFR or creatinine	X			X		X		X		X		X		
	Pregnancy test - as per standard †	X†			X†		X†		X†		X†				
	ECOG Performance Status		!! X		X		X		X		X		X		
Inclusion Checklist	confirm inclusion just prior to onset of tx		X												
Confirm weekly scheduled treatment is on track	(patients beingtreated outside MCW system or			X	X	X	X	X	X	X	X	X	X		
Survival assessment														X	X

~ BORDERLINE patients On Study will participate in Visits 1, 2, 5, 6, 7, 8, 13-19+. Visits 3,4,9,10,11,& 12 may or may not occur depending on the molecular profile.

◘ MRI abd/pelvis using a 3.0 Tesla see Section 7.2.3. PET & MRI at Baseline & for RESECTABLE at restage 1; for BORDERLINE at restage 1 and/or restage 2.

🕮 When it is determined a patient's disease has progressed, the patient will move to off-study follow-up.

* Pre-study tests and examinations are required within 4 weeks prior to treatment onset unless otherwise specified.

!! ECOG must be < 2 at onset of initial treatment; ECOG above 2 after onset of initial treatment is captured in AE assessment.

☼ Physical Exam to include: vital signs, weight, review of systems, symptom assessment, and should be completed at least once from one staging to the next.

♦ Bilirubin must be ≤ 2 when measuring Ca19-9. Only necessary for patients who express the CA19-9.

7. ASSESSMENT OF ACTIVITY

7.1. Definition of Treatment Response

Response to neoadjuvant therapy will be assessed at the time of restaging and recorded as:

1. Clinical benefit: defined as stable or improved performance status
2. Biochemical benefit: defined as a stable or lower Ca19-9 in those patients whose Ca19-9 was abnormal at the start of therapy
3. Radiographic benefit: the absence of disease progression and a primary tumor which is smaller (as assessed by measurement of the maximum transverse diameter of the tumor)

All patients who receive at least 2 treatment cycles and undergo at least one on-study disease assessment or experience early progression will be considered evaluable for response.

7.2. Evaluation of Treatment Response

7.2.1. CT Imaging

Imaging studies will be reviewed at the respective site by abdominal imaging specialists. Tumors will be assessed at the established staging intervals by CT scan of the abdomen/pelvis and CT of chest or Chest X-ray. Treatment response will be classified by the RECIST version 1.1 criteria (see Appendix G). In addition, tumors will be assessed for conversion of tumor from borderline resectable to resectable based on previously defined criteria. For progression that is operable vs. inoperable progression see sections *3.1.2., 3.1.3., and 3.1.4.*

7.2.2. PET-Scan Imaging

^{18}F-FDG PET scans from the coordinating site will be evaluated semi quantitatively by SUV analysis. SUV's normalized to injected activity, patient's body weight and hyper metabolic activity in the cerebellum will be calculated from the mean activity concentration in the tumor VOIs between 40 and 70 min after injection, which is the last time frame of the dynamic scan. A volume-weighted mean value of each PET scan will be derived from all lesions to give one average SUV (SUV_{avg}) for each PET scan. The percentage change in SUV between the ^{18}F-FDG PET at baseline and at completion of neoadjuvant therapy will be calculated. PET scans are per physician discretion.

7.2.3. Diffusion Weighted MRI Imaging

At the coordinating site, diffusion-weighted MRI of the abdomen will be performed by a commercially available 3.0 tesla MRI system with a coil combination as appropriate for patient body habitus. The protocol will include standard T1 and T2 weighted sequences, in and out of phase imaging, and pre- and post-contrast imaging with the standard gadolinium-based contrast agents used in abdominal

imaging. A power injector will be used for the intravenous administration of the contrast agent to ensure correct timing of the early arterial, late arterial/parenchymal and venous phase. Diffusion weighted imaging will also be performed. Apparent diffusion coefficient (ADC) maps will be generated by the console from the diffusion weighted imaging data. The ADC map will be used to determine the hyper cellular/malignant portions of the tumor. Tumor response assessments will be made based on the anatomic and functional comparison of the tumors before and after therapy. MRI's per physician discretion.

7.2.4. Biochemical Testing

Ca19-9 will be evaluated serially in all patients with documented elevated Ca19-9 at initial screening. The Ca19-9 value documented at study inclusion and subsequent staging is considered reliable (evaluable) when bilirubin is $\leq$2.

7.3. Survival

PFS will be calculated only in patients who underwent resection, from the date of cytologic or histologic diagnosis until the date of recurrence or the last date at which the patient was known to be free of disease. OS will be calculated from the date of cytologic or histologic diagnosis until the date of death or last contact.

OS and PFS will be calculated on all treated patients. Patients without disease progression at 5 years will be censored at that time. Patients lost to follow-up without documented disease progression will be censored at the time of last contact. This is also true of patients discontinuing due to toxicity. Patients undergoing post-study therapeutic surgery/resection or radiation prior to progression will be censored at the initiation of that therapy if all macroscopic evidence of the tumor was resected. The date of progression will be the earlier of the dates of progression determined by CT or MRI imaging (increased lesion size, new metastases, new arterial/venous involvement) and rising Ca19-9 if the patient produces Ca19-9.

8. ASSESSMENT OF SAFETY, RISKS, AND BENEFITS

8.1. Adverse Events

8.1.1 Recording Adverse Events

An adverse event is defined as any untoward medical occurrence temporally associated with any study procedure or treatment, regardless of whether it is considered related to the study procedure or treatment. This includes changes in laboratory parameters. The National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 4.0 will be used to grade adverse events (see

Appendix C). All unexpected grade 3 and all grade 4-5 adverse events (AE) occurring during the study protocol will be recorded, noting severity and causality. AE's will be collected in a summary format as delineated in the study calendar (sections 6.6 and 6.7).

8.1.2 Reporting Adverse Events (AE)

AEs will be recorded in OnCore and an alert of a new AE will be sent to the multicenter study coordinator. AE reporting to the IRB will be per policy of the approving IRB (for the coordinating site, see Appendix D Medical College of Wisconsin Office of Research SOP Requirements for Reporting to the IRB). See Appendix N for the communication plan for participating site reporting of SAE's to the coordinating site.

8.2. Serious Adverse Events (SAEs)

All SAEs, whether or not considered related to a study procedures or treatments, occurring during the study protocol or within 24 hours of coming off protocol, will be recorded. An SAE is any untoward medical occurrence that results in: (1) death including all deaths occurring within 4 weeks of the last treatment administration, (2) life-threatening events, (3) events requiring hospitalization or prolonged hospitalization, or (4) events which are incapacitating, or permanently disabling. Medically important events that may not be immediately life-threatening, or result in death or hospitalization, but may jeopardize the patient or require intervention to prevent one of the other listed above outcomes, will be considered serious. If the patient dies, any post-mortem findings including histopathology must be provided. SAE reporting to the IRB will be per policy of the approving IRB. See Appendix N for the communication plan for participating site reporting of SAE's to the coordinating site.

8.3. Study Risks

The known risk associated with participating in this study is similar to the risk of standard care. All activities of the study are standard care except for the risks of obtaining extra passes during the EUS/FNA (at screening), and obtaining up to 10 blood draws of 30 cc of extra blood at several time points during the study. Research blood will be obtained only for subjects enrolled at the coordinating site.

8.3.1. Known Risks

The slight risk of extra passes during FNA represents an increase in the already standing risks associated with EUS/FNA. Because this study takes extra samples during the routine FNA procedure, the extra risks of the research are the additional side effects that could occur because the procedure will last a few minutes longer and because the FNA will require several additional samples.

Less frequent side effects related to EUS include drug reaction from medication for sedation, irritation and/or tenderness at the site of sedative injection, including the rare chance of clotting at the vein. A rare side effect of EUS is perforation of the GI tract requiring surgical repair.

Less frequent side effects of FNA include infection. Rarely, pancreatitis can occur and usually resolves with conservative treatment within a few days. Very rarely, surgery would be required for pancreatitis. Another rare side effect of FNA is minor bleeding where the needle is passed through the gut wall. Very rarely, unusual bleeding may require hospitalization and/or blood transfusion and/or surgery.

8.3.2. Risk Discussion

This study is assessing a treatment approach. It is not assessing safety or efficacy of the individual therapies. This study is isolating a prescriptive approach (molecular profiling) that relies on clinical application of the results of studies involving tumor biomarkers (targets) to identify best treatments. The major risk is that conclusions from recent scientific studies (focused on treating the individual pancreatic tumor based on biomarkers specific to the tumor itself) will not support treatment decisions equally or better than the earlier scientific studies that were focused on the treatment response of groups of patients and that are currently used by many oncologists as the basis of their prescriptive decisions. The prescriptive approach that is the focus of this study is currently used as standard care by some clinicians (such as academicians who stay current with recent research), yet this prescriptive use is disparate within the larger oncology community, thus requiring future research.

The discussion of risk (other than the risks of blood draw and extra passes during FNA), therefore, falls to the oncologist's standard discussion of risk with his/her patient when prescribing the FDA-approved treatment that is identified as the appropriate treatment.

8.4. Study Benefits

This is a new treatment approach, and the exact degree of efficacy is unknown. The patient may benefit from participating in this study by having a better chance of successful resection of his/her tumor. The knowledge gained from this study may benefit future patients with pancreatic adenocarcinoma.

9. PATIENT DISCONTINUATION

If an investigator removes a patient from the study or if the patient declines further participation, a final assessment of the patient's disease status should be performed prior to any therapeutic intervention. These results, along with a reason for study discontinuation will be recorded. The status of a patient who is discontinued for purposes other than recurrent or metastatic disease should be monitored in on-study follow-up (see Section 6.5) whenever possible as long as the patient agrees. Patients will discontinue

treatment if any of the following occur: (1) recurrent or metastatic disease, (2) unacceptable toxicity, (3) patient withdrawal of consent, (4) investigator decision, or (5) non-compliance.

10. DISCONTINUATION OF THE STUDY

The entire trial will be stopped if evidence has emerged that makes the study continuation unnecessary or unethical or when the stated objectives are achieved.

11. STATISTICAL METHODS

Assumptions:

1. 60% of the patients are borderline resectable
2. Resectable patients have a resectability rate of 80%
3. Borderline resectable patients have a resectability rate of 60%
4. Two-sided 5% significance level, 80% power

Assumptions for effect on survival

1. The median survival is 40 months for those who are resected, and 12 months for those who are not resected.
2. Exponentially distributed survival time for resected and non-resected patients.

Some implications:

1. The overall resectability rate is 69%
2. Median survival of all resectable patients is 23.7 months
3. Median survival of all borderline resectable patients is 18.3 months
4. Median survival of all patients is 20.2 months
5. 170 historical controls
6. 120 study subjects
7. Primary outcome: resectability rate
8. Secondary outcomes: overall survival, progression-free survival

The proportion of patients whose tumors are successfully resected will be compared between the historical controls and the experimental group via a Mantel-Haenszel test with two strata: resectable tumors and borderline resectable tumors. We expect 60% of the patients to fall into the borderline

resectable stratum. With 170 control patients and 120 patients in the experimental group the study will have an 80% power to detect an increase in resectability if the true odds ratio is 2.35.. This corresponds to an increase of resectability from 60% to 78% for borderline resectable patients, and from 80% to 90% for resectable patients, and a 85% overall rate of resectability.

Assuming that all the gains for survival will be from moving patients from the non-resected to the resected group, and that survival has an exponential distribution, the median survival should improve from 23.7 months to 30.7 months among resectable patients, from 18.3 months to 24.5 among borderline resectable patients, and from 20.2 months to 26.8 months overall.

Overall survival will be calculated from the date of cytologic or histologic diagnosis until the date of death or last contact; time to progression will be calculated only in patients who underwent resection, from the date of cytologic or histologic diagnosis until the date of recurrence or the last date at which the patient was known to be free of disease. The survival curves will be estimated using the Kaplan-Meier method, and the two groups will be compared via a stratified log-rank test at a two-sided 5% significance level.

12. ADJUNCT TRANSLATIONAL STUDIES at Coordinating Site only

12.1. Generation of Direct Xenograft Tumors

12.1.1. Rationale

The identification of the molecular targets prior to treatment allows for the selection and early delivery of optimal therapeutic regimens. While response to therapies may be guided by molecular phenotypes, it is still unclear which individual targets may be of greatest therapeutic value. In order to address this problem, we propose to implant human pancreas tumors in mice. By establishing a renewable xenograft model from resected human tumors, tumor samples can be expanded and characterized in depth at the genetic and epigenetic levels. The major advantage of utilizing human pancreatic xenografts lies in the ability of the tumor to maintain an identical genetic and morphological phenotype to the primary tumor. In addition, it appears that no major variations in the status principal genes are mutated through early passaging of carcinoma in mice, suggesting that the fundamental pathogenetic elements remain stable.[25]This murine model can be used to apply, test, and validate novel treatment regimens. Therefore, the efficacy and pharmacodynamic effect of multiple single treatments or combination of treatments on a single tumor may be examined in manner which may not be feasible in a clinical trial setting. Furthermore, the xenograft models may be used to study other aspects of tumor biology including angiogenesis, tumor microenvironment, and cancer stem cells.

This protocol provides us with an opportunity to assess the feasibility of generating xenografts of resected and metastatic tumors. To generate human pancreatic cancer xenografts we would utilize a previously described method, which reported engraftment rates ranging from 20-100%.[3] In this model, fresh human tumors are either implanted into immunodeficient mice in an orthotopic or heterotopic fashion. The tumors are then expanded and may be stored for further use. The primary determinants of successful tumor engraftment are related to the viability, sterility, and processing time of the specimen. This protocol will allow us the opportunity to implement and further refine the procurement and processing of resected tumors to optimize xenograft engraftment.

12.1.2. Murine Model

NOD/SCID mice will be utilized in the generation of xenograft tumors as this model has been demonstrated to have superior efficiency of tumor formation. The mice will be housed in specific pathogen-free conditions to prevent sickness and infectious outbreak. After implantation the mice will be monitored regularly for general health and weekly body weights will be obtained. All animal-related protocols will be submitted for the Institutional Animal Care and Use Committee (IACUC) review and approval. See *Laboratory Manual: Section 3* for details of tumor engraftment and expansion (Appendix J). Laboratory procedures may be revised as required to maximize processing quality.

12.2. Characterization of Resected Primary & Metastatic Tumors

12.2.1. Rationale

The expected CR response after neoadjuvant chemo radiotherapy for pancreatic cancer is approximately 1%. Even in the setting of favorable clinicopathologic features such as node negativity and negative margins, the majority of pancreatic cancers will recur. Following completion of neoadjuvant therapy, the residual viable tumor present in the resected primary specimen may represent a population of cells which are resistant to the administered therapy. Further characterization of the residual primary tumor may improve future treatment options for inevitably recurrent disease.

Patients who develop metastatic disease may be candidates for biopsy or resection of these lesions. Further analysis of metastatic lesions may potentially provide important information regarding the pathogenesis of genetic alterations which are associated with pancreatic cancer metastases or molecular biologic correlates of adjuvant therapy failure. Importantly, unlike previous rapid autopsy series, resection of evolving metastatic lesions allow for further insight into the temporal sequence of genetic alterations leading to cancer metastases and death. This protocol will allow patients to have repeated characterization of primary and metastatic tumors.

12.2.2. Molecular Characterization of Primary Resected and Metastatic Tumors

Residual and metastatic tumors will be assessed for phenotypic changes in histology. In addition, using IHC and quantitative real-time polymerase chain reaction (qRT PCR), the resected tumors will undergo molecular characterization of the previously tested targets: SPARC, RRM1, ERCC1, TYMS, TOP1 and hENT1. The initial tumor molecular phenotype will be compared to the subsequent resected tumor molecular phenotype to evaluate for changes suggestive of new chemotherapeutic resistance.

12.2.3. Biomarkers in peripheral blood

Inherent in the tumor biology of cancer, cells or cell components may be found within the blood stream prior to gross identification of metastatic disease either with radiographic techniques or at the time of surgery. We hypothesize that prior to the development of metastatic disease, circulating tumor cells or exosomes may be identified. Using peripheral blood samples from patients at different stages of treatment, we plan to assess for changes in circulating tumor cell numbers. In addition, we will evaluate changes in exosomal microRNA expression within patient serum as it relates to treatment and prognosis. Finally, we seek to be able to identify the presence of cell-free DNA as a marker of tumor stage and prognosis from patient plasma.

13. ADMINISTRATION

13.1. Training

Investigator and staff training will be conducted to share information regarding study design, study requirements and amendments subsequent to study onset.

13.2. Multi-site Approval and Activation

The Multi-Site Research Coordinating Office is responsible for oversight of regulatory documentation for each Participating Institution(s). Documents should be provided to the MCW CTO Coordinating Office either via the OnCore Clinical Trials Management System (CTMS) or by Fax (414) 805-9025. For questions, please call (414) 805-9001. See address and contact information;

CCCTO Multi-Site Research Coordinating Office

Medical College of Wisconsin/Cancer Center

9200 W. Wisconsin Avenue

Milwaukee, WI 53226

Phone-(414)805-9001 Fax- (414) 805-9025

E-mail-kjensik@mcw.edu

See Appendix N for Procedures related to Multi-site Approval, Activation, Site Monitoring, and Ongoing Management

13.2.1 Site Initiation

Site initiation will be performed to assure that each Investigator and his/her staff understand the protocol, applicable regulations, human subject protections requirements, and the Investigator's obligations. The site initiation process will ensure that required documentation with the appropriate approval is in place prior to subject enrollment.

13.2.2 Monitoring

The Medical College of Wisconsin Cancer Center Clinical Trials Office will provide monitoring for this study. The monitor(s) is qualified by training and experience to oversee the progress of the study at the participating site to ensure continuing adequacy of facilities and adherence to the clinical study protocol, and applicable regulations and laws that pertain to the conduct of the clinical study. The monitor(s) will review the data collection and source documentation, the timely submission of accurate records to the Sponsor, and the maintenance of proper records. A report will be written following site monitoring and a follow-up letter will be provided with a summary of findings.

13.3 Modification of the Protocol

Amendments to the study that could adversely affect patient safety, alter the scope of the investigation, the quality of the study, design, duration of therapy, number of patients or selection criteria must be made only after consultation with the Principal Investigators. These amendments must be submitted to and approved by the MCW IRB in accordance with MCW regulations. Subsequently, the amended protocol must be submitted by the participating site to its local IRB for approval.

13.4. Completion of Case Report Forms

Case report forms will be used to collect and enter the data into an electronic database. Source documents, original reports and films, will remain in each respective institution's medical records for future reference. Data will be collected according to research activities specified in Protocol Sections 6.6 and 6.7.

13.5 Access to Source Data and Study Documents

Subject-specific Research Files (SsRF), maintained on site, will include study-specific source documents such as the Enrollment Checklist, the original signed consent and any additional source notes obtained by research personnel. In addition, the SsRF will include copies of source documents (such as copies of lab or imaging reports or copies of Medical Record notes) as specified in Appendix N. (See Appendix N for procedures regarding maintenance of Subject Research File).

All study records and source data will be available for inspection by the study Coordinating monitor(s), IRB and other regulatory authorities. The coordinating site and the participating site will record data associated with assessment of the primary objective; certain data associated with secondary objectives may be collected for patients enrolled only at the coordinating site (as noted by asterisks in Section 2.1.2 Secondary Objectives). Once entered, data will be evaluated to ensure that it is complete, consistent and logically sound. If changes to the data are required, all changes, reason for changes and persons making the changes will be documented.

13.6. Data Safety Monitoring

This study will be monitored by the FH/MCW Cancer Center Data Safety Monitoring Committee (FH/MCW CC DSMC). A record of the membership of the FH/MCW CC DSMC will be maintained in the study research file and updated when membership changes. The FH/MCW CC DSMC will review DSM reports from the study PI semi-annually or more frequently if needed.

Patients will be monitored throughout the course of therapy for toxicity. Safety evaluations will consist of physicians and/or their designees' assessments and examinations and laboratory measurements prior to initiating each cycle of chemotherapy. For purposes of DSMB reporting, adverse events will be described and graded according the NCI Common Toxicity Criteria version 4.03 (see Appendix C).

A summary of the FH/MCW CC DSMC activities are as follows:

- Review the clinical trial for data integrity and safety.
- Review all unexpected grade 3, and all grade 4, and 5 adverse events, as well as any others requiring expedited reporting as defined in this protocol. (Grades 4 & 5 events must be reported to the DSMC within 5 calendar days of study staff's knowledge.)
- Grade 4 (life threatening) hematologic toxicities are reported every 6 months. All other grade 4 toxicities (life threatening) are reported within 5 calendar days.
- Review all DSM reports.
- Submit a summary of any recommendations related to study conduct.
- Terminate the study if deemed unsafe for patients.

A copy of the MCWCC Data and Safety Monitoring Plan and membership roster will be maintained in the study research file and updated as membership changes. The committee will review reports from the study PI twice annually (or more frequently if needed) and provide recommendations on trial continuation, suspension or termination as necessary.

Any available DSMC letters will be submitted to the IRB of record as required.

The participating site will submit DSMB reports to the Coordinating site, and the Coordinating site will forward all reports to the DSMB.

13.7. Retention of Study Documentation

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. The patient's involvement in the study should be clearly documented in the clinical records. Details are to include the protocol number, the patient's identification number, the patient's consent(s) to take part in the study, the date of all study visits and the dates of treatment. Copies of CRFs must be retained by investigators, for as long as legally required after completion of the study. All study data including master files, CRFs, source data, and correspondence with the Coordinating site, an IRB, or study subject will be stored for at least 10 years according to MCW Office of Research SOP (see Appendix E).

Clinical study records will not be disposed of, nor custody of the records transferred, without prior Coordinating site approval.

13.8. Ethics Consideration

The study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines and the Office of Human Research Protection. The investigators will inform the IRB of subsequent protocol amendments.

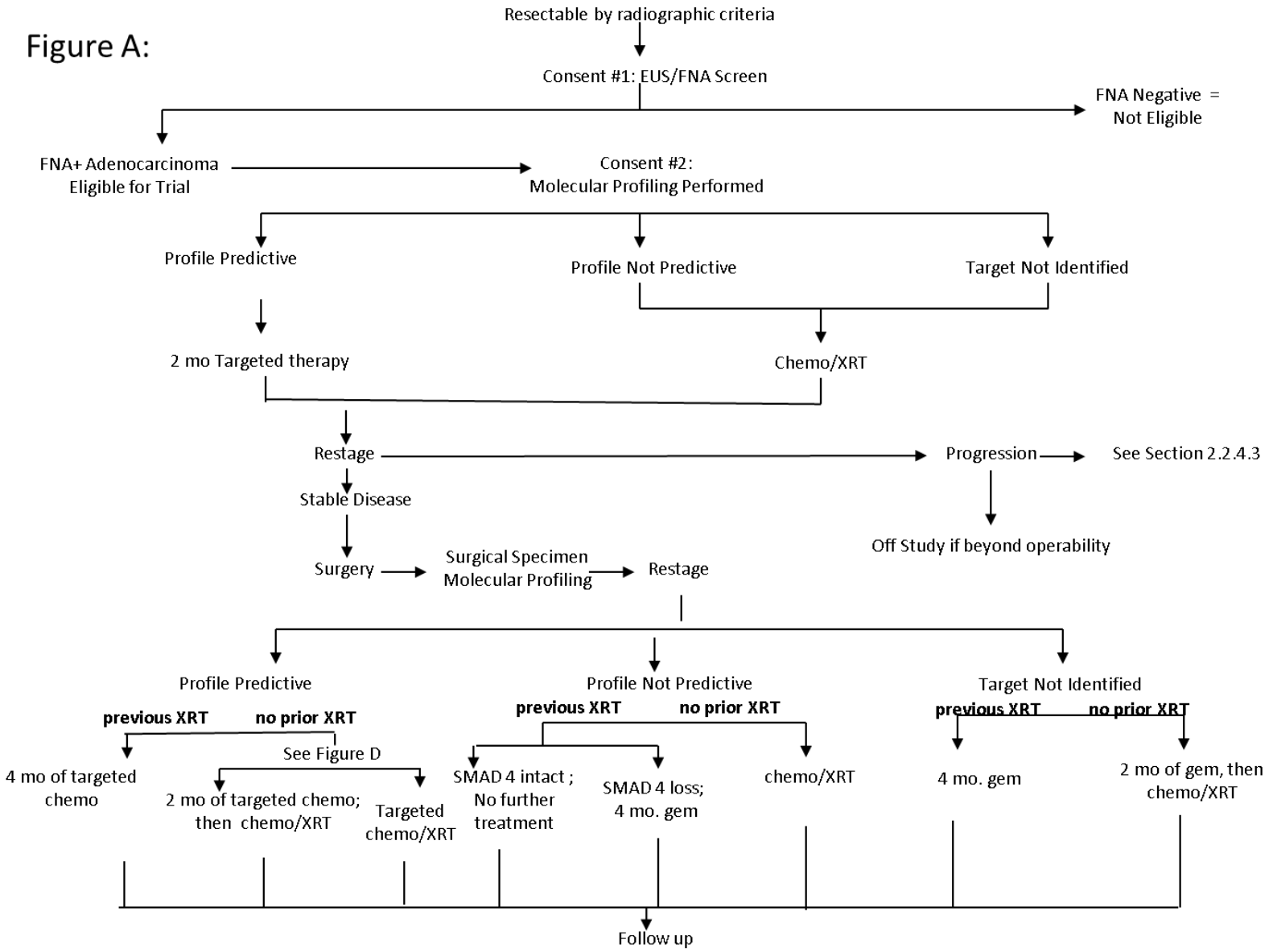
The investigator must inform the patient about the background and present knowledge of treatment via molecular profiling. The investigator must ensure the following items are discussed:

1. The patient must be provided the patient information and informed consent form consistent with the protocol version used and approved by the IRB. The patient must be informed that this is a new treatment approach and that the exact degree of efficacy is unknown, and that treating him/her will contribute to further knowledge.
2. The patient will be given time to discuss his/her participation with the investigator and members of their family. Before the patient is entered into the study, the patient's written consent must be obtained. A copy of the signed consent form will be provided to the patient and the original scanned into the electronic database created for this study.
3. The patient may refuse to provide a biopsy or may refuse treatment proposed in the context of the study before or at any time during the study. Refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled.
4. An explanation of whom to contact for answers to pertinent questions about the research and the patient's rights, and who to contact in the event of a research-related injury must be given to the patient.

13.9. Publication Policy

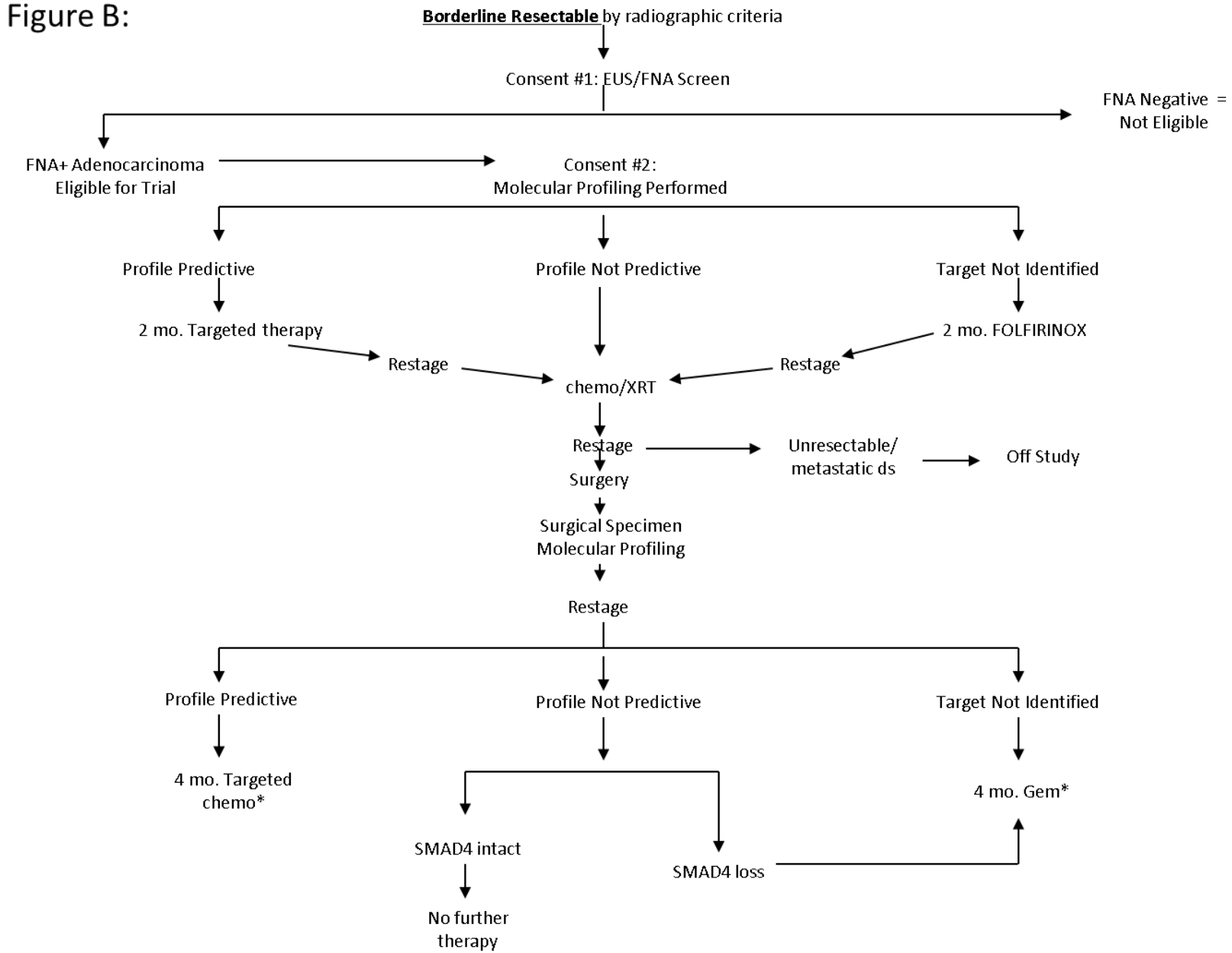
All the results are the property of the Principal investigators. Investigators may not submit for publication or presentation study results without allowing the PIs 30 working days to review and comment on the pre-publication manuscript. Co-authorship will be discussed and mutually agreed upon before submission of a manuscript to a publisher.

Figure A



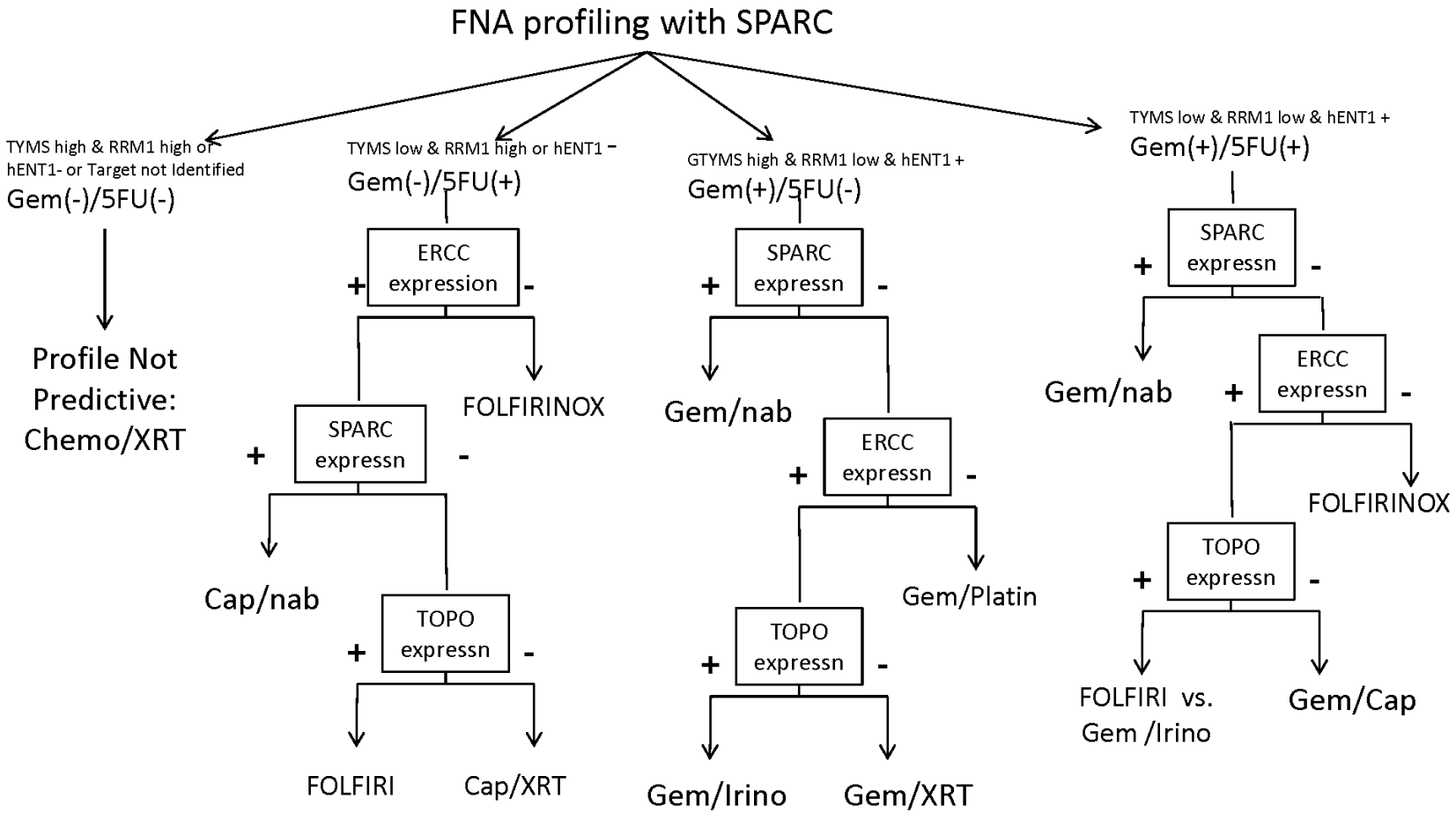
*During adjuvant therapy, restaging will be performed after the first 2 months of therapy. Patients with disease progression will come off study and be followed for survival every 6 months.

Figure B



*During adjuvant therapy, restaging will be performed after the first 2 months of therapy. Patients with disease progression will come off study and be followed for survival every 6 months.

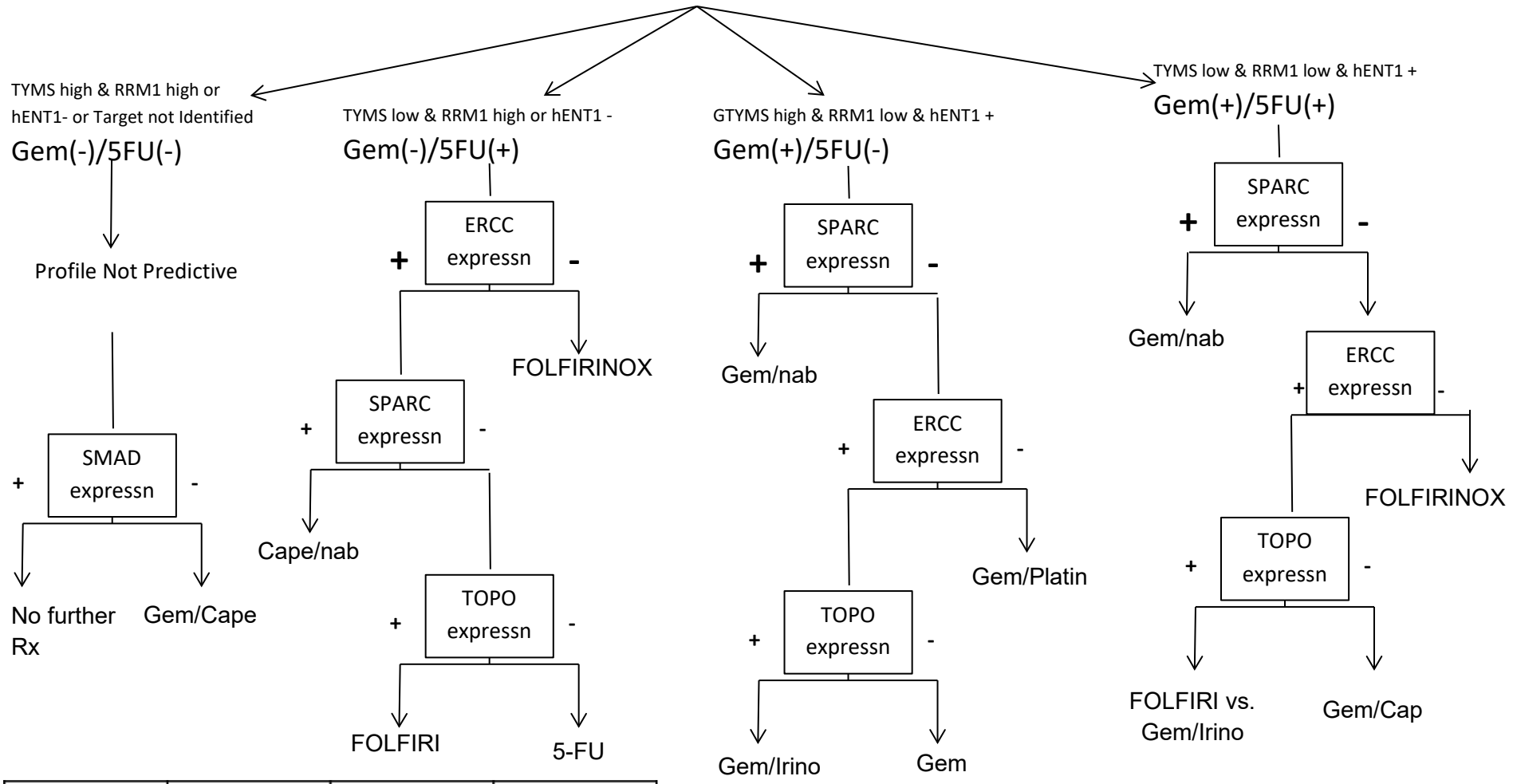
Figure C



Biomarker	Intensity	% Stain	Recommend
SPARC			Nab
TYMS			5FU
RRM1			GEM
ENT1			GEM
ERCC1			Platin
TOPO1			Irinotecan

Target not identified (resectable): chemoXRT
Target not identified (BL resect): FOLFIRINOX

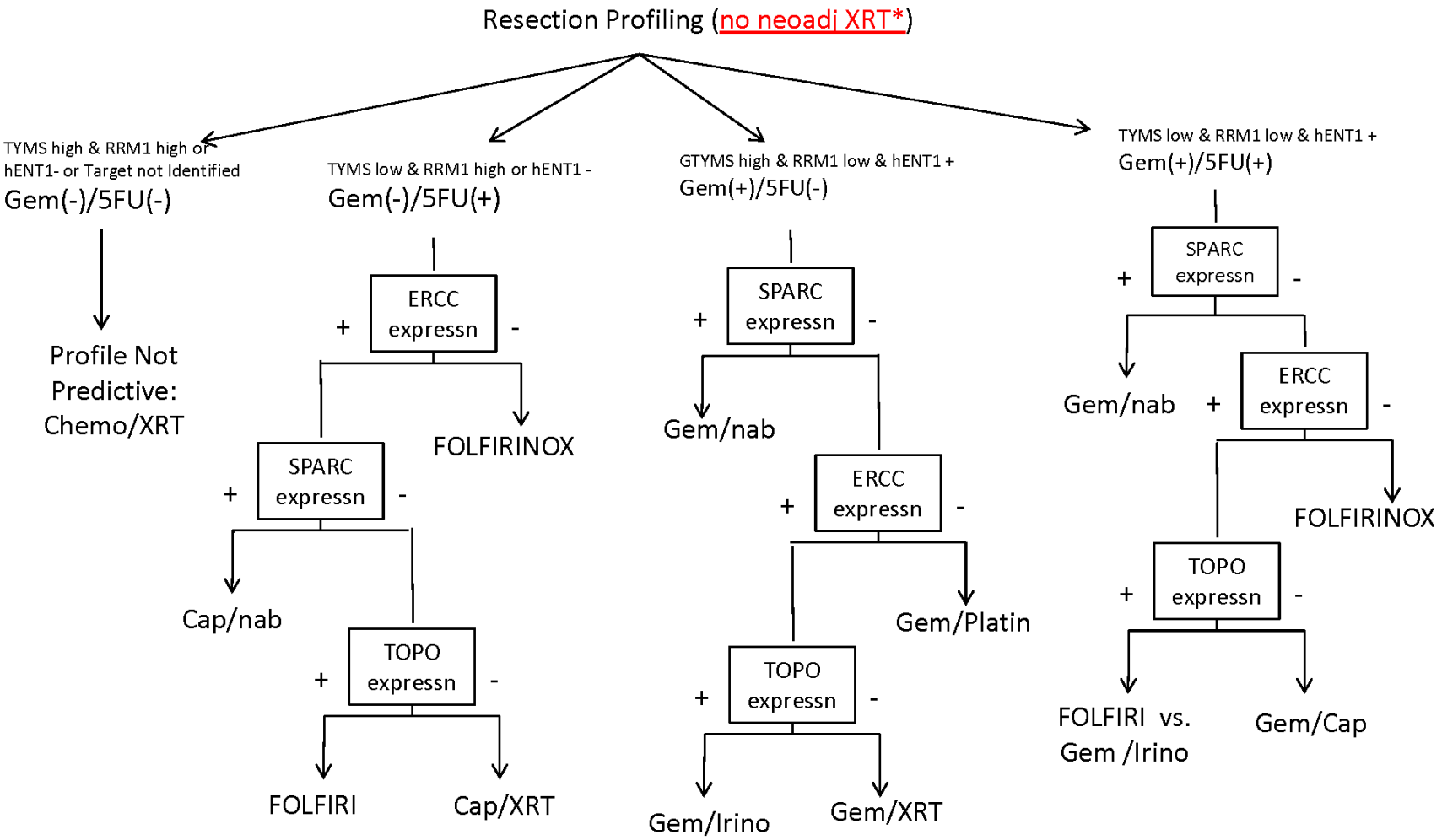
Figure D



Biomarker	Intensity	% Stain	Recommend
SPARC			Nab
TYMS			5FU
RRM1			GEM
ENT1			GEM
ERCC1			Platin
TOPO1			Irinotecan

Target not identified: 4 mo Gem/Cape

Figure E



Biomarker	Intensity	% Stain	Recommend
SPARC			Nab
TYMS			5FU
RRM1			GEM
ENT1			GEM
ERCC1			Platin
TOPO1			Irinotecan

Target not identified (resectable): chemoXRT
Target not identified (BL resect): FOLFIRINOX

2

Appendices A – M (see separate Appendices document)

14. REFERENCES

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