Pancreatic Cancer Radiotherapy Study Group (PanCRS) Trial: A Randomized Phase III Study Evaluating Modified FOLFIRINOX (mFFX) with or without Stereotactic Body Radiotherapy (SBRT) in the Treatment of Locally Advanced Pancreatic Cancer

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PROTOCOL SYNOPSIS

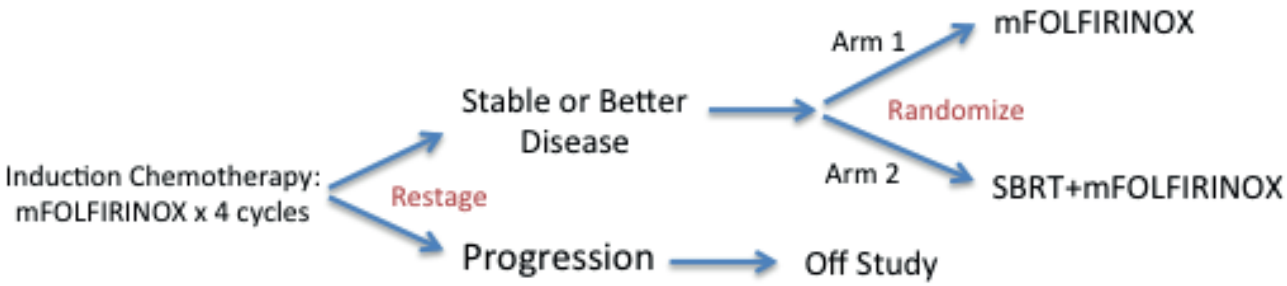
TITLE	**A Randomized Phase III Study Evaluating Modified FOLFIRINOX (mFFX) with or without Stereotactic Body Radiotherapy (SBRT) in the Treatment of Locally Advanced Pancreatic Cancer**
	A PanCRS Group Trial
PRIMARY OBJECTIVE	To compare the median progression free survival for patients treated with mFFX+ SBRT with the median progression free survival for patient treated with mFFX only.
SECONDARY OBJECTIVES	▪ To compare metastasis-free survival for pancreatic patients following chemotherapy +/- SBRT. ▪ To compare the one year progression free survival for patients treated with mFFX +/- SBRT. ▪ To determine the overall survival for patients treated with mFFX +/- SBRT. ▪ To determine local progression-free survival for patients treated with mFFX +/- SBRT. ▪ To evaluate acute (within 3 months of treatment) grade 2 or greater gastritis, fistula, enteritis, or ulcer and any other grade 3-4 gastrointestinal toxicity within 3 months of treatment. ▪ To evaluate the utility of FDG-PET for treatment planning and estimation of progression free survival. ▪ To identify new biomarkers in pancreatic cancer.15% ▪ ▪ To evaluate the quality of life before and after therapy for patients treated with mFFX +/- SBRT.
HYPOTHESES	Systemic chemotherapy followed by radiotherapy improves overall survival in patients with locally advanced pancreatic cancer. Recent clinical studies have shown that FOLFIRINOX chemotherapy is more effective than gemcitabine as first-line treatment in patients with metastatic disease. Similarly, aggressive local radiotherapy in combination with systemic chemotherapy has also been demonstrated to improve overall survival. We hypothesize that optimizing local radiotherapy following aggressive systemic chemotherapy will further improve overall survival.

STUDY DESIGN	Multi-center phase III randomized study anticipated to accrue approximately 172 patients total at all participating institutions.

SUMMARY OF SUBJECT ELIGIBILITY CRITERIA	**Inclusion:** ▪ Histologically confirmed adenocarcinoma of the pancreas. ▪ Determined unresectable by a pancreatic cancer surgeon or a multi-disciplinary or gastrointestinal oncology Tumor Board ▪ Stable or better disease on re-staging scans following induction mFOLFIRINOX. ▪ Typically, pancreatic tumors must be less than 8.0 cm in greatest axial dimension at the time of treatment planning but final determination of eligibility will be based upon satisfying the radiation normal tissue constraints as specified below in section 6.1.3 Radiation Treatment Planning ▪ No prior systemic therapy EXCEPT patients may be consented and enrolled if they have already started mFOLFIRINOX for up to four cycles. ▪ ECOG 0, 1, or 2 (see Appendix II). ▪ Acceptable organ and marrow function (as defined in protocol section 3.1). ▪ Ability to understand and the willingness to sign an informed consent form. ▪ Life expectancy >6 months. **Exclusion:** ▪ Metastatic disease. ▪ Children/Age<18 (rarely occurs in this age group) ▪ Prior radiotherapy to the upper abdomen/liver. ▪ Patients who received chemotherapy for pancreatic cancer other than up to 4 cycles of mFOLFIRINOX as noted above. ▪ Uncontrolled illness including, but not limited to, ongoing or active infection (or infections requiring systemic antibiotic treatment), symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements. ▪ Any concurrent malignancy other than non-melanoma skin cancer, non-invasive bladder cancer, or carcinoma in situ of the cervix. Patients with a previous malignancy without evidence of disease for > 5 years will be allowed to enter the trial. ▪ Pregnant and breastfeeding women are excluded; as well as women of child-bearing potential who are unwilling or unable to use an acceptable method of birth control (hormonal or barrier method eSEof

PROCEDURES	*Optional*: Pancreatic biopsies obtained at the time of fiducial placement or in a separate procedure, and blood collected for biomarker analysis pre-and post-treatment.
STATISTICAL CONSIDERATIONS	See statistics section.

SCHEMA



1. OBJECTIVES

1.1. Primary Objective

- To compare the median progression-free survival between arm 1 (mFOLFIRINOX) vs arm 2 (mFOLFIRINOX+SBRT).

1.2. Secondary Objectives

- To compare metastasis free survival for pancreatic patients following chemotherapy +/- SBRT.
- To compare the one year progression-free survival for patients treated with mFFX +/- SBRT.
- To determine the overall survival for patients treated with mFFX +/- SBRT.
- To determine local progression-free survival for patients treated with mFFX +/- SBRT.
- To evaluate acute (within 3 months of treatment) grade 2 or greater gastritis, fistula, enteritis, or ulcer and any other grade 3-4 gastrointestinal toxicity within 3 months of treatment.
- To evaluate the utility of FDG-PET for treatment planning and estimation of progression free survival.
- To identify new biomarkers in pancreatic cancer.
- To evaluate the quality of life before and after therapy for patients treated with mFFX +/- SBRT.

2. BACKGROUND

2.1 Natural History and Management of Pancreatic Cancer

Every year in the United States, there are more than 30,000 newly diagnosed cases of pancreatic cancer. Despite aggressive combined modality treatment approaches, the five-year survival of this disease remains less than 5%(1). Clearly, more innovative treatments are needed to improve overall survival in this group of patients.

Surgical resection is considered to be the only treatment option with curative potential(2). However, the majority of pancreatic cancer patients do not have resectable disease at presentation. More than 85% of patients have locally advanced or metastatic disease when initially diagnosed.

Since the late 1990's, first-line chemotherapy for locally advanced/metastatic pancreatic cancer has been gemcitabine, a nucleoside analog. In the pivotal trial for which the FDA approved this drug, patients treated with gemcitabine had a modest improvement in survival compared to patients treated with 5-fluorouracil (5FU)(3). The median survival was improved from 4.41 months to 5.56 months. However, nearly 25% of patients receiving gemcitabine were noted to have a clinical benefit compared to 5% of patients receiving 5FU. In a recent meta-analysis, the addition of platinum analogs to gemcitabine demonstrated a survival benefit in patients with a good performance status. However, additional studies are necessary to determine which therapeutics are best combined with gemcitabine(4).

More recently, Conroy et al reported that a non-gemcitabine containing chemotherapy regimen, FOLFIRINOX (5FU, leucovorin, irinotecan, oxaliplatin), provided a significant survival benefit compared to gemcitabine (30) in patients with metastatic pancreatic cancer. Although there was increased toxicity in those patients treated with FOLFIRINOX, this was the first randomized study showing a clinically significant advancement in the treatment of patients with advanced pancreatic cancer since gemcitabine was approved by the FDA. We hypothesize that more aggressive systemic chemotherapy followed by intensive local radiotherapy will improve overall survival in patients with locally advanced pancreatic cancer.

In a single arm multi-center (Stanford University, Johns Hopkins University, Memorial Sloan Kettering) phase II study in locally advanced pancreatic cancer, we have previously shown that integrating stereotactic body radiotherapy (SBRT, 33 Gy in 5 fractions) with systemic gemcitabine chemotherapy resulted in a 1 year freedom from local progression of 78% and a median overall survival of 13.9 months (Herman et al, Cancer 2014). There was minimal toxicity associated with SBRT and the entire radiotherapy course was delivered in 1 week. Shortening the duration of radiotherapy from 5-6 weeks (conventional IMRT) to 1 week (SBRT) minimizes any delay in the administration of systemic chemotherapy.

Another study in locally advanced pancreatic cancer compared full-dose gemcitabine (1000 mg/m2) alone to a lower dose of gemcitabine (600 mg/m^2) combined with standard fractionated radiation (50.4 Gy over 5.5 weeks). Although the study was closed prior to reaching its planned accrual, there was a significant improvement in survival with combined gemcitabine and radiation compared to gemcitabine alone(5), suggesting that the addition of local radiation therapy in pancreatic cancer confers a further survival advantage to systemic chemotherapy. Objective responses were observed in 2.7% in the gemcitabine alone arm (95% CI [0.09%, 14.1%]) and 8.8% in the combined arm (95% CI [1.9%, 23.7%]). In this trial, the dose of gemcitabine was reduced to 600 mg/m^2 with radiation and patients required a 4-week break prior to resuming full dose gemcitabine. Grade IV toxicity, principally gastrointestinal and hematologic, was more common in the combined group (41.2 vs. 5.7%; $p<0.0001$). Although there was an improvement in survival, patients who received combined chemoradiation had substantially more toxicity when compared to gemcitabine alone. Because of the highly conformal and precise nature of SBRT, we hypothesize that this radiotherapy approach will improve local control and decrease radiation-related toxicity in patients with locally advanced pancreatic cancer.

Here, we will conduct a multi-institutional randomized trial to compare the effects of chemotherapy alone versus chemotherapy and SBRT in patients with locally advanced pancreatic cancer. All patients will receive a modified FOLFIRINOX regimen prior to and

following radiotherapy. The primary endpoint will be progression-free survival.

2.2 Rationale for SBRT for Pancreatic Cancer

Radiation therapy is a widely accepted treatment for pancreatic cancer. The Gastrointestinal Tumor Study Group (GITSG) carried out a series of landmark studies demonstrating the effectiveness of radiation therapy as both adjuvant and definitive treatment in pancreatic cancer(6, 7). Modern radiation treatments have increasingly used conformal fields and dose escalation to enhance tumor control(8, 9). Efforts to increase radiation dose to the pancreatic tumor without risking normal tissue injury have generally required relatively invasive techniques such as interstitial implantation of radioactive metals or intraoperative radiotherapy (IORT)(10, 11). Historically, the local control rates for conventionally fractionated radiotherapy have ranged from 25-50%. Local progression of pancreatic cancers can result in considerable morbidity, including gastric outlet obstruction and pain (12).

The mortality rate for pancreatic cancer approaches 100%. Current therapies provide only partial palliation of symptoms and slight prolongation of survival. Better treatment is clearly needed. SBRT has the potential of significantly improving local progression free survival, which could translate into both more effective palliation and longer patient survival. Koong *et al.* previously used the Cyberknife™ stereotactic radiosurgery system to demonstrate that a single dose of 25 Gy stereotactic body radiotherapy was feasible to administer in patients with locally advanced pancreatic cancer(13). Furthermore, this dose of radiation resulted in nearly 100% local progression-free survival and effectively palliated symptoms related to the local growth of pancreatic tumors. Based upon this study, these investigators also completed a phase II study assessing the efficacy of combining a standard five-week course of chemoradiotherapy followed by a stereotactic radiosurgery boost to the primary tumor in patients with locally advanced pancreatic cancer. In this cohort of 19 patients, 100% of tumors were without local progression. However, all patients eventually developed metastases with a median time to progression of 5.5 months (Koong et al, IJROBP 2005).

Another phase II study treated locally advanced pancreatic cancer patients with gemcitabine followed by 25 Gy of SBRT delivered with Cyberknife and maintenance gemcitabine chemotherapy. In this study, the excellent progression free survival was confirmed from previous studies (81%). The median overall survival was 11.4 months, median time to progression was 9.7 months and 1 year survival was 50%(14). There were no significant acute GI toxicities however, of the 15 patients alive >6 months after SBRT, 7 (47%) experienced Grade 2 or greater GI toxicity, with 2 (13%) of the 15 experiencing Grade 3 or greater GI toxicity.

More recently, another phase II study of 25 Gy in a single fraction using a linac-based approach (Trilogy™, Varian Medical Systems, Palo Alto, CA) integrated with gemcitabine chemotherapy resulted in a 50% overall survival at 1 year and a 94% freedom from local progression at 1 year. Four patients (15%) developed Grade 2 ulcers and 1 patient (5%) developed a duodenal perforation (Schellenberg et al, IJROBP 2011).

Recently, we completed a multi-center phase II trial demonstrating the efficacy of SBRT (33

Gy in 5 fractions) in combination with gemcitabine chemotherapy. No significant toxicities were observed and median overall survival was 18 months. These data compare favorably to other studies reported in the literature. Based upon these promising data, we hypothesize that adding SBRT to a more aggressive systemic chemotherapy (FOLFIRINOX), will result in further improvement in OS in patients with locally advanced pancreatic cancer.

The proposed randomized study is a logical extension of the previously reported studies and will establish the efficacy of adding SBRT to FOLFIRINOX chemotherapy. Our prior multi-center phase II experience demonstrated the feasibility and efficacy of this approach in patients with locally advanced pancreatic cancer.

2.3 Quality of Life Assessment

The major potential benefit of combining SBRT with chemotherapy for locally advanced pancreatic tumors is to improve local control and palliation of symptoms related to local progression of these tumors. In addition, radiosurgical ablation of the primary tumor can theoretically prevent distant seeding from the pancreatic tumor itself. Ultimately, these improvements in the treatment of pancreatic cancer may translate into an improved quality of life and overall survival.

Quality of life will be assessed using The European Organization for Research and Treatment in Cancer quality of life core cancer questionnaire with the pancreatic cancer module (EORTC QLQ C-30/ PAN26). The European Organization for Research and Treatment in Cancer Quality of Life Questionnaire (EORTC QOL-C30) is a multidimensional, 30-item questionnaire which assesses five functional scales (physical, role, cognitive, emotional and social), three symptom scales (fatigue, pain and nausea/vomiting), a global health /QOL scale, as well as 6 single items (18). The EORTC QLQ-PAN26 supplements the core questionnaire with 26 items specific for patients with pancreatic cancer (19, 20). These instruments have been validated in patients receiving treatment for metastatic and resected pancreatic cancer and are sensitive to identify treatment related changes in quality of life. The quality of life of patients in this study will be directly compared between the 2 randomized arms. These questionnaires were also used in our previous phase II multi-institutional study evaluating SBRT and gemcitabine in patients with locally advanced pancreatic cancer.

2.4 Correlative Studies Background

Protein-based biomarkers in blood hold a great promise as diagnostic markers indicative of disease states and outcomes in clinical cancer management. In order to validate large sets of candidates markers in bio-banked sample collections, multiplexed and sensitive detection technologies with low sample consumption are required. Such technologies will not only be critical for the discovery of biomarker panels potentially leading to increased predictive power in diagnostics but may eventually enable early stage disease detection(21-22).

Most conventional immunoassays rely on a solid support for capture of the target protein and for the removal of excess secondary reporter antibody by washing. These sandwich assays' susceptibility to nonspecific binding of the secondary reporter to the surface limit their sensitivity. Also, any single non-cognate binding event by a detection antibody will give rise to a false positive signal. This is especially challenging when performing

multiplexed reactions with many detection antibodies thus requiring extensive and careful optimization through selection of particular antibody combinations in order to minimize non-specific cross reactivity(23-24).

We have developed a method of protein detection (proximity ligation assay) utilizing an antibody-based method of detection coupled with a qPCR amplification step (25). The assay consumes 1 μL of sample with low femto-molar sensitivity, five log linear range, and can be multi-plexed without cross-reactivity. The procedure typically relies upon a single polyclonal antibody batch for each target protein, simplifying affinity reagent creation for novel biomarker candidates.

Based upon our previous studies (26), we will measure plasma levels of the following proteins prior to initiating treatment and 3 months following SBRT as outlined in the protocol: VEGF, MIF, CTGF, IL-1alpha, IL-7, galectin-1, TNF-alpha, EpCAM, CEA, Adam8, CPA1, ErbB2, IGF-2, CA 19-9, SLPI, Ch3L, EGFR, Osteopontin, Mesothelin, CA-125. We hypothesize that biomarker profile from this group of proteins will be predictive of outcome in this group of pancreatic cancer patients with locally advanced disease.

Collection of specimens as outlined above will not be required from all participating institutions. Additional protein biomarkers may also be assessed.

3. PATIENT SELECTION

3.1 Inclusion Criteria

- Histologically confirmed adenocarcinoma of the pancreas.
- Determined unresectable by a pancreatic cancer surgeon or a multi-disciplinary or gastrointestinal oncology Tumor Board.
- Stable or better disease on re-staging scans following induction mFOLFIRINOX..
- Typically, pancreatic tumors must be less than 8.0 cm in greatest axial dimension at the time of treatment planning but final determination of eligibility will be based upon satisfying the radiation normal tissue constraints as specified below in section 6.1.3 Radiation Treatment Planning.
- No prior systemic therapy EXCEPT patients may be consented and enrolled if they have already started mFOLFIRINOX for up to four cycles.
- ECOG 0, 1, or 2 (see Appendix II).
- Patients must have acceptable organ and marrow function as defined below and within 30 days of eligibility confirmation:

  - leukocytes (WBC) $\geq$3,000/μL
  - absolute neutrophil count (ANC) $\geq$1,500μL
  - platelets $\geq$50,000/μL

- total bilirubin ≤1.5 X institutional upper limit of normal
- AST(SGOT) / ALT(SGPT) ≤2.5 X institutional upper limit of normal
- Creatinine not above the upper limit of normal institutional limits.

- Ability to understand and the willingness to sign an informed consent form.

- Life expectancy > 6 months.

3.2 Exclusion Criteria

- Children/Age<18 (rarely occurs in this age group)

- Metastatic disease.

- Prior radiotherapy to the upper abdomen/liver.

- Patients who have received chemotherapy for pancreatic cancer, other than up to 4 cycles of mFOLFIRINOX as noted above.

- Uncontrolled illness including, but not limited to, ongoing or active infection (or infections requiring systemic antibiotic treatment), symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

- Any concurrent malignancy other than non-melanoma skin cancer, non-invasive bladder cancer, or carcinoma in situ of the cervix. Patients with a previous malignancy without evidence of disease for > 5 years will be allowed to enter the trial.

- Pregnant and breastfeeding women are excluded; as well as women of child-bearing potential who are unwilling or unable to use an acceptable method of birth control (hormonal or barrier method of birth control; abstinence) to avoid pregnancy for the duration of the study. Male subjects must also agree to use effective contraception for the same period as above. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

- Women who are not post-menopausal (as defined in Appendix III) and have a positive urine or serum pregnancy test or refuse to take a pregnancy test.

4. STUDY ENROLLMENT

4.1 General Guidelines

Subjects will be identified per the recommendation of referring surgeons, Combined Modality Tumor Board or equivalent combined modality assessment, or through self-referral and the advice of their attending physician. No advertisement will be used to recruit

subjects.

See Diagram in Section 16.2 for phases and workflow of study.

4.2 Registration and Enrollment

Research staff at each participating center will ensure that all requisite procedures and tests have been performed and complete an Eligibility Checklist (See Appendix IV) to submit to Stanford research staff for review. Stanford research staff will contact the center regarding approval of patient's study participation, and the patient may then be enrolled and registered.

The participating center will register subjects according to their institutional guidelines and as per this protocol.

In some patients, an optional additional core biopsy may be obtained for research purposes if consent is provided by the patient. It may be done at the time of fiducial implantation (in patients randomized to SBRT) as described in Section 12.1, Laboratory Correlative Studies; or as a separate procedure (for patients randomized to mFFX alone). This option will vary by participating institution.

4.3 Informed Consent

Consent will be obtained after a clear and thorough discussion between the patient and the principal investigator at each participating center. Consent may be obtained either prior to starting induction chemotherapy or at any point up through the first 4 treatment cycles. Any patients deemed by the principal investigator or co-investigators to be mentally or physically incapable of consent will not be included in the study.

Patients may be consented by a PI, Co-Investigator, Research Nurse, or Study Coordinator. All research staff will have completed institutional trainings related to research, institutional regulatory and HIPAA policies, and managing protected health information (PHI).

5. INDUCTION CHEMOTHERAPY

5.1 mFOLFIRINOX

After study enrollment, patients will receive (or continue with) mFOLFIRINOX (omission of bolus 5FU) as outlined below, allowing for modifications of dose and schedule as per clinical judgment of patient's treating physician. For patients who have received FOLFIRINOX chemotherapy including a 5FU bolus prior to study entry, once consent is signed, the 5FU bolus must be omitted. Because of its improved safety profile without sacrificing efficacy, mFOLFIRINOX is commonly administered in the treatment of pancreatic cancer (31). Modified FOLFIRINOX regimen with improved safety and maintained efficacy in pancreatic adenocarcinoma. Pancreas 2013 Nov 42(8):1311-5.

mFOLFIRINOX may be administered in a community practice setting as long as the treating oncologist assumes responsibility for all reporting and follow-up requirements.

Prophylactic growth factors may be administered at any time before, during, or after chemotherapy cycles. It is recommended that the patient be evaluated at one of the participating centers every 3-6 months. As standard practices are changing and Leucovorin is not widely used, we will allow the omission of this drug during both induction and treatment phases of the study.

mFOLFIRINOX to complete a total of 4 cycles, (1 cycle = 14 days)

- Oxaliplatin 85 mg/m² IV over 2 hours on Day 1, followed by
- Irinotecan 180 mg/m² IV over 90 minutes on Day 1, followed by
- Leucovorin* 400 mg/m² IV over 2 hours on Day 1, followed by
- 5FU** 2,400 mg/m² IV over 46 – 48 hours

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

**5FU is administered via infusion only; there is no bolus injection of 5FU.

5.2 Restaging Following mFOLFIRINOX

After induction chemotherapy (up to 4 cycles), patients will have a CT scan for re-staging. Re-staging scans should be scheduled within 2 weeks following completion of induction mFOLFIRINOX. To allow for scheduling complications, outside sites may perform the simulation (SIM) scan during the final cycle of chemotherapy up to 4 weeks prior to start of treatment. It the subjects are randomized to the SBRT arm and the SIM was more than 4 weeks prior to treatment start date, a re-SIM will be performed to ensure that the plan is still appropriate for tumor treatment.

- If there is radiological or clinical evidence of disease progression, patient will not continue with the randomized portion of this study, but should be treated according to treating physician's discretion. (Based upon the study by Conroy *et al*, the progression-free survival at 3 months is estimated to be 75%; therefore the number of patients evaluated for the protocol and ultimately enrolled will be adjusted accordingly.) These patients will continue to be followed as part of the study.
- If a patient has radiologically responding or stable disease, s/he may proceed with randomization as described in the following section. Patients may undergo surgical resection at any time if clinically appropriate after surgical evaluation.

5.3 Randomization to +/- SBRT

Participating centers will submit re-staging scan reports (and images as requested) within 5 business days of the scan's final report date to Stanford, along with documentation of consent. These should be sent in a secure electronic mail message or fax to the PI (Dr. Daniel Chang) and Clinical Research Coordinator Rachel Freiberg with subject line: "SECURE: STUDY PATIENT FOR RANDOMIZATION". Stanford research staff will randomize the subject by participating site and within the next business day, will send an electronic message to the PI and Research Coordinator from the participating center with the outcome and instructed treatment plan.

Randomization will be done with R software, a randomized block design. It will be performed by a Stanford Statistician or the Stanford study coordinator who will maintain a password-protected list and assign patients to the treatment arms as each patient is enrolled at each institution. Randomization Arm will be confirmed by two coordinators prior to electronic notification and written documentation (Note to File) of the treating physician and outside research coordinators.

Subjects **randomized to SBRT** are allowed up to an 8-week break between induction chemotherapy and radiation treatments.

Subjects **randomized to mFOLFIRINOX** can continue directly with that treatment. Any breaks between mFOLFIRINOX cycles will be determined by the treating Medical Oncologist and are permitted for up to 8 weeks.

If a subject exceeds the allowable 8-week break between treatments, s/he may continue treatment "off protocol" and as recommended by the treating Medical Oncologist or according to local standard of care. These subjects will be followed for overall survival and progression-free survival. Subsequent data analysis will be performed on an intention-to-treat basis.

6. RADIATION TREATMENT PLANNING AND SBRT ADMINISTRATION

6.1 Pre-SBRT Tests, Procedures, and Planning

The following will be completed **prior to SBRT**:

a) Consultation with medical history and physical examination.
b) Pathology with report confirming malignancy.
c) Labs: CBC with differential, CMP (Comprehensive Metabolic Panel) and CA199. CEA is optional. Additionally, up to 20ml of additional blood may be drawn for research purposes (study bloods may also be collected in follow-up visits). For specific information regarding collection and processing, see Section 12.1 Laboratory Correlative Studies.
d) Seed placement: Gold fiducial seed placement percutaneously, intraoperatively, or under endoscopic ultrasound guidance, which may be performed prior to study enrollment. In some patients, an optional additional core biopsy may be obtained for research purposes if consent is provided by the patient, and may be done at the time of fiducial implantation (See Section 12.1, Laboratory Correlative Studies) or in a separate procedure. For patients who are planned to be treated with active breathing coordinator (ABC) or 4D kV CBCT IGRT, fiducial seed placement is optional.
e) Scans: CT or MR. PET/CT scan is recommended though not required.
f) Signed informed consent.
g) Negative Pregnancy Test (urine or serum) for females of childbearing potential OR menopausal as defined in Appendix III – Definition of Menopausal Status.
h) Eligibility confirmation.
i) Study registration and randomization.
j) Quality of Life Survey: Baseline collection of EORTC QLQ C-30/ PAN26 QOL.

6.1.1 Fiducial Placement

Prior to SBRT, 3 to 5 gold fiducials or 'seeds' (99.9% pure, 1-5 mm length, or visicoils) will be placed directly into the tumor and/or periphery, and when possible in the proximal duodenum directly adjacent to the pancreatic tumor. The fiducials will be used as surrogates for targeting the tumor position during radiation treatment. The procedure will be done typically under endoscopic ultrasound, or if there is a contraindication to endoscopic placement in Interventional Radiology under CT guidance; and is expected to be on an outpatient basis. Fiducials or clips may also be implanted prior to enrollment, as when done intraoperatively at the time of attempted surgical resection, which is within the standard of care and may occur regardless of patient eligibility.

6.1.2 Radiotherapy Simulation

1) Simulation should be done 5 days or more following placement of fiducials; however this may vary per participating institution and is at the discretion of each study investigator.
2) Typically, patients will be positioned supine in an Alpha Cradle or equivalent immobilization device will be custom made for each patient.
3) Standard free-breathing CT and respiratory-correlated 4-D pancreatic protocol CT will be obtained on each patient. The 4D-CT scan will be used for characterizing target motion during quiet respiration. For more accurate tumor delineation, an arterial phase pancreatic protocol CT may be obtained (typically during expiration breath hold, 1.25 mm slices). The simulation scan should include T4/T5 to L5/S1 (upper abdomen).
4) IV and oral contrast must be used for simulation, unless the patient has an allergy that cannot be adequately premedicated. In these situations, the plan should be fused with an IV contrast CT scan or MRI (ideally in a similar treatment position).
5) Motion management can be addressed using respiratory gating or breath-hold, (Varian, Elekta, Novalis), respiratory tracking (Cyberknife), or abdominal compression. When fiducials are used, fluoroscopy will be used to assess motion of implanted gold markers before and after compression. The goal is to reduce motion from typically 11-22 mm peak to less than 5 mm. If the fiducial motion cannot be decreased to 5 mm or less, then another respiratory compensation strategy will be utilized for treatment delivery. Prior to simulation, standard guidelines will be followed.
6) The selection of which radiotherapy treatment machine to use is left to each investigator. As long as the specified dosimetric parameters for SBRT are reached, patients may be treated on any IGRT-enabled machine.
7) **All patients must start SBRT within 4 weeks of the simulation scan and may have up to an 8 week break between radiation and chemotherapy.**

6.1.3 Radiation Treatment Planning

1) When available, an FDG-PET scan is preferred for treatment planning purposes and will be acquired on a flat table top whenever possible with the

same immobilization devices used for the treatment planning CT simulation.

2) An SBRT treatment plan will be developed using Eclipse™, Multi-Plan™ or Pinnacle™ based on tumor geometry and location at each institution. Institutional standards for radiation quality assurance and radiation delivery will be utilized.
3) The final tumor volume (GTV) as identified on the treatment planning CT, will be defined by the attending radiation oncologist after reviewing the diagnostic CT, respiratory-correlated 4D-CT scan, pancreas protocol CT, and the FDG-PET/CT scan. These scans will be used to define the ITV (internal target volume). The final PTV (planning treatment volume) expansion will consist of an additional 2-3 mm of margin expansion, except if the margin results in expansion into the duodenum or stomach. In these cases, margin expansion is allowed to be non-uniform. The dose will be prescribed to the isodose line that completely surrounds the PTV. It is recommended that either 6-12 co-planer fields or 2-4 conformal arcs be used in the radiation treatment plan.
4) When fiducials are used, contours of the fiducials used for target localization will be generated on the applicable image sets, to be used for patient setup on treatment.
5) Radiation dose to the adjacent normal tissue will be minimized and these dose constraints should be met:
   - **Duodenum**: Dmax<40 Gy, V35 < 1cc, V30 < 10cc, V20 < 30cc. V35, V30, and V20 are defined as the volume receiving 35, 30, and 20 Gy, respectively. The duodenum (duo@PTV) as defined for these dosing parameters includes entire duodenum on the same axial plane as the PTV and duodenum 1 cm above and 1 cm below the PTV. The remainder of the normal tissues will be limited as follows:
   - **Liver** (excluding tumor): 50% should be limited to <12 Gy
   - **Kidney**: Combined volume for both should have 75% <12 Gy
   - **Stomach**: Dmax<40 Gy, V35 < 1cc, V30 < 10cc, V20 < 30cc. (no more than 1 cc of stomach can receive >35 Gy)
   - **Spinal Cord**: no more than 1cc can receive >15 Gy
6) No more than 1cc of the PTV can receive >130% of the prescription dose.
7) Greater than 90% of the PTV should receive 100% of the prescription dose.
8) If above constraints cannot be met, 100% of the GTV must receive at least 33 Gy and a request for a minor deviation should be submitted. If this constraint still cannot be met, the patient should be withdrawn from the study and treated according to local standard of care.

6.2 SBRT Treatment Delivery

All patients will receive 5 fractions of 8 Gy allowing up to 30% dose heterogeneity, delivered over a five-day period (ideally all 5 fractions should be delivered Monday through Friday however the 5 fractions may be delivered over 2 weeks as long as the patient receives at least 2 fractions per week). SBRT treatment planning and delivery must be completed at a participating site. The recommended interval between induction chemotherapy followed by SBRT and between SBRT followed by chemotherapy is 2-4 weeks. However, it is acceptable to administer SBRT and chemotherapy within 8 weeks of each other.

If a patient is unable to adhere to the protocol schedule for SBRT treatment, the patient will continue treatment off protocol and as recommended by the treating Medical Oncologist or according to local standard of care. These patients will be followed for overall survival. Subsequent data analysis will be performed on an intention-to-treat basis.

All patients must start SBRT within 4 weeks of the simulation scan and may have up to an 8-week break between radiation and chemotherapy.

For LINAC-based, treatment should entail:

1) Initial patient positioning based on either kV or volumetric kV (cone-beam CT) imaging with shifts to bony anatomy as appropriate.
2) Orthogonal kV/MV or kV/kV projection imaging to verify the location of the fiducials prior to delivery of first treatment beam. A secondary shift based on the location of fiducials may be utilized, as indicated by the position of the fiducials. For free-breathing treatments, kV fluoroscopic images should be obtained to confirm the anticipated position of these fiducials during the entire respiratory cycle.
3) Active monitoring of treatment delivery accuracy using kV and/or MV projection imaging, either immediately before or during all (or a subset of) treatment fields.
4) Patient-specific dosimetric QA performed as per standard practice at each participating institution.

For SBRT, treatment should entail:

1) Initial orthogonal images obtained to confirm location of fiducial seeds.
2) Synchrony respiratory tracking system must be used to correct for respiratory associated tumor motion. This system utilizes a series of optical diodes placed upon the patient's chest wall. While the orthogonal images are obtained, the computer generates a model correlating the position of the chest wall with the position of the internal fiducials. This model is continuously updated during treatment to correct for subtle changes in tumor location.
3) QA performed as per standard practice at each participating institution.

For LINAC-based, treatment without fiducial markers should entail:

1) Patient positioning based on either kV fluoroscopy or volumetric kV (cone-beam CT), using vertebral body and stent for initial positioning.
2) 4D CBCT (for quiet free breathing) or active breathing coordinator (ABC) breath hold stop and go CBCT to be used for IGRT. Oral water (with a small volume of contrast) may be used to help in visualization of the duodenum. Any biliary stents may also be complimentary in patient positioning.
3) QA performed as per standard practice at each participating institution.

6.2.1 Use of Radioisotopes / Rad Machines

Stereotactic radiotherapy will be performed using Trilogy™ or TrueBeam™ (Varian, Palo Alto CA), Novalis™ (BrainLab, Feldkirchen, Germany), or Synergy™ (Elekta AB, Stockholm, Sweden), radiation machines that are designed to use multiple beams of radiation to concentrate large doses of radiation within a tumor. The Cyberknife (Accuray, Sunnyvale, CA) is another

stereotactic radiotherapy machine that may be used in this study. Each of these machines was specifically designed for image guided radiation therapy (IGRT). Because of the innovations in image-guided radiotherapy capabilities associated with each of these machines (or future generation machines), it is possible to deliver highly accurate, stereotactic radiation treatments. Uncertainties in tumor location are minimized because these machines have on-board, volumetric imaging for accuracy in initial patient setup; kV and MV projection imaging during treatment is used to monitor delivery accuracy and/or make corrections to the patients' position.

The radioactive tracer FDG will be used to perform PET scans, a special imaging procedure. Positron emission tomography (PET) is a type of nuclear medicine examination, which is based on the administration of a small amount of a radioactive FDG agent. The tracer (FDG) is a modified form of glucose, a sugar normally found in the bloodstream and used by cells in the body for energy. FDG is eliminated in the urine. With special imaging equipment, it is possible to detect radiation from the administered radioactive agent and obtain images of the body.

RISK INFORMATION

It is difficult at this time to predict with confidence the percentage rate of complications from the proposed SBRT treatment. However it is reasonable to extrapolate from the current experience with radiotherapy in and around the pancreas. Based upon prior phase I and phase II studies, we anticipate that the toxicities associated with this treatment will be acceptable.

Toxicity commonly associated with radiation includes nausea, vomiting, fatigue, anorexia and weight loss. Severe side effects such as gastrointestinal (GI) obstruction, perforation, or hemorrhage are uncommon complications, occurring in <5% of patients undergoing standard radiation therapy for pancreatic cancer. Although we expect a comparable rate of complications with fractionated radiotherapy, it is important to note that vomiting, GI obstruction, GI hemorrhage, anorexia and weight loss are also commonly associated with pancreatic cancer progression. Clinical and radiographic assessments will be performed in an effort to identify these effects, ascertain their etiology and provide the most appropriate palliative measures. Hepatic and renal toxicity is not anticipated given the expectation of limited incidental irradiation of these organs. Complications, if any, will be graded according to the CTCAE, National Cancer Institute, version 4.0 or greater. We will utilize the RTOG scale as necessary for grading acute and chronic radiotherapy toxicities.

6.2.2 Prophylactic and Supportive Medications for SBRT

Patients receiving SBRT should be prescribed antiemetics prophylactically and for relief of nausea and vomiting symptoms. We recommend 1 dose of ondansetron (Zofran) or prochlorperazine (Compazine) 30-60 minutes prior to each SBRT and if needed another dose after 8-12 hours, and as needed twice

daily for 5 days following completion of SBRT. Additional antiemetic measures may be used at the discretion of the treating physician. Administration of Lorazepam is permitted to aid in anxiety and to help with reduction of motion.

Patients should also be advised to take a proton pump inhibitor (PPI) from the start of SBRT (Day 1) and continuing for 6 months following completion of SBRT. Over-the-counter PPIs are acceptable and an increase in medication dose or duration for symptomatic relief is left to the discretion of the treating physician.

For symptoms of diarrhea and/or abdominal cramping, patients can take loperamide (Imodium) and/or additional antidiarrheal measures at the discretion of the treating physician. In cases of diarrhea, patients should be instructed to increase fluid intake to help maintain fluid and electrolyte balance and should be monitored according to the participating center's guidelines.

Administration of prophylactic growth factors at any time during the study is permissible. This decision will be at the discretion of the PI or patient's treating physician.

6.2.3 Other Concomitant Medications

Medications should be monitored by the treating Medical Oncologist. Therapies considered necessary for the patient's well-being may be given at the discretion of the investigator and/or treating physician. Other concomitant medications should be avoided except for analgesics, chronic treatments for concomitant medical conditions, or agents required for life-threatening medical problems. In general, medications will be prescribed by the attending medical oncologist.

Patients' reports of proton-pump inhibitor (PPI), if applicable, and pain medications should be recorded at each visit and entered into REDCap.

7. Chemotherapy and Follow-up after Randomization

7.1 Chemotherapy following SBRT

For patients randomized to SBRT, mFOLFIRINOX should resume within 8 weeks following completion of SBRT. If this schedule cannot be met, the subject may continue treatment "off protocol" and as recommended by the treating Medical Oncologist or according to local standard of care. These patients will be followed for overall survival and progression-free survival. Subsequent data analysis will be performed on an intention-to-treat basis.

Dosing and modification guidelines for mFOLFIRINOX are provided in Section 9, ***however,*** **chemotherapy schedule modifications and dose reductions are allowed and are left to the discretion and clinical judgment of the treating medical oncologist**. A total of at least 6 cycles of mFOLFIRINOX is recommended but the total number of cycles

is left to the clinical judgement of the treating oncologist. As standard practices are changing and Leucovorin is not widely used, we will allow the omission of this drug during both induction and treatment phases of the study.

Participating centers at all times should follow the Study Calendar (Section 14) and ensure that all records and study materials are collected and reported properly.

Since mFOLFIRINOX is an accepted standard of care, chemotherapy may be administered in a community setting as long as the treating oncologist assumes responsibility for the follow up care and reporting requirements. It is recommended that the patient be evaluated at a participating site every 3-6 months.

7.2 Follow-up

All patients will be monitored with clinic visits, labs, and serial imaging (CT or MR scans and PET/CT if possible), and other tests as needed.

Patients deemed resectable at any time during follow-up may proceed to surgery. These patients will be withdrawn from the protocol and followed for survival.

Patients will have consultations in the first year every three months following study treatment as defined in the Study Calendar (Section 14); a follow up at 4-6 weeks is optional and may be done to assess subject's resectability, or if clinically indicated by study PIs or patient's treating physician.

For years 2 and 3, follow-up is recommended every 6 months, or until death or study withdrawal (due to progression, patient withdrawal, or noncompliance as defined in Section 7.5 Criteria for Removal from Study). Follow up intervals may be more frequent as indicated clinically. In the event of intolerable toxicity from mFFX, subjects will still be followed per protocol although chemotherapy may be altered or discontinued, the decisions of which will be left to the treating Medical Oncologist. Visits should include:

- Consultation with physical examination
- Labs: CBC, CMP, CA199. CEA and research bloods are optional.
- Scans: CT or MR and PET/CT if possible (PET/CT is recommended at 3 month follow-up visit but is not required)
- QOL (Quality of Life) Assessment with EORTC QLQ C-30 / PAN26 survey
- Adverse Event (AE) evaluation
- Concomitant Medications: PPIs and pain medications as applicable
- Other tests as appropriate.

Patients who remain on-study will be followed until death and cause of death should be obtained when possible.

7.3 Duration of Study

It is anticipated that the total duration of the study will last approximately 72 months (60 months for recruitment and a minimum of 12 months of follow-up per individual). Patients

may be followed for up to 3 years.

7.4 Duration of Follow Up

Patients will remain enrolled on this protocol until there is evidence that their disease has progressed either locally or distantly; or until study withdrawal for any reason. These patients will be followed for survival.

Progression may be determined by imaging or clinical criteria, i.e., increasing ascites and cachexia. We estimate that most patients will remain a subject in this study for approximately one year. Schedule of follow-up will be as according to the Study Calendar in Section 14.

7.5 Criteria for Removal from Study

Patients will be withdrawn from the study for any of the following reasons:

- disease progression (as defined in Section 15.1.2 Disease Parameters)
- patient withdrawal
- pregnancy
- patient noncompliance, or failure of the patient to follow instructions of the study staff
- protocol director decides that continuing participation could be harmful to the patient
- treatment needed for patient that is not allowed in the study
- patient is deemed resectable and proceeds to surgery
- study cancellation
- other administrative reasons
- unanticipated circumstances.

Patients will continue mFFX on-study until one of these endpoints; in the event of intolerable toxicity from mFFX, subjects will still be followed per protocol although chemotherapy may be altered or discontinued, the decisions of which will be left to the treating Medical Oncologist.

Patients withdrawn from the study will be followed for overall survival only.

7.6 Alternatives

Alternative therapies include chemotherapy alone, standard chemotherapy/radiation, or no further treatment. Additionally, patients may choose to receive treatment to improve quality of life but which may have no affect on the growth of their cancer. The risks of chemotherapy and standard chemotherapy/radiation include nausea, vomiting, diarrhea, fatigue, bone marrow suppression, and sepsis. The potential benefits of chemotherapy or standard chemotherapy/radiation are prolonged survival. The risk of pursuing no further treatment is tumor progression or spread.

7.7 Compensation

Subjects will not be paid to participate in the study.

8. PHARMACEUTICAL INFORMATION

8.1 Investigational Agent or Device

Not applicable.

8.2 Availability

Not applicable.

8.3 Agent Ordering

Not applicable.

8.4 Agent Accountability

Not applicable.

9. TOXICITIES AND mFOLFIRINOX DOSING AND MODIFICATIONS

9.1 Modified Folfirinox (mFFX) Dosing

Modified Folfirinox dosing is below, **however modifications of dose and schedule are allowed as per clinical judgment of patient's treating medical oncologist**. Recommendations for toxicity management are in Section 9.1.1.

mFOLFIRINOX, 1 cycle = 14 days

- Oxaliplatin 85 mg/m² IV over 2 hours on Day 1, followed by
- Irinotecan 180 mg/m² IV over 90 minutes on Day 1, followed by
- Leucovorin* 400 mg/m² IV over 2 hours on Day 1, followed by
- 5FU** 2,400 mg/m² IV over 46 – 48 hours

*Leucovorin may be administered concurrently with the last 30 minutes of oxaliplatin, and the entire 90 minutes of irinotecan
**5FU is administered via infusion only; there is no bolus injection of 5FU

Subjects should be assessed for Adverse Events (AEs) once during each chemotherapy cycle, and AEs should be recorded in the AE Tracking Form in Appendix V. Serious Adverse Events (SAEs) should be reported promptly as according to the guidelines in this protocol. (See Section 11 for more information regarding documenting and reporting SAEs and AEs.)

Chemotherapy infusion records should be kept in the patient's study chart, either with

the Medication Administration Record (MAR) or other clinic records which contain: Date of infusion, dose completed of each agent, modifications if any and reason for modification with supporting source documents as needed. Laboratory results prior to infusion should also be supplied in the patient study chart, as well as the consultation note if the patient is seen by the treating physician.

Laboratory results and administration dates and doses of each agent should also be entered into REDCap.

9.1.1 Recommended Modifications for Toxicity

Below are recommendations and **not** requirements; **modifications of chemotherapy dose and schedule are allowed as per clinical judgment of patient's treating medical oncologist.**

9.1.1.1 Hematologic Toxicity

NOTE: mFOLFIRINOX dose modifications for hematologic toxicity are not based on CTCAE severity grades.

- *For ANC 1,000/mm^3–1,200/mm^3:* Delay mFOLFIRINOX until ANC > 1,200/mm^3 then resume mFOLFIRINOX at the same dose level.
  - *Second or More Occurrence of ANC 1000/mm^3-1200/mm^3*: Delay mFOLFIRINOX until ANC > 1,200/mm^3 then resume mFOLFIRNOX with one dose level reduction for all subsequent cycles. **NOTE**: The dose of leucovorin is not reduced.

- *For ANC < 1,000/mm^3:* Delay mFOLFIRINOX until ANC > 1,200/mm^3, then resume mFOLFIRINOX with one dose level reduction for all subsequent cycles. **NOTE**: The dose of leucovorin is not reduced.

- *For Febrile Neutropenia (defined as ANC < 1,000/mm^3 and temperature ≥ 100.5°F):* Delay mFOLFIRINOX until resolution of fever and ANC > 1,200, then resume mFOLFIRINOX with one dose level reduction for all subsequent cycles. **NOTE**: The dose of leucovorin is not reduced.

- *For Platelets 50,000 K/ul – 75,000 K/ul:* Delay mFOLFIRINOX until platelets > 75,000 then resume mFOLFIRINOX at the same dose level.
  - *Second or More Occurrence of platelets 50,000 K/ul - 75,000 K/ul:* Delay mFOLFIRINOX until platelets > 75,000*K/ul*, then resume mFOLFIRINOX with one dose level reduction for all subsequent cycles. **NOTE**: The dose of leucovorin is not reduced.

- *For Platelets < 50,000 K/ul:* Delay mFOLFIRINOX until recovery to Plts > 75,000 *K/ul* then resume mFOLFIRINOX with one dose level reduction for all subsequent cycles. **NOTE**: The dose of leucovorin is not reduced.

9.1.1.2 Non-Hematologic Toxicity

Diarrhea

- *For grade 2 Diarrhea (despite optimal medical management*: see Section 9.1.3):
  - *First Occurrence*: Delay mFOLFIRINOX until recovery to grade ≤ 1 or baseline then resume mFOLFIRINOX at the same dose level.
  - *Second or More Occurrence*: Delay mFOLFIRINOX until recovery to grade ≤ 1 or baseline, then resume mFOLFIRINOX with one dose level reduction for all subsequent cycles. **NOTE**: The dose of leucovorin is not reduced.

- *For grade 3 Diarrhea (despite optimal medical management:* see Section 9.1.3):
  - *First Occurrence*: Delay mFOLFIRINOX until recovery to grade ≤ 1 or baseline, then resume 5-FU, leucovorin, and oxaliplatin, at the same dose level and irinotecan with one dose level reduction for all subsequent cycles.
  - *Second or More Occurrence*: Delay mFOLFIRINOX until recovery to grade ≤ 1 or baseline, then resume mFOLFIRINOX with one dose level reduction for all subsequent cycles. **NOTE**: The dose of leucovorin is not reduced.

- *For grade 4 Diarrhea (despite optimal medical management):* Delay mFOLFIRINOX until recovery to grade ≤ 1 or baseline then resume mFOLFIRINOX with one dose level reduction for all subsequent cycles. **NOTE**: The dose of leucovorin is not reduced.

Nausea/Vomiting

The following dose modifications are based on toxicity experienced during a cycle.

- *For grade 3 Nausea/Vomiting (despite optimal medical management):*
  - *First Occurrence*: Delay mFOLFIRINOX until recovery to grade ≤ 1 or baseline, then resume 5-FU and leucovorin, at the same dose level and oxaliplatin and irinotecan with one dose level reduction for all subsequent cycles.
  - *Second or More Occurrence*: Delay mFOLFIRINOX until recovery to grade ≤ 1 or baseline, then resume mFOLFIRINOX with one dose level reduction for all subsequent cycles. **NOTE**: The dose of leucovorin is not reduced.

- *For grade 4 Nausea/Vomiting (despite optimal medical management):* Delay mFOLFIRINOX until recovery to grade ≤ 1 or baseline, then resume mFOLFIRINOX with one dose level reduction for all subsequent cycles. **NOTE**: The dose of leucovorin is not reduced.

Mucositis

The following dose modifications are based on toxicity experienced at any time during a cycle.

- *For grade 3 Mucositis:*
  - *First Occurrence*: Delay mFOLFIRINOX until recovery to grade ≤ 1, then *resume irinotecan, oxaliplatin, and leucovorin at the same dose level and 5*-FU with one dose level reduction for all subsequent cycles.
  - *For Second or More Occurrence*: Delay mFOLFIRINOX until recovery to grade ≤ 1, then resume mFOLFIRINOX with one dose level reduction in irinotecan and oxaliplatin for all subsequent cycles. Dose of 5FU is reduced two dose levels for all subsequent cycles). **NOTE**: The dose of leucovorin is not reduced.

- *For grade 4 Mucositis:*
  Delay mFOLFIRINOX until recovery to grade ≤ 1, then resume mFOLFIRINOX with one dose level reduction for all subsequent cycles. **NOTE**: The dose of leucovorin is not reduced.

Peripheral Sensory Neuropathy

NOTE: Dose modifications for sensory neuropathy are **not** based on CTCAE severity grades.

- *For paresthesia/dysethesia interfering with function and persisting between treatments:* decrease oxaliplatin by one dose level for all subsequent cycles.

- *For painful paresthesia/dysesthesia or symptoms that interfere with function and ADL, but improve (no longer painful or no longer interfering with ADL) between treatments:* decrease oxaliplatin by one dose level for all subsequent cycles.

- *For painful paresthesia/dysesthesia or symptoms that interfere with function and ADL that persists between treatments*: Discontinue oxaliplatin.

- *For persistent disabling or life-threatening paresthesia/dysesthesia: Discontinue oxaliplatin.*

- *For pharyngo-laryngeal dysesthesia:* increase the duration of oxaliplatin infusion to 6 hours for subsequent cycles.

Oxaliplatin-induced pharyngolaryngeal dysesthesias

Should a patient develop oxaliplatin-induced pharyngolaryngeal dysesthesia, her/his oxygen saturation should be evaluated via a pulse oximeter; if normal, an anxiolytic agent may be given and the patient observed in the clinic until the episode has resolved. Following resolution of symptoms, patients may

continue/resume oxaliplatin if the reaction is NOT determined to be an allergic reaction.

A table comparing pharyngo-laryngodysesthesia to platinum hypersensitivity reactions is presented below.

Table 1 - Comparison of the Symptoms and Treatment of Pharyngolaryngodysesthesias and Platinum Hypersensitivity Reactions

Clinical Symptoms	**Pharyngo-Laryngeal Dysesthesias**	**Platinum Hypersensitivity**
Dyspnea	Present	Present
Bronchospasm	Absent	Present
Laryngospasm	Absent	Present
Anxiety	Present	Present
O2 saturation	Normal	Decreased
Difficulty swallowing	Present (loss of sensation)	Absent
Pruritis	Absent	Present
Urticaria/rash	Absent	Present
Cold-induced symptoms	Yes	No
Blood pressure	Normal or increased	Normal or decreased
Treatment	Anxiolytics, observation in a controlled clinical setting until symptoms abate or at the physician's discretion	Oxygen, steroids, epinephrine, broncho-dilators; fluids and vasopressors, if appropriate

Venous Thrombembolic Events

- *For grade 2 or 3 venous thromboembolic event:* Continue mFOLFIRINOX at the same dose level. Do not use warfarin for therapeutic anticoagulation.

- *For grade 4 venous thromboembolic event: Discontinue mFOLFIRINOX.*

Liver Function Tests

- *For grade 2 Increased Blood Bilirubin:* Skip irinotecan until bilirubin improves to ≤ grade 1.
  - For hyperbilirubinemia considered at least possibly related to irinotecan, then resume irinotecan with one dose level reduction for all subsequent cycles.
  - For hyperbilirubinemia considered unrelated to irinotecan, resume irinotecan at the previous dose level.

- *For grade 3 or 4 Increased Blood Bilirubin:* Delay mFOLFIRINOX until bilirubin improves to ≤ grade 1. If bilirubin is thought to be due to a chemotherapy drug, then resume that drug at the next lower dose level

and the other drugs at the same dose level when total bilirubin improves to ≤ grade 1.

- For hyperbilirubinemia considered at least possibly related to treatment (any drug) resume mFOLFIRINOX with one dose level reduction in suspect drug(s) for all subsequent cycles.
- For hyperbilirubinemia considered unrelated to treatment (all drugs), resume mFOLFIRINOX at the previous dose levels.

Allergic Reactions

- *For grade 2 allergic reactions*: Interrupt infusion(s). Manage reaction according to institutional policy. Restart the infusion(s) when symptoms resolve to ≤ grade 1 and pre-treat before all subsequent doses.

- *For grade 3 or Grade 4 allergic reactions:* Discontinue infusion. Manage reaction according to institutional policy. Discontinue mFOLFIRINOX.

Irinotecan dosing and UGT1A1*28 allele homozygosity

Caution should be exercised when dosing irinotecan in patients who express homozygous for the UGT1A1*28 allele. The toxicity is dose-dependent. The FDA recommends reducing the dose by one dose level for patients expressing UGT1A1*28 allele. For additional information, please refer to the package insert.

Other non-hematologic toxicities

- *For all other grade 3 non-hematologic toxicities considered at least possibly related to mFOLFIRINOX:* Skip the responsible drug(s) until toxicity improves to ≤ grade 1, then resume the responsible drug(s) with one dose level reduction for all subsequent cycles.

- *For grade 4 non-hematologic toxicities considered at least possibly related to mFOLFIRINOX:* Discontinue the responsible drug(s).

9.1.2 Management of Diarrhea during Systemic Treatment prior to Chemoradiation

- *Early Diarrhea (e.g., developing in less than 24 hours after irinotecan infusion:*
  Lacrimation, rhinorrhea, miosis, diaphoresis, hot flashes, flushing, abdominal cramping, diarrhea, or other symptoms of early cholinergic syndrome may occur during or shortly after receiving irinotecan. Atropine, 0.25-1. mg IV or SC may be used to treat these symptoms. In patients with troublesome or recurrent symptoms, prophylactic administration of atropine shortly before irinotecan therapy may be considered. Additional antidiarrheal measures may be used at the discretion of the treating physician. Combination anticholinergic medications containing barbiturates or other agents (e.g., Donnatal®) should not be used because these may affect irinotecan

metabolism. Anticholinergics should be used with caution in patients with potential contraindications (e.g., obstructive uropathy, glaucoma, tachycardia, etc.).

- *Late Diarrhea (e.g., developing more than 24 hours after irinotecan infusion):*
  Manage with loperamide, as per standard of care guidelines and package insert for irinotecan. Dose modifications are based on toxicity experienced at any time during a cycle.

Patients should be optimally managed with anti-diarrheal medications before dose modifications are made.

9.1.3 SBRT Toxicities and Potential Risks

Prior studies investigating 25 Gy given in a single fraction resulted in a combined Grade 3 or higher toxicity in 8% of patients. In our recently completed multi-center Phase II study, we did not observe significant toxicities related to SBRT with a dose of 33 Gy in 5 fractions.

In another recent study of SBRT for unresectable locally advanced pancreas cancer, with a prescription dose of 45Gy (7.5 Gy in 6 fractions), no Grade $\geq$ 3 toxicities were reported and FFLP was $\geq$ 91% at 6 months.(29)

Given these recently reported data of improved FFLP and no increase in toxicity, the SBRT prescription dose will be 40 Gy (in 5 fractions of 8 Gy).

Hepatic and renal toxicity is not anticipated given the expectation of limited incidental irradiation of these organs and we have not observed any to date in the patients treated with SBRT. Complications, if any, will be graded according to CTCAE v4.0 or higher.

10. DRUG FORMULATION, AVAILABILITY, AND PREPARATION

Qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents in a self-contained, protective environment. Chemotherapy treatment is standard-of-care and can be administered at any qualified medical facility.

Discard unused portions of injectable chemotherapeutic agents that do not contain a bacteriostatic agent or are prepared with unpreserved diluents (i.e., Sterile Water for Injection USP or 0.9% Sodium Chloride for Injection USP) within eight hours of vial entry to minimize the risk of bacterial contamination.

The total administered dose of chemotherapy may be rounded up or down within a range of 5% of the actual calculated dose.

10.1 Oxaliplatin

Please refer to the package insert for complete product information.

Availability

Oxaliplatin is commercially available a solution in vials containing 50 mg, 100 mg, and 200mg at a concentration of 5 mg/mL. The vials do not contain any preservative and they are intended for single use.

Storage and Stability

Intact vials should be stored at room temperature. According to the manufacturer, solutions diluted in D5W are stable for 6 hours at room temperature or 24 hours under refrigeration. Solutions diluted in D5W to a concentration of 0.7 mg/mL are reported to be stable (sterility not tested) for up to 30 days at room temperature or under refrigeration.

Preparation

The calculated dose of oxaliplatin should be diluted for infusion with 250 mL to 500 mL D5W. Oxaliplatin should not be diluted with a chloride-containing solution. Needles, syringes, catheters or IV administration sets containing aluminum should not be used with oxaliplatin. As with other platinum compounds, contact with aluminum may result in a black precipitate.

Administration

Oxaliplatin will be administered by intravenous infusion over 2 hours prior to irinotecan, and prior to or concurrent with leucovorin. Infusion time may be prolonged (up to 6 hours) in patients experiencing pharyngolaryngeal dysesthesia.

Toxicity

The most commonly observed oxaliplatin toxicities include neurotoxicity, GI toxicity, and myelosuppression. Three neurotoxicity syndromes have been seen: acute sensory neuropathy develops within hours to 2 days after oxaliplatin administration. Symptoms include, paresthesias, dysesthesias, and hypothesia of the hands, feet and perioral region. Jaw spasm, abnormal tongue sensation, dysarthria, eye pain and a sensation of chest pressure have also been noted. Acute sensory neuropathy symptoms may be exacerbated by exposure to cold temperature or cold objects. Symptoms are reversible, usually resolving within 14 days and commonly recurring with further dosing. This syndrome has been observed in about 56% of patients receiving oxaliplatin with 5-FU and leucovorin.

Acute pharyngolaryngeal dysesthesia is reported to occur in 1-2% of patients. This syndrome is characterized by a subjective sensation of difficulty breathing or swallowing without laryngospasm or bronchospasm or objective evidence of hypoxia. Avoidance of cold drinks, food and air is suggested in order to minimize pharyngolaryngeal dysesthesia. Antianxiety agents (e.g., lorazepam) may be used to treat pharyngolaryngeal dysesthesias once oxygen saturation has been documented to be normal.

Peripheral neuropathy persisting > 14 days is characterized by paresthesias, dysesthesias, and hypothesia. Abnormalities in proprioception may also be seen. Symptoms of persistent neuropathy may improve upon discontinuation of oxaliplatin.

Various agents have been used in an attempt to minimize neurotoxicity of oxaliplatin (e.g. carbamazepine, Mg+, Ca++). Calcium and magnesium infusions appear to be beneficial in preventing neurotoxicity. Contrary to preliminary findings described in

2007, calcium and magnesium do not appear to interfere with tumor response to FOLFOX. Calcium and magnesium infusions are generally given before and after oxaliplatin, and should not be prepared in the same infusion solution as FOLFOX or FOLFIRINOX components.

Gastrointestinal toxicities include nausea, vomiting (oxaliplatin is considered to be moderately emetogenic) and diarrhea. Grade 3 or 4 neutropenia was reported in 46% of patients receiving FOLFIRINOX, and grade 3 or 4 thrombocytopenia was reported in 9%.

Allergic reactions, similar to those seen with other platinum compounds, have also been observed in patients treated with oxaliplatin. Reactions range from rash to anaphylaxis.

Rarely, oxaliplatin has been associated with pulmonary fibrosis, which may be fatal. Oxaliplatin should be discontinued in the presence of unexplained pulmonary symptoms (e.g. nonproductive cough, dysphagia) or pulmonary infiltrates until interstitial lung disease or pulmonary fibrosis have been ruled out.

Recent reports of oxaliplatin extravasation suggest that tissue necrosis may result and that oxaliplatin should be considered a vesicant. No standard treatment exists for oxaliplatin extravasation although heat and sodium thiosulfate have both been suggested.

Veno-occlusive disease (VOD) of the liver is a rare complication associated with oxaliplatin and 5-FU. Clinical manifestations of VOD include hepatomegaly, ascites, and jaundice. Histologically, VOD is characterized by diffuse damage in the centrilobular zone of the liver. Sequelae of VOD include hepatomegaly, splenomegaly, portal hypertension, and esophageal varices. A recent analysis of resected liver metastases in 153 patients indicated histological findings consistent with VOD in 6/27 patients who received 5-FU alone, 4/17 patients who received 5-FU and irinotecan, 20/27 patients who received 5-FU and oxaliplatin, and 14/16 who received 5-FU, oxaliplatin and irinotecan. The remaining 66 patients had not received chemotherapy prior to resection. There were no such findings in these patients.

For more information on toxicities associated with oxaliplatin, please see the package insert.

10.2 5-Fluorouracil (5-FU)

Please refer to the package insert for complete product information.

Availability

5-FU is commercially available as a 50 mg/mL solution for injection in 10 mL, 20 mL, 50 mL and 100 mL vials.

Preparation

Inspect for precipitate; if found, agitate or gently heat in water bath.

46-48 hour infusion of 5-FU should be prepared for administration via ambulatory infusion pump according to the individual institution's standards. These solutions may be prepared in D5W or 0.9% NaCl. 5-FU should not be mixed in the same solution with most parenteral antiemetics.

Storage and Stability

Intact vials should be stored at room temperature and protected from light. Slight yellow discolor does not usually indicate decomposition. Stability in ambulatory pumps varies

according to the pump, manufacturer of drug, concentration and diluent. Please refer to appropriate reference sources for additional information.

Administration

In this study, 5-FU is administered as an IV infusion over 46 – 48 hours. There is no bolus injection of 5-FU.

Toxicity

GI: Nausea, diarrhea, vomiting (mild); stomatitis: 5-8 days after treatment initiation; Myelosuppression: neutropenia (9-14 days); thrombocytopenia (7-14 days);

Dermatologic: Alopecia; nails changes; vein pigmentation; photosensitivity; maculopapular rash; palmar–plantar erythrodysethesias,

CNS effects: cerebral ataxia (rare);

Cardiotoxicity: MI, angina; asymptomatic S–T changes;

Ocular effects: excessive lacrimation and less commonly, tear duct stenosis.

Drug Interactions

Leucovorin enhances the cytotoxicity of 5-FU by forming a more stable tertiary complex with thymidylate synthase. Concommitant adminstration of 5-FU with warfarin has been reported to result in increased INR/prolonged prothrombin time.

10.3 Leucovorin Calcium (Folinic Acid) (calcium folinate; citrovorum factor; N 5-formyltetrahydrofolate; 5-formyl-FH4; folinic acid)

Please refer to the package insert for complete product information.

Availability

Leucovorin calcium is commercially available in 50 mg, 100 mg, 200 mg, and 350 mg vials for reconstitution, and 50 mL vials of solution at a concentration of 10 mg/mL.

Storage and Stability

Intact vials of powder for reconstitution should be stored at room temperature and protected from light. Solutions reconstituted with bacteriostatic water for injection are stable for up to 7 days at room temperature. Solutions reconstituted with sterile water for injection should be used immediately.

Intact vials of solution should be stored under refrigeration and protected from light.

Solutions further diluted for infusion are stable for 24 hours at room temperature, and 4 days under refrigeration.

Preparation

Leucovorin may be reconstituted with Bacteriostatic Water for Injection or with Sterile Water For Injection. Solutions should be further diluted in D5W, 0.9% NaCl or Ringers solution for IV infusion over two hours.

Administration

Leucovorin will be administered as a 400 mg/m^2 IV infusion over 2 hours after, or concurrent with, oxaliplatin and irinotecan. For administration concurrent with oxaliplatin (30 minutes) and irinotecan (90 minutes), leucovorin is administered as a separate infusion (i.e, not in the same IV solution).

Toxicity

The only adverse reactions associated with leucovorin are allergic reactions. These are

rare.

10.4 Irinotecan (CPT-11, CAMPTOSAR®)

Please refer to the package insert for complete product information.

Availability

Irinotecan is commercially available as a 20 mg/mL solution for injection in 2 mL and 5 mL vials.

Storage and Stability

Intact vials should be stored at controlled room temperature 59° to 86° F (15° to 30° C) and protected from light. Solutions diluted in D5W are reported to be stable for 24 hours at room temperature, or 48 hours under refrigeration and protected from light.

Preparation

Irinotecan is diluted in 5% dextrose (D5W) 500 mL to a final concentration of 0.12 – 2.8 mg/mL. Stability is improved in D5W as compared with NaCl.

Administration

In this study irinotecan will be administered as an IV infusion over 90 minutes, following oxaliplatin, and prior to, or concurrent with, leucovorin.

Toxicities

Neutropenia and/or late diarrhea (diarrhea occurring more than 24 hours after irinotecan administration) are frequently dose-limiting. Other commonly observed adverse events include nausea and vomiting, anorexia (irinotecan is considered moderately emetogenic), abdominal cramping, alopecia, asthenia, lymphocytopenia, and anemia. Dehydration has occurred as a consequence of diarrhea, particularly when associated with severe vomiting. Patients may experience an acute syndrome of lacrimation, diaphoresis, abdominal cramping, and diarrhea (early diarrhea) during or shortly after irinotecan administration; this syndrome is thought to be cholinergically mediated and may be treated and subsequently prevented with atropine. Elevations of bilirubin and alkaline phosphatase have been reported in up to 84% and 13% of patients, respectively. Sporadic cases of pulmonary toxicity, manifested as shortness of breath, nonproductive cough, and transient infiltrates on chest X-ray have been reported. Infrequent occurrences of mucositis or colitis (sometimes with gastrointestinal bleeding) have been observed. Irinotecan is metabolized to Sn-38, an active metabolite. SN-38 is conjugated by UGT1A1. Homozygosity for the UGT1A1*28 allele increases the risk of severe neutropenia with irinotecan, and known homozygotes are not eligible for this trial.

Further information regarding irinotecan may be obtained from the package insert.

11. ADVERSE EVENTS, UNANTICIPATED PROBLEMS, AND DEVIATIONS

As Coordinating Center, we will follow guidelines from Stanford's Research Compliance Office and Cancer Clinical Trials Office (CCTO) for defining, identifying, and reporting events as defined below.

11.1 Serious Adverse Events (SAEs)

A Serious Adverse Event (SAE) is defined as: Any adverse event that meets any of the following criteria:

- Fatal (i.e., the adverse event actually causes or leads to death)
- Life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death). This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).(28)

11.1.1 Reporting SAEs

SAEs should be graded according to the NCI Common Terminology Criteria for Adverse Events, Version 4.0, available at http://ctep.cancer.gov/reporting/ctc.html.

SAEs Grade 3 and above require prompt reporting – within 24 hours of learning of the event. Reporting should be done by entering the event into OnCore (Stanford's clinical trials management system) and sending an email to Stanford Cancer Clinical Trials Office (CCTO) at ccto-safety@stanford.edu, copying Dr. Daniel Chang and Stanford research staff (Research Nurse or Research Coordinators) with subject line: "SECURE: PanCRS STUDY Serious Adverse Event." A Case Report Form (CRF) describing the event must be supplied and can be sent as an attachment to the email. It could be generated from the OnCore entry (as a pdf or report), or using the Case Report Form in Appendix V.

Stanford research staff will notify Stanford IRB via 'eProtocol' as per regulatory guidelines. The SAE may also be forwarded to other Stanford regulatory boards, e.g., DSMC, as applicable.

Any questions, issues, or need for clarification of the event by Stanford IRB will go through Stanford study PIs or Coordinators to the participating center research staff.

Participating centers are responsible for reporting the SAE to their IRB within their institutional timeframes and guidelines.

Participating sites should also:

- Place copies of the SAE Report in the patient's study chart and in the regulatory binder (electronic regulatory binder is allowed).

- Follow patient and provide update to Stanford until any of the below:
  - Resolution of event
  - Resolution of event with sequelae
  - Death of patient

11.2 Unanticipated Problems (UPs)

Per Stanford IRB, UPs are events involving risks to participants or others and must meet ALL 3 criteria below:

1. **Unexpected**: in terms of nature, severity, or frequency, given (a) the research procedures described in the protocol-related documents, and (b) the characteristics of the subject population being studies; AND
2. **Related** to participation in the research: or there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research; or if a device is involved, probably caused by, or associated with the device; AND
3. **Harmful**: suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

UPs *generally will warrant consideration of substantive changes in the research protocol or informed consent process/document, or other corrective actions, in order to protect the safety, welfare, or rights of subjects or others.(27) Due to this, UPs will be reported promptly to Stanford IRB following the below guidelines.*

A UP may also be an AE or SAE and can be noted as both on CRFs and in OnCore.

11.2.1 Reporting UPs

UPs should be entered into OnCore and reported within 24 hours of learning of the event. Reporting can be done via email to Stanford Cancer Clinical Trials Office (CCTO) at ccto-safety@stanford.edu, copying Dr. Daniel Chang and Stanford research staff (Research Nurse or Research Coordinators), with subject line: "SECURE: PanCRS STUDY Unanticipated Problem." A Case Report Form (CRF) describing the event must be supplied and can be sent as an attachment to the email. It could be generated from the OnCore entry (as a pdf or report), or using the Case Report Form in Appendix V.

Stanford research staff will notify Stanford IRB via 'eProtocol' as per regulatory guidelines. The UP may also be forwarded to other Stanford regulatory boards, e.g., DSMC, as applicable.

Any questions, issues, or need for clarification of the UP by Stanford IRB will go through Stanford study PIs or Coordinators to the participating center research staff.

Participating centers are responsible for reporting Unanticipated Problems or similar events to their IRB within their institutional timeframes and guidelines.

Participating sites should also:

- Place copies of the UP Report in the patient's study chart and in the regulatory binder (electronic regulatory binder is allowed).
- Follow patient and provide update to Stanford until any of the below:
  - Resolution of event
  - Resolution of event with sequelae
  - Death of patient

SAE and UP Reporting Requirements				
Hospitalization	Grade 1	Grade 2	Grade 3	Grade 4/5
Hospitalization≤ 24 hrs	UP's within 24 hours	UP's within 24 hours	Report SAE and UP within 24 hours	Report SAE and UP within 24 hours
Hospitalization≥ 24 hrs	UP's within 24 hours	UP's within 24 hours	Report SAE and UP within 24 hours	Report SAE and UP within 24 hours
SAE Definition: Fatal, life threatening, requires hospitalization or prolongs hospitalization, results in persistent or significant disablility, causes congenital anomaly/birth defect or significant medical event.				
Unexpected Problem (UP) Definition: Unexpected in terms of nature, severity, or frequency. Related to participation in the research. And Harmful suggesting that the research places subjects or others at a greater risk of harm.				
To report all UP's and SAEs Grade 3 and above: 1)Enter the event into OnCore, 2)send eamil to Dr. Daniel Chang and Stanford research staff (Rachel Freiberg) with the subject line: "SECURE: PanCRS STUDY Serious Adverse Event" and 3)Include Case Report Form describing the event and submit follow up reports for the resolution of the event. For any questions regarding whether an event is an SAE or a UP, please email Dr. Chang and Rachel.				
Dr. Albert Koong: **akoong@stanford.edu** Rachel Freiberg: **rachelf@stanford.edu**				

11.3 Adverse Events (AEs) and AE Monitoring

An AE is defined as any untoward medical occurrence in a clinical investigation subject, regardless of causal attribution.

All AEs should be graded according to the NCI Common Terminology Criteria for Adverse Events, Version 4.0, available at http://ctep.cancer.gov/reporting/ctc.html.

AEs should be:

- Assessed at each consultation or follow-up visit,
- Assessed during each mFFX cycle (prior to infusion is acceptable), and
- Recorded on the AE Tracking form in Appendix V.

Laboratory tests (CBC with differential and CMP) should also be obtained with each mFFX administration, and abnormal values also noted on the AE Tracking Form indicating AE Grade if applicable.

AEs should also be:

- Reported to Stanford as per protocol guideline and upon request
- Noted in patient study charts and binder
- Entered into REDCap CRFs
- Reported to the participating center's IRB as per their institutional guidelines.

AEs in REDCap CRF should remain current and may be requested by Stanford for study renewals, audits, reports, analyses or other submissions for Stanford IRB, SRC, or DSMC. AEs may also be reviewed by members of the study monitoring group in meetings, audits, and/or site visits.

Updates and outcomes of AEs, SAEs, UPs, and deviations may take place during teleconferences or more frequently as needed.

11.4 Deviations

A protocol deviation is any unapproved discrepancy from a protocol research plan or Good Clinical Practice (GCP) guidelines, except where necessary to eliminate an immediate hazard to trial subjects.

11.4.1 Documenting and Reporting Deviations

Serious or Major Deviations

Research staff should promptly report serious or major deviations, or those that affect participant eligibility, informed consent, or protocol endpoints; and/or any deviation that could potentially result in harm to participants. These should be reported within 24 hours of the deviation or of learning of the deviation, by entering them into OnCore. The OnCore record should include the following:

- description of the deviation,
- corrective action taken,
- a statement whether the patient was harmed or could have been potentially harmed by the deviation, and

- whether the deviation was reported to the participating center's IRB, and/or Stanford IRB.

Stanford research staff should also be immediately notified of the deviation, via email to Dr. Daniel Chang, copying the study Research Nurse or Research Coordinator with subject line: "SECURE: PanCRS STUDY Major Deviation." A Case Report Form (CRF) describing the event is required and could be generated from the OnCore entry (as a pdf or report) and attached to the email.

Stanford DSMC reviews deviations in OnCore to ensure completeness of the deviation report and ensure the safety of trial participants. The DSMC may request corrective action and/or prompt reporting to Stanford IRB. If reporting to Stanford IRB is required, Stanford's research staff (Study Nurse or Coordinator) will assist with this by entering the deviation in 'eProtocol'.

Any questions, issues, or need for clarification of the event by Stanford IRB will go through Stanford study PIs or Coordinators to the participating center research staff.

Participating sites should also:

- Place copies of the Deviation Report or CRF in the patient's study chart and in the regulatory binder (electronic regulatory binder is allowed).
- Follow patient and provide update to Stanford until any of the below:
  - Resolution of event
  - Resolution of event with sequelae
  - Death of patient

Participating centers are responsible for reporting deviations to their IRB within their institutional timeframes and guidelines.

Minor Deviations

Deviations not meeting the above criteria for major or 'serious,' or that do not have a significant effect on the subject's rights, safety, or welfare, or on the integrity of the data -- e.g., conducting a protocol-required visit out of the protocol 'window' -- should be documented on the Deviation Log in Appendix V.

Deviations in OnCore or in Deviation logs should remain current at all time, and may be requested by Stanford for study renewals, audits, reports, analyses or other submissions for Stanford IRB, SRC, or DSMC.

11.5 Study and Subject Reviews

Teleconferences will be held every other month for purposes of study and subject reviews, issues, and updates. Participating centers will have at least 1 research

team member partake and any pertinent study information will be communicated to PIs by the attending research team member(s). Any issues with patient compliance, database entry, toxicities, AEs, UPs, or SAEs, protocol updates or reviews, or other items will be discussed in calls.

Also, at times of study renewal and safety or interim analyses, research staff for each participating center will compile and submit requested patient data and clinical trial efficacy endpoints. These and other pertinent study data will be discussed and reviewed by the monitoring group to confirm whether outcomes favor continuation of the study.

Teleconferences will be coordinated by Stanford Research staff and any resultant reports will be distributed to participating centers' PI or assigned research team member.

12. CORRELATIVE/SPECIAL STUDIES

12.1 Laboratory Correlative Studies

12.1.1 Analysis of patient plasma for biomarker development

12.1.1.1 Collection of Specimen(s) (optional):

Collaborating centers who partake in this part of the study can have patients elect to participate in this portion of the study on the consent form.

Blood Samples

a) Blood (EDTA preserved) for research purposes may be drawn after re-staging scans when patient is enrolled and registered on-study, and then at each follow-up along with the patient's clinical labs. For each collection, up to 20ml (2 large lavender tubes at 10ml each) will be drawn.

b) Immediately after collection, blood will be centrifuged at 3000 RPM for 10 minutes and plasma collected. The supernatent will be aliquoted for storage at -80°C into separate tubes. The pellet will also be stored in a separate tube at -80°C.

12.1.1.2 Shipping of Specimen(s)

Samples may be shipped to Stanford for analysis. Samples will be shipped overnight by federal express on dry ice and sent in batches.

12.1.1.3 Site(s) Performing Correlative Studies

All biomarker studies will be performed at Stanford by Dr. Daniel Chang or in the laboratory of a research collaborator.

We will utilize proximity ligation assay (PLA) to simultaneously interrogate a panel of 60-100 secreted proteins that we have developed for pancreatic cancer patients. PLA is an antibody-based method of detection in which complementary single-stranded oligonucleotides are linked to each antibody pair. When the 2 antibodies bind in close enough proximity, the local concentration increases, allowing for PCR amplification of this signal. PLA is more sensitive than conventional ELISA and can be reliably multi-plexed for the detection of multiple protein panels (Fredrikkson et al). In a pilot study, we have shown that when using this method of detection (Chang et al), we can accurately identify patients with pancreatic cancer. In this study, we will expand the number of biomarkers and collect plasma at multiple time points during therapy. The goal is to identify a biomarker panel that is predictive of patient outcome and/or response to therapy. We hypothesize that not only is the pattern of secreted biomarkers important but the change in these biomarkers may be even more critical for prediction of clinical outcomes.

12.1.1.4 Coding of specimens for privacy protection

At the time of enrollment each patient will be given a specific confidential identification number (IDN). Specimens will be stored under the patient's IDN. The information can be shared with other investigators listed on this protocol. Study data will be maintained in password protected computer files (protected online database through Johns Hopkins). Only research personnel will have access to this information.

12.2 Collection of Pre- and Post- Treatment Scans, Treatment Planning Scans, and Treatment Plans

12.2.1 Data and Image Collection

12.2.1.1 All images (CT, PET, or MR) including re-staging scans, treatment planning scans and follow-up scans will be transferred electronically to a secured database or on password-protected discs or encrypted drives, using an IDN assigned at registration for each patient. Specific parameters will be prospectively collected such as treatment volume and dose to adjacent structures.

The JHU database is set up to store ROI geometries and dose distributions along with the CT. This design facilitates the investigation of dosimetric effects on tumor response and complication utilizing DVH or other attributes of the 3D dose. For Pinnacle, the data can be directly placed in the JHU database via scripts. For other planning systems, DICOM RT data transfer will be used.

13. INVESTIGATOR RESOURCES

13.1 Qualifications

The study staff will include, but is not limited to, the Principal Investigator, Co-Investigators, research coordinators, research nurses, and any residents or fellows working with the study physicians at each institution. Also, laboratory personnel in the Principal Investigator's laboratory will be involved in analyzing the plasma and tumor specimens collected from patients.

All study staff will have completed the required training specific for their responsibilities in this study. Furthermore, each member of the research team from each institution will be given a thorough explanation of the protocol and their responsibilities. All research investigators will be required to complete proper training through their facility and institutional review boards.

13.2 Use of Cancer Center Facilities

Patients will be evaluated and treated in their respective institutions. All radiotherapy for this study will be performed in the department of radiation oncology at the participating institution. Other procedures related to this study (i.e., blood draws, tissue biopsy, imaging studies) will be carried out at each institution.

13.3 Conflict of interest

There is no potential conflict of interest among the research personnel involved in this study.

14. STUDY CALENDAR

Activity	Induction Chemotherapy				RANDOMIZE	Study Treatment		Follow-up (Time From Completion of Study Treatment)[j]						
	Screen-ing	Study Enroll-ment	Induction Chemo / mFFX[g]	Re-staging[c]		SBRT[d]	mFFX 2 cycles[f]	4-8 wks[k]	3[j] mos	6[j] mos	9[j] mos	12[j] mos	Yr 2-Q 6[j] mos	Yr 3-Q 6[j] mos
Biopsy	X													
Negative Pregnancy test[a]	X													
Consultation	X	X	X[g]					X[k]	X	X	X	X	X	X
ECOG PS	X	X						X[k]	X	X	X	X	X	X
Labs: CBCD, CMP, CA19-9 (CEA optional)	X	X[b]	X[g]				X[h]	X[k]	X	X	X	X	X	X
Study/research labs[i] (optional)		X[i]					X[i]	X[k]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]
Eligibility		X												
Informed Consent		X												
Study Registration		X												
QOL		X						X[k]	X	X	X	X	X	X
Scan: CT or MR	X			X[c]				X[k]	X	X	X	X	X	X
PET/CT[e]	X[e]								X[e]					
AE evaluation						X	X[h]	X[k]	X	X	X	X	X	X
Seed placement						X								
Meds: PPI and pain meds[j]								X[k]	X	X	X	X	X	X
Sim/setup scans						X								
SBRT						X[d]								
Maintenance mFOLFIRINOX[fh]								X-------X[fh]						

[a] Pregnancy test by urine or serum, for women who are not post-menopausal as defined in Appendix III.

[b] Labs should be done within 30 days of eligibility confirmation.

[c] Re-staging scan should be done within 2 weeks following completion of induction mFOLFIRINOX cycles.

[d] SBRT should begin within 4 weeks of simulation and 8 weeks of the last chemotherapy; dose is 40 Gy (8Gy in 5 fractions).

[e] PET-CTs are recommended but not required; if only 1 follow-up PET-CT is possible, recommendation is at 3 months.

[f] mFOLFIRINOX should resume within 8 weeks after study treatment, and any breaks between chemotherapy cycles should not exceed 8 weeks. Patients may continue on maintenance mFFX as tolerated or per clinical judgment of treating physician.

[g] Induction chemo/mFFX prior to enrollment is allowed through the 4th cycle of mFFX. No more than 4 cycles are allowed prior to randomization. The re-staging scan could be done within 2 weeks of completion of the chemotherapy cycle; records from labs and clinic visits are not required; mFFX infusion records should be collected.

[h] Labs during mFFX cycles are as per institutional standard or treating Medical Oncologist. AEs should be assessed with each cycle of mFFX.

[i] Study labs are optional and for research purposes as explained in Section 12. Correlative/Special Studies; and may be drawn if patient agrees to this in the consent form.

[j] Follow-up appointments 1 month before or after will be permitted, e.g. for 6-month follow-up, visit, labs, scan and QOL surveys can be done at 5-7 months.

[k] 4-6 week follow-up visit and corresponding activities are *optional* and may be added if clinically indicated.

15. MEASUREMENT OF EFFECT

15.1 Anti-Tumor Effect

Patients will be evaluated for anti-tumor effect by follow-up imaging (CT and PET-CT imaging) as outlined above. Initial follow-up scans post-treatment will be compared to the patient's baseline scan, defined as the scan prior and closest to the date of initiating chemotherapy.

15.1.1 Definitions

Patients will be evaluable for toxicity and evaluable for objective response at follow-up intervals specified in the Calendar above (Section 14).

15.1.2 Disease Parameters

Pancreatic tumor response will be based upon standard radiographic criteria for the treated lesion and will be prospectively recorded in the combined JHU secure database. Radiographic response of the pancreatic tumor by diagnostic CT scans will be defined according to RECIST criteria as described below:

CR = complete disappearance of index lesion
PR = at least 30% decrease in the longest diameter of the index lesion
PD= more than 20% increase in the longest diameter of the index lesion
SD = does not meet criteria for PR or PD

Pancreatic tumor response will also be assessed by FDG-PET scans (when available) according to the following criteria:

CR = target lesion becomes photopenic or standardized uptake value (SUV) ratio of tumor/liver less than or equal to 1
PR = decrease in SUV ratio of tumor/liver (at least 30%)
PD = increase in SUV ratio of tumor/liver (at least 20%)
SD = no significant change in SUV ratio of tumor/liver

Definitions of Progression

Local tumor progression will be defined as >=20% increased size on follow-up CT scan as compared to baseline CT (scan prior and closest to the date of initiating chemotherapy).

Distant progression will be defined as any tumor found outside of the pancreas on CT scan. Local and/or distant progression by both PET and CT scan will be recorded separately. FDG-PET is not required but highly recommended as a complementary method for determining response. We will also determine PET response with the new PERCIST criteria as reported by Wahl et al. (J Nuc Med 2009; 50:122S-150S).

15.1.3 Methods for Evaluation of Measurable Disease

Pancreas protocol CT or chest abdomen pelvis CT (biphasic imaging, 1.25 mm cuts) will be obtained at follow-up intervals as described in Section 14. Study Calendar. PET-CT scans should be done at baseline (pre-study) and repeated if possible at the 3-month follow-up.

Standard radiographic criteria will be utilized for non-target lesions. Any disease outside of the pancreas will be considered metastatic disease. If possible a biopsy
should be obtained to confirm metastasis.

15.1.4 Duration of Response

The criteria for overall response will be the time from randomization and first sign of local progression or development of metastatic disease.

15.1.5 Progression-Free Survival (or other time-to-event parameters)

The criteria for time to progression and progression-free survival (PFS) will be the time from randomization to documented progression or death. Individuals will be censored at the date of last evaluation for progression if neither event is observed. Overall survival will be defined as time from randomization until death from any cause. Participants will be censored at the date of last contact if the date of death is not observed. Local PFS will be the duration from randomization to local progression or death if death occurs before local progression. Metastasis free survival will be the duration from randomization to metastasis or death from any cause, if death occurs before metastasis. Individuals will be censored at the time of the last evaluation for local or distant progression, respectively, if neither progression nor death is observed.

15.1.6 Response Review

All responses will be reviewed independently by a board certified radiologist at the study's completion. Each image will be reviewed by the PI from each institution periodically and recorded to assess for variability. Simultaneous review of the patient's chart will also occur at this time.

16. MONITORING PLAN AND DATA MANAGEMENT

16.1 Monitoring Plan

Stanford will serve as the coordinating institution and will conduct study audits to review each participating centers' regulatory binders and patient study charts. These

audits will ensure guidelines set forth in this protocol are followed for all aspects of the study including but not limited to regulatory approvals and renewals; patient eligibility, enrollment, treatment, and follow-up; proper documentation and record-keeping; and adverse event and deviation reporting. Audits will be performed yearly by Stanford DSMC; more frequent monitoring will occur as needed. Preliminary reviews may also take place by Stanford research staff prior to audits.

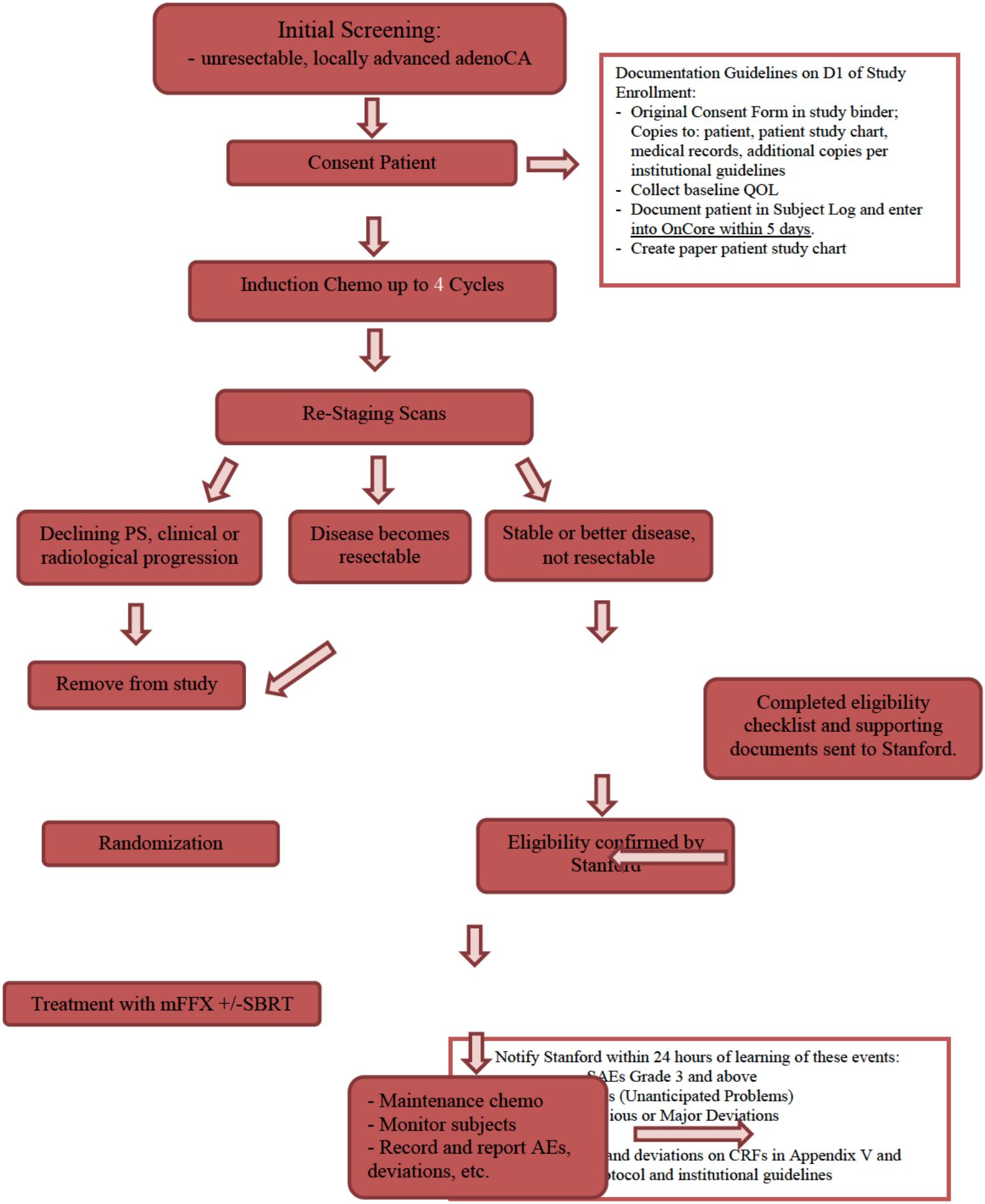
Each participating center will create and maintain a paper chart for each subject enrolled. Research staff at each center will also enter subject information into REDCap as per guidelines set forth in this protocol.

Participating centers will supply radiation treatment plan data upon request by uploading scan images and information. If uploading is not possible, images and reports may be supplied electronically or on encrypted and/or password-protected discs or drives. Further data may be requested from each institution for study analyses.

All tools, computers, and systems used for monitoring and analyses will be secure, password-protected, and HIPAA compliant. Shared data will be de-identified and unique identifiers will be assigned to ensure patient confidentiality.

See below diagram for phases and workflow of study.

16.2 Study Diagram



16.3 Trial Monitoring

All outcome data (toxicity and efficacy) will be reviewed yearly by the Principal Investigator and key Co-Investigators. This study will also be monitored by the Stanford DSMC as stated above in Section 16.1.

Interim reports and/or study renewals will be completed every 10-12 months from study open date, which will be defined as date the study is approved by Stanford IRB. Additional and/or more frequent reports may be done if determined necessary by the study monitoring group (described in Section 11.2.3). These reports may include information about:

- Patient accrual and follow-up: overall and at each institution
- The frequency and severity of adverse events due to protocol therapy
- Compliance rates of treatment delivery with respect to the protocol prescription

Adverse event rates will be compared between treatment groups and with the stopping guideline thresholds (Section 17.5.1). With the exception of a single, planned interim efficacy analysis (Section 17.5.2), the interim reports will not contain the results from the treatment comparisons with respect the primary outcome (progression free survival) or secondary efficacy analyses. See Section 17.5 Stopping Guidelines for additional details.

16.4 Data Management

Study and subject information will be entered and maintained in REDCap database. Research Coordinators at participating institutions will be given access to REDCap and enter data directly. Access will be created once the participating center has obtained all regulatory approvals and becomes a participating center in the study. Once REDCap access is established, research staff at each participating center will be provided educational materials or training on its use.

Participating centers can only view and enter data from their institution; Stanford research staff will have access to study and subject data from all participating centers.

Sections or topics required for entry in REDCap include but are not limited to:

- Diagnosis and Pathology
- Demographics
- Consent
- Eligibility
- On-Study Information
- Off-Study Information
- Arm Assignment/Randomization
- Chemotherapy dates, doses, and modifications as applicable
- Deviations
- SAEs and AEs
- Consultation information
- Pertinent medications
- Results of scans, laboratory and other tests

- Quality of Life responses

Other information for entry into REDCap may be requested or added.

Each center must also begin a patient paper study chart to collect and maintain subjects' records and study-related documents. Patient study charts may be reviewed by Stanford research team or Stanford DSMC to ensure data validity, integrity, and safety of subjects throughout the trial.

Shared data will be de-identified and unique identifiers will be assigned to ensure patient confidentiality.

16.4.1 Monitoring and Study Data Review

When all participating institutions have successfully received IRB approval *and* started enrolling patients, teleconferences will be held every 2 months between research staff from the Coordinating Center and each participating institution. A study monitoring group consisting of PIs and/or Research Coordinators from Stanford University, Johns Hopkins, and Memorial Sloan Kettering will discuss and monitor study-related events and issues in these calls. Included in this monitoring Group are:

- Daniel Chang, Stanford
- Rachel Freiberg, Stanford
- Albert Koong, and Joe Herman, MD Anderson

Discussions may include enrollment and accrual information; data updates and entry issues; adverse events, deviations, or patient-related issues; and other study-related matters. Calls may occur more frequently as needed. Data review and updates will also occur with analysis and completion of Interim Reviews as required per protocol.

16.5 Confidentiality

Study data will be maintained in password protected databases, computer, and/or electronic files. Only research personnel listed on this protocol will have access to this information. Only the patients unique IDN will be used. Specimens will be stored under the patient's IDN. The patient's name or other public identifiers will not be included in any information shared with other investigators.

17. STATISTICAL CONSIDERATIONS

17.1 Endpoints

17.1.1 Primary Endpoints

- To compare the median progression free survival between individuals treated

with mFOLFIRINOX +/- SBRT.

17.1.2 Secondary Endpoints

- To compare the one year progression-free survival in pancreatic cancer patients following chemotherapy alone or chemotherapy and SBRT.
- To compare metastasis free survival in pancreatic cancer patients following chemotherapy alone or chemotherapy and SBRT.
- To compare the overall survival in pancreatic cancer patients treated with chemotherapy alone or chemotherapy and SBRT.
- To compare local progression-free survival in pancreatic cancer patients after chemotherapy +/- SBRT.
- To evaluate acute (within 3 months of treatment) grade 2 or greater gastritis, fistula, enteritis, or ulcer and any other grade 3-4 gastrointestinal toxicity within 3 months of treatment.
- To identify new biomarkers in pancreatic cancer.
- To evaluate the quality of life of patients before and after either chemotherapy alone or chemotherapy and SBRT.

17.2 Analysis Populations

Efficacy analysis will be conducted on the intent-to-treat population which includes all randomized patients and on the per-protocol population. The per-protocol population will include patients who have completed 6 or more cycles of mFolfirinox treatment +/- SBRT.

17.3 Sample Size

17.3.1 Accrual estimates

The study accrual goal is 172 randomized subjects over 60 months among all participating institutions (i.e. 2-3 patients per month). Due to varying eligible patient populations, enrollment may differ at participating centers.

Stanford accrual goal is 6-12 randomized patients annually.

17.3.2 Sample Size Justification

Progression free survival is defined as the time from randomization until progression or death. Individuals who are lost to follow-up prior to death or progression will be censored at the date of last progression evaluation. Based upon previous research, the median progression free survival for individuals treated with mFolfirinox alone is estimated to be 6 months. A sample size of 172 randomized participants (86 per arm) has 91% power to detect an increase to 10.2 months for individuals treated with mFolfirinox plus SBRT as compared to 6 months for those receiving mFolfirinox alone assuming that the data follows an exponential distribution as well as a 60 months of accrual and a minimum of 12 months of follow-up after randomization in a 2-sided test with a type 1 error rate of 0.05.

17.3.3 Criteria for Future Studies

We anticipate that fractionated SBRT with IGRT based linac systems will result in similar progression free survival at one year (80-90%) to single fraction SBRT but with a (20%) decrease in late gastrointestinal toxicity at one year. The current patient population will serve as a comparator for the future trials in terms of time to progression and provide additional information with regards to radiation treatment planning.

17.4 Plan of Analysis

Demographic and clinical characteristics of patients and the characteristics of treated lesions (volume, location, and modality) will be summarized by means, medians, standard deviations, ranges and proportions as applicable.

Time to event outcomes (overall survival, metastasis free survival, and progression free survival) will be summarized using Kaplan-Meier curves and medians with 95% confidence intervals calculated using Greenwood's formula. Cox proportional hazards models will be used to compare treatment groups and to assess risk factors (e.g. biologic markers and PET volume). The effect of site will be tested in the Cox models; the effect of whether or not the patients received Leucovorin will also be tested in the Cox models. The level of response (and other categorical outcomes) will be tabulated at each follow-up interval. Logistic regression and Cox models will be used to assess the proportion with a response category depending upon the level of censoring prior to the annual visit.

The measurements of the volume of the pancreatic tumors based upon CT and PET-CT scans will be compared using paired t-tests or Wilcoxon signed-rank tests as appropriate. The agreement between pancreatic tumor measurements will be compared among the three institutions using correlation coefficients, percentage agreement, and inter-correlation coefficients.

Quality of life outcomes will be assessed at each time interval and compared using the recommended guidelines from the module. Differences in QOL for the two treatment groups will be explored using a repeated measures model in order to account for the within-patient correlation. Special interest will be placed on exploring the aspects of QOL which are known to be impacted by SBRT.

At this time all research on biomarkers for disease progression is exploratory. The goal is to potentially identify biomarkers that are associated with disease progression. Should any biomarkers be identified, their impact on the time to event outcomes will be summarized using Kaplan Meier curves and they will be tested using Cox proportional hazards models.

Quality of life at each interval will be calculated and compared using the recommended guidelines from the module (available by E-mail: c.d.johnson@soton.ac.uk). Efficacy outcomes with repeated measurements over time (e.g. quality of life) will be analyzed using a generalized estimating equation (GEE) approach to account for within-patient

correlation.

Adverse events will be tabulated by type and grade at each follow-up. All adverse events will be reported to the Data Safety and Monitoring Board (DSMB), GI Clinical Research Groups (CRG) if applicable, and each institution's IRB, as well as to Stanford as the Coordinating Center according to the guidelines set forth in this protocol. The expected toxicity rate is 12% or less and a continuous Bayesian stopping guideline has been developed (see section 17.5.1, p 64) representing the 12% toxicity rate. The study may be stopped before reaching the accrual goal at the recommendation of any of these groups based upon stopping guidelines for toxicity as described below.

17.4.1 Stratification

We will stratify by ECOG performance status (0 and 1 vs 2).

17.5 Stopping Guidelines

17.5.1 Toxicity Monitoring

Adverse events or toxicities will be monitored throughout the study and follow-up periods with Grade 4 and higher events reported to Stanford promptly, as outlined in Section 11. Toxicities, Adverse Events, and Reporting Requirements. Grade 3 and lower adverse events will be recorded on AE logs at each institution and reported to Stanford as requested (See Section 11.2.3). An interim review of toxicities between the two arms will be conducted by all co-investigators when 16 evaluable patients have been enrolled. If there is a >20% increase in G3 or higher toxicities in the treatment arm compared with to the control arm, then we will revise the protocol as appropriate.

In our recently completed Phase II study using 33Gy in 5 fractions, there were no Grade 5 toxicities and the Grade 3-4 toxicity rate attributable to SBRT was 8%. For this study, we would expect the observed rate of grade 3 or higher toxicities with the first 6 months to be slightly higher due to the toxicity related to Folfirinox and to the expansion to additional sites; however, we expect the overall rate to be less than 12%. A toxicity level of 20% would be considered the upper boundary.

We have developed a continuous Bayesian stopping guideline with a prior distribution of Beta (6, 44), representing a toxicity rate of 15% (just above our expected rate). The guidelines will recommend that the therapy be re-evaluated if the posterior probability that the toxicity rate exceeds the 20% boundary is greater than 65%. Once an initial cohort of 10 participants has been enrolled and followed for 6 months, toxicity will be monitored continuously. Table 1 below summarizes the stopping guideline boundaries for SBRT related events.

Table 1

Cohort size	Observed number of toxicities that trigger re-evaluation
11-14	5
15-20	6
21-27	7
28-33	8
34-39	9
40-46	10
47-52	11
53-58	12
59-65	13
66-71	14
72-78	15
79-84	16
85-86	17

The probability of triggering the stopping guidelines was assessed for a range of underlying toxicity rates based upon simulations with 5000 replicates (Table 2). In the expected range of toxicity, the probability of stopping to re-evaluate was less than 5% if the underlying toxicity was 10%; whereas the probability of stopping to re-evaluate for unacceptable levels was 74.2% or higher.

Table 2

True underlying toxicity rate	Probability of triggering stopping guideline boundaries
1%	0%
5%	0.1%
8%	1.4%
10%	4.2%
12%	11.3%
15%	31.2%
20%	74.2%
25%	95.7%

17.5.2 Interim Analysis for Efficacy of Primary Endpoint: Progression Free Survival

A single interim efficacy analysis will be performed at 36 months, the calendar mid-point for the trial. Given the expected median time to progression given in Section 17.3.2, we expect to observe the progression endpoint (progression or death due to any cause) for 160 participants (83 in the folfirinox alone arm and 77 in the SBRT + folfirinox arm). After 36 months, we anticipate observing 71 progressions, which translates to 44% of the total information. Monitoring will be performed via an O'Brien-Fleming alpha spending function with an interim assessment at 44% of information time. The calculations are made assuming two-sided symmetric boundaries with a total of 2 analyses (1 interim and one final) and a total alpha 0.05. The trial will be stopped early for efficacy if the

99.695% confidence interval of the hazard ratio does not contain 1, i.e. a two-sided alpha spending of 0.00305 on the first interim analysis (0.001525 in each direction).

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Block randomization: blockrand package information can be found at `https://CRAN.R-project.org/package=blockrand`

A P E N D I C E S

Appendix I

EORTC QLQ-C30 and

EORTC QLQ-PAN26

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ | | | | ⌋

Your birthdate (Day, Month, Year): ⌊ | | | | | | | | ⌋

Today's date (Day, Month, Year): 31 ⌊ | | | | | | | | ⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ - PAN26

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at all	A little	Quite a bit	Very much
31. Have you had abdominal discomfort?	1	2	3	4
32. Did you have a bloated feeling in your abdomen?	1	2	3	4
33. Have you had back pain?	1	2	3	4
34. Did you have pain during the night?	1	2	3	4
35. Were you uncomfortable in certain positions (e.g. lying down)?	1	2	3	4
36. Were you restricted in the types of food you can eat as a result of your disease or treatment?	1	2	3	4
37. Were you restricted in the amounts of food you could eat as a result of your disease or treatment?	1	2	3	4
38. Did food and drink taste different from usual?	1	2	3	4
39. Have you had indigestion?	1	2	3	4
40. Were you bothered by gas (flatulence)?	1	2	3	4
41. Have you worried about your weight being too low?	1	2	3	4
42. Did your arms and legs feel weak?	1	2	3	4
43. Did you have a dry mouth?	1	2	3	4
44. Have you had itching?	1	2	3	4
45. To what extent was your skin yellow?	1	2	3	4
46. Did you have frequent bowel movements?	1	2	3	4
47. Did you feel a sudden urge to have a bowel movement?	1	2	3	4
48. Have you felt physically less attractive as a result of your disease and treatment?	1	2	3	4

Please go to the next page

During the past week:	Not at all	A little	Quite a bit	Very much
49. Have you been dissatisfied with your body?	1	2	3	4
50. To what extent have you been troubled with side-effects from your treatment?	1	2	3	4
51. Have you worried about what your health might be like in the future?	1	2	3	4
52. Were you limited in planning activities in advance (e.g. meeting friends)?	1	2	3	4
53. Have you received adequate support from your health care professionals?	1	2	3	4
54. Has the information given about your physical condition and treatment been adequate?	1	2	3	4
55. Have you felt less interest in sex?	1	2	3	4
56. Have you felt less sexual enjoyment?	1	2	3	4

Appendix II

ECOG Performance Status*

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

* As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Appendix III

Definition of Menopausal Status:

Menopausal will be defined according to the following criteria:

Post-menopausal:

- Woman 60 years of age or older
- Woman aged 45-59 years with spontaneous cessation of menses for at least 12 months prior to registration
- Woman aged 45-59 years with cessation of menses for less than 12 months prior to registration AND an FSH level in the postmenopausal range (or >34.4 IU/L if institutional range is not available)
- Woman aged 45-59 years on hormone replacement therapy who have discontinued hormone replacement therapy at diagnosis of breast carcinoma and have an FSH level in the postmenopausal range according to institutional/laboratory standards (or 34.4 IU/L if the institutional range is not available)
- Prior bilateral oophorectomy
- Woman younger than 60 years of age who have had a prior hysterectomy (without bilateral oophorectomy) AND who have an FSH level in the postmenopausal range (or >34.4 IU/L if institutional range is not available)

Pre- or peri-menopausal: Not meeting definition for postmenopausal outlined above

Appendix IV

Eligibility Checklist

Protocol Information

Title	Pancreatic Cancer Radiotherapy Study Group (PanCRS) Trial: A Randomized Phase III Study Evaluating Modified FOLFIRINOX (mFFX) with or without Stereotactic Body Radiotherapy (SBRT) in the Treatment of Locally Advanced Pancreatic Cancer
Number	27492
Principal Investigator	Daniel Chang

Subject Information

Subject Name: _____
Study ID: _____
Gender: ☐ Male ☐ Female

Inclusion/Exclusion Criteria

Inclusion Criteria (From IRB approved protocol)	**Yes**	**No**	**Supporting Documentation***
1. Histologically confirmed adenocarcinoma of the pancreas	☐	☐	
2. Induction mFOLFIRINOX up to 4 cycles	☐	☐	
3. Stable or better disease on re-staging scans	☐	☐	
4. Determined unresectable by a pancreatic cancer surgeon or a multi-disciplinary or gastrointestinal oncology Tumor Board	☐	☐	
5. Typically, pancreatic tumors must be < 8.0 cm in greatest axial dimension at time of treatment planning but final determination of eligibility will be based upon satisfying the radiation normal tissue constraints as specified in protocol (Section 6.1.3 - Radiation Treatment Planning).	☐	☐	
6. ECOG 0, 1, or 2	☐	☐	

7. Acceptable organ and marrow function as defined below and within 30 days of eligibility confirmation: a. Leukocytes ≥3,000/μL b. ANC ≥1,500μL c. Platelets ≥50,000/μL d. Total bilirubin ≤1.5 X institutional upper limits of normal e. AST (SGOT)/ALT (SGPT) ≤2.5 X institutional upper limit of normal f. Creatinine not above the upper limit of normal institutional limits	☐	☐	
8. Ability to understand and the willingness to sign a written informed consent document	☐	☐	
9. Life expectancy >6 months	☐	☐	

Exclusion Criteria (From IRB approved protocol)	**Yes**	**No**	**Supporting Documentation***
1. Children / Age <18 years	☐	☐	
2. Metastatic disease	☐	☐	
3. Prior radiotherapy to the upper abdomen/liver	☐	☐	
4. Prior chemotherapy for pancreatic cancer, other than up to 4 cycles of mFOLFIRINOX	☐	☐	
5. Uncontrolled illness including, but not limited to, ongoing or active infection (or infections requiring systemic antibiotic treatment), symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.	☐	☐	
6. Any concurrent malignancy other than non-melanoma skin cancer, non-invasive bladder cancer, or carcinoma in situ of the cervix. Patients with a previous malignancy without evidence of disease for > 5 years will be allowed to enter the trial.	☐	☐	
7. Pregnant and breastfeeding women are excluded, as well as women of child-bearing potential who are unwilling or unable to use an acceptable method of birth control (hormonal or barrier method of birth control; abstinence) to avoid pregnancy for the duration of the study. Male subjects must also agree to use effective contraception for the same period as above.	☐	☐	
8. Women who are not post-menopausal (as defined in Appendix III) and have a positive urine or serum pregnancy test or refuse to take a pregnancy test	☐	☐	

*Supporting documentation is required to confirm subject eligibility and can include but is not limited to: clinic notes, laboratory results, pathology results, radiology reports, subject self-report, or MD documentation.

IV. Statement of Eligibility

By signing this form of this trial I verify that this subject is [☐**eligible** / ☐**ineligible**] for participation in the study. This study is approved by the Stanford Cancer Institute Scientific Review Committee, the Stanford IRB, and has finalized financial and contractual agreements as required by Stanford School of Medicine's Research Management Group.

Study Coordinator Signature:	Date:
Printed Name:	
Secondary Reviewer Signature:	Date:
Printed Name:	
Treating Physician Signature:	Date:
Printed Name:	

Appendix V

Case Report Form and Patient Logs:

- **Case Report Form for SAEs, AEs, and UPs**
- **Subject Log**
- **Protocol Deviation Log**
- **AE (Adverse Event) Tracking Form**

STANFORD CANCER INSTITUTE

Received On:_____
Date Submitted to CCTO:_____
Date Submitted to SUMC IRB:_____

Case Report Form for SAEs, AEs, and UPs

Protocol: ***Pancreatic Cancer Radiotherapy Study Group (PanCRS) Trial: A Randomized Phase III Study Evaluating Modified FOLFIRINOX (mFFX) with or without Stereotactic Body Radiotherapy (SBRT) in the Treatment of Locally Advanced Pancreatic Cancer***

Stanford eprotocol #: 27492 **OnCore #: PANC0015**

Date of Report: _____

Participating Site and

Location:_____

Date of Event:_____

Subject's Initials: _____

Subject's OnCore #:_____

Research Staff Completing Form:

Name: _____

Phone: _____

Email: _____

Principal Investigator / Treating Physician at study site has reviewed and agrees with information in this report:

Printed Name: _____

Signature: _____ Date: _____

Answer all questions below. Provide additional pages as needed.

1. Check if event was:
   ○ Serious Adverse Event (SAE)* ○ Adverse Event (AE)* ○ Unanticipated Problem (UP)#

   *Note Grade: _ (According to CTCAE, V 4 or greater, available at http://ctep.cancer.gov/reporting/ctc.html.)

   #If also UP, check that it meets criteria for: ☐ Unexpected
   ☐ Related
   ☐ Harmful

2. Check the box of which therapy the event was related or possibly related to:
   ☐ mFOLFIRINOX ☐ SBRT ☐ Other, indicate: _____

3. Indicate how much treatment the subject received up to the event:

   - For mFOLFIRINOX, Cycles_____ and Days or Doses_____

   - For SBRT, fractions_____ and cGy_____

4. Provide a brief description of the event, including:
   - symptoms reported and when (dates)
   - results of scans, labs, or other procedures or tests
   - if hospital ED visit or admission, give dates and length of hospitalization
   - If Grade 5, indicate date of death, primary cause, if death certificate obtained, and if autopsy performed

_____

_____

_____

_____

_____

_____

5. Following the event:
   - Was therapy discontinued? ☐ No ☐ Yes ☐ N/A
   - Was dose modified? ☐ No ☐ Yes ☐ N/A
     If **Yes**, note modified dose(s): _____

_____

—

6. Define the action plan and follow-up, including:
   - Next visit and follow-up schedule if not per protocol
   - Referrals for tests, procedures, specialty or other clinics
   - Other pertinent information:

_____

_____

_____

Participating Center: _____

Subject Log

#	Subject Name	Subject Initials	Subject ID or OnCore #	Date On-Study (Date of Randomization)	Treatment Arm	Treatment Start Date (Day 1)	Date Off-Study	Reason Off-Study
1					☐ mFFX ☐ +SBRT			
2					☐ mFFX ☐ +SBRT			
3					☐ mFFX ☐ +SBRT			
4					☐ mFFX ☐ +SBRT			
5					☐ mFFX ☐ +SBRT			
6					☐ mFFX ☐ +SBRT			

7					☐ mFFX ☐ +SBRT			
8					☐ mFFX ☐ +SBRT			
9					☐ mFFX ☐ +SBRT			
10					☐ mFFX ☐ +SBRT			

Participating Center: _____

Protocol Deviation Log

#	**Subject Initials**	**Subject ID or OnCore #**	**Date of Deviation**	**Category** (see next page)	**Code** (see next page)	**Brief Description**	**Date IRB notified,** if applicable	**Corrective Action**
1								
2								
3								
4								

5								
6								
7								
8								
9								
10								
11								
12								

Deviation Categories

A. Safety
B. Informed Consent
C. Eligibility
D. Protocol Implementation
E. Other, specify in log

Deviation Codes (associated with Deviation categories)

Safety (Category A) 1. Not reporting SAE within 24 hours 2. Laboratory tests not done 3. AE/SAE not reported to IRB 4. Other, specify on log	Eligibility (Category C) 12. Participant did not meet eligibility criteria 13. Randomization of an ineligible patient 14. Participant randomized prior to Baseline Assessment 15. Randomization or treatment of a patient prior to IRB approval of protocol 16. Other, specify in log
Informed Consent (Category B) 5. Failure to obtain informed consent 6. Consent form used was not current IRB approved version 7. Consent form does not include updates or information required by IRB 8. Consent form missing 9. Consent form not signed and dated by participant 10. Consent form does not contain all required signatures 11. Other, specify in log	Protocol Implementation (category D) 17. Failure to keep IRB approval up to date 18. Participant receives wrong treatment 19. Participant seen outside of window visit 20. Use of unallowable concomitant treatments 21. Prescribed dosing outside of protocol guidelines 22. Missed Assessment 23. Missed Visit 24. Other, specify in log

AE Tracking Form: PanCRS Trial - Phase III Rand mFFX w/ or w/o SBRT		Site:					PI:				
Pt Last Name:		Subject ID #:					Inst. MRN:				Page #:
AE by system	Hints for grading	___f/u visit or ___FFX- Cycle:_____ f/u timept, if applicable:_____ Date _____ ☐Oncore					___f/u visit or ___FFX- Cycle: _____ f/u timept, if applicable:_____ Date _____ ☐Oncore				
		Lab Results/ Date:	Grade	Attribution*		Comment	Lab Results/ Date:	Grade	Attribution*		Comment
				FFX	SBRT				FFX	SBRT	
Blood/Bone marrow	**Abnormals only**										
WBC	low										
Hgb	low										
Hct	low										
Platelets	low										
Neut ABS/ ANC	low										
Lym ABS	low										
Other-											
Metabolic Panel	**Abnormals only**										
Sodium											
Potassium											
Chloride											
Creatinine	high										
Glucose											
Calcium											
Bilirubin											
AST											
ALT											
Alk phos											
Albumin	low										
Protein											
Other-											
Constitutional											
Fatigue	Affecting ADLs?										
Weight loss	< 5, 10 or 20% from basline?										
GI											
Anorexia											
Nausea	IVF needed?										
Vomiting	Episodes/d? IVF?										
Diarrhea	BMs/d? 2/2 tx or malabsorption?										
Constipation	Last BM?										
Heartburn/dyspepsia	PPI daily?										
Upper bleed	Procedure?										
Lower bleed	Procedure?										
Ulcer	Symptoms?										
Other											
Neurology											
Periph neuropathy	Interfering w/ fxn?										
Pain											
Abdominal pain											
Other location											
Other											
Signature		**Inv signature / date:**					**Inv signature / date:**				

***Attribution - Note # under FFX or SBRT column:** 1-unrelated 2-unlikely 3-possible 4-probable 5-definite